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Occupational Exposure to Respirable Crystalline Silica -- Review of Health Effects Literature and Preliminary Quantitative Risk Assessment

Occupational Safety and Health Administration

Docket OSHA-2010-0034

Occupational Exposure to Respirable Crystalline Silica -- Review of Health Effects Literature and Preliminary Quantitative Risk Assessment

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I. Health Effects Literature Review.

I.A. *Introduction.*

I.A.1. Background Information on Crystalline Silica and the Literature Review.

Silica is comprised of silicon and oxygen (SiO_2) and is one of the most abundant compounds on earth. It occurs in either a crystalline or non-crystalline (amorphous) form. Crystalline silica, in which the silicon and oxygen atoms are arranged in a tetrahedron structure, exists in several forms, or polymorphs. The most commonly encountered polymorph is quartz; crystobalite and tridymite are two other naturally-occuring polymorphs of crystalline silica. The importance of the crystalline feature is that it is highly stable, insoluble in water, and possesses on its surface reactive oxygen species when fractured (Castranova et al., 1996). The presence of these reactive species on the crystal surface is largely responsible for the toxicity of crystalline silica particles when inhaled. OSHA currently enforces an occupational exposure limit for respirable dust that contains quartz, as well as for respirable dust that contains crystobalite or tridymite.

Quartz is a common component of rock and soils. Consequently, workers are exposed to quartz-containing dust when performing operations that disturb or break up soils and rock, or materials derived from them such as concrete and masonry. Crystobalite and tridymite are also naturally occurring but to a much lesser degree than quartz. These polymorphs are formed from quartz that has been subjected to high temperatures. Work operations that involve subjecting quartz-containing materials to high temperatures may cause quartz to morph into crystobalite, resulting in worker exposures to dusts containing crystobalite.

Health hazards associated with exposure to crystalline silica-containing dusts arise from the inhalation of the respirable dust fraction, which is comprised of particles sufficiently small to reach the deep lung. The respirable fraction is broadly defined as particles having a diameter of 10 μm or less (IARC, 1997). It is this portion of crystalline silica-containing dust that is of most concern to OSHA and is the focus of this health effects section. The occupational diseases associated with inhalation of respirable crystalline silica and discussed in detail in this section include: silicosis and other non-malignant respiratory diseases; pulmonary tuberculosis; chronic bronchitis with airflow limitation, and emphysema (both more commonly referred to as “chronic obstructive pulmonary disease,” or COPD); and several extra-pulmonary diseases (renal and immunologic) and cancer (lung and other). These occupational diseases, either alone or in concert, are life-altering and debilitating disorders that annually affect thousands of workers across the United States. Many of these diseases are also life-threatening. The preponderance of evidence for the adverse health effects associated with inhalation of crystalline silica, as described extensively in the scientific literature consists of studies of exposed workers. However, many animal and *in vitro* studies have also been conducted in an effort to elucidate the mechanisms by which crystalline silica increases the risks of adverse health effects.

The purpose of providing an extensive review of the scientific literature in this health effects section is to present OSHA’s preliminary findings on the nature of the hazards presented

by exposure to respirable crystalline silica, and to present an adequate basis for the quantitative risk assessment section to follow. The health effects section is organized by type of disease with silicosis addressed first, in Section B.

The next section, Section C, deals with the carcinogenic effects of inhalation of respirable crystalline silica which have been investigated in numerous epidemiological studies, almost all dealing with workplace exposures. The section mostly focuses on studies of lung cancer but also includes discussion of suggestive evidence that exposure to silica may increase the risk of esophageal cancer and possibly other cancers. In addition to the OSHA analysis, the International Agency for Research on Cancer (IARC) has concluded that there is sufficient evidence of lung carcinogenicity in humans exposed to crystalline silica (IARC, 1997).

Section D discusses and evaluates the scientific literature describing emphysema, chronic bronchitis, pulmonary function impairment, and other non-malignant respiratory diseases. The subsequent section, Section E, discusses non-respiratory diseases; in particular, renal disease and auto-immune diseases associated with inhalation of respirable crystalline silica. Finally, Section F evaluates the evidence on the physical characteristics of silica that may affect its toxicity. Information on mechanisms of action of silica and results from *in vivo* and *in vitro* studies are also reviewed and summarized in Section F.

OSHA has included in its review all published studies that the Agency deems relevant to assessing the hazards associated with exposure to respirable crystalline silica. These studies were identified from numerous scientific reviews that have been published previously such as the IARC (1997) and NIOSH (2002) evaluations of scientific literature as well as from literature searches and contact with experts and stakeholders. Not included in this review are studies primarily of historical interest and numerous case studies describing silicosis and other silica-related diseases. Some of the studies reviewed by OSHA contain sufficient quantitative information on exposures and disease incidence or mortality rates that the Agency believes them appropriate for use in its quantitative risk assessment (Section II).

The epidemiological studies reviewed here concern exposures of worker populations dating back several decades, as early as in the 1930's. Over this period of time, the assessment of worker exposures, a crucial element in epidemiological study, evolved dramatically. Consequently, epidemiological studies have had to rely on exposure information derived form a wide array of different kinds of data, a factor that complicates interpretation of the studies. To aid the evaluation of the epidemiological literature base, the remainder of this section presents background information on the various methods that have been used to measure workplace dust concentrations and to assess worker exposures to respirable crystalline silica.

I.A.2. Background and Terminology for Measuring Worker Exposures to Dust.

Exposure data for dusts can reflect measurements of total dust or respirable dust. The term "respirable dust" generally refers to particles small enough to reach the alveolar spaces in the lung (i.e., < 10 µm in aerodynamic diameter). Exposures to dusts are expressed either as a particle concentration (i.e., millions of particles per cubic foot of air or mppcf) or a gravimetric

concentration (i.e., unit mass of particles per unit volume of air, such as mg/m^3). Particle concentrations are determined by microscopically counting the number of respirable-sized particles collected from an air sampling device that either deposited an air sample onto a slide (i.e., a thermal precipitator) or into a liquid, after which an aliquot was deposited on a counting slide (such as is done when using an impinger). Gravimetric concentration is determined from the mass of respirable dust collected on a filter media by a particle-size-selective air sampling device (i.e., a device designed to exclude non-respirable particles from the collection media).

It is important to state whether a measurement of dust concentration reflects exposure to all airborne respirable dust or just to the respirable crystalline silica fraction. Following the convention used in most of the studies reviewed here, exposure to *"respirable dust"* means exposure to all airborne respirable particles (or the mass concentration of all respirable particles), and exposure to *"respirable crystalline silica"* (or "respirable quartz") means exposure only to the crystalline silica (or quartz) fraction of airborne respirable dust (such as the mass concentration of respirable dust times the percent quartz content of the dust).

When an air sample is taken over a period of time, the resulting measure of exposure represents an average concentration to which a worker was exposed over the sampling period; this is referred to as a "time-weighted average" (TWA) concentration. As used in this document, a TWA exposure usually refers to an average concentration over a full work shift, such as for an 8-hour TWA concentration. When the sampling period approximates a full-shift exposure, the resulting TWA measure is considered to be the most useful metric to characterize chronic disease risk caused by exposure to crystalline silica and other pneumoconiosis-producing dusts. Reliance on shorter-term airborne dust measurements (as was done with sampling technologies that pre-dated current sampling methods) adds uncertainty to the characterization of full-shift exposures and, consequently, exposure-related risks.

Epidemiologic investigations use data on past exposures of a cohort to an air contaminant in an effort to quantitatively relate exposure to risk of disease. Cumulative exposure, which is the product of average exposure and exposure duration (or the sum of such products over several exposure periods), is the exposure metric that tends to best predict chronic disease risk. As the discussion in the sections that follow demonstrates, cumulative exposure is the exposure metric that has been consistently demonstrated to be associated with risk of silicosis, lung cancer, and other non-malignant respiratory diseases. Investigators often use other measures or surrogates of long-term exposure as well, such as average exposure or duration of employment in an industry where exposure is known to occur. In the case of crystalline silica, most epidemiological studies characterize cumulative exposure from particle count data (yielding particle-years of exposure) or from gravimetric measures (yielding mg/m^3-years of exposure). It may be the case that the total surface area of the airborne particles is an even better predictor of risk, since it is the surfaces of insoluble particles that interact with cells in the lung (see Section I.F). However, because surface area measurements require sophisticated and expensive analytical instrumentation that is not readily available to most employers, it is not practical for routine risk management.

A brief discussion of OSHA's current and proposed permissible exposure limits (PELs) for quartz serves to illustrate the concepts discussed above. OSHA's current PELs for respirable quartz are expressed both in terms of a particle count as well as a gravimetric concentration (both are listed in OSHA's general industry Air Contaminants standard, while only the particle count formula applies to construction and shipyard employment). The PELs are formulas that impose a limit on the 8-hour time-weighted average (TWA) concentration to respirable dust, with the PEL varying depending on the percent quartz content of the respirable dust. In general industry, the gravimetric formula PEL for quartz is:

$$\text{PEL (mg/m}^3\text{ respirable dust)} = 10\text{ mg/m}^3 / \%\text{ Quartz} + 2.$$

So, for example, the PEL for a dust containing 18 percent quartz is 0.5 mg/m^3 as a limit on the *respirable dust* concentration. As the quartz content of the dust increases, the limit on respirable dust exposure decreases reaching a lower limit of 0.100 mg/m^3 for respirable dust comprised of 100 percent quartz. For respirable dusts having a quartz content of from 5 to 100 percent, the formula PEL equates to a *respirable quartz* concentration of from 0.083 to 0.1 mg/m^3. Therefore, for the purposes of this document, the gravimetric PEL formula is considered to be approximately equivalent to a respirable quartz concentration of 0.100 mg/m^3. For general industry, the current PELs for two other polymorphs of crystalline silica, cristobalite and tridymite, are half the value of the quartz formula PEL.

The formula PEL for the construction and shipyard industries, based on particle concentration is:

$$\text{PEL (mppcf respirable dust)} = 250\text{ mppcf} / \%\text{ Quartz} + 5.$$

The relationship between these two formula PELs is discussed further below and in Section II, Preliminary Quantitative Risk Assessment.

OSHA is proposing a PEL of 0.05 mg/m^3 for respirable crystalline silica, as an 8-hour TWA, a value that is half that of the current general industry formula PEL for quartz and equal to the current general industry formula PEL for dust cristobalite and tridymite. Thus, the proposed PEL is expressed, not as a limit on respirable dust mass concentration that varies with the content of crystalline silica, but as a limit on respirable crystalline silica mass concentration.

To illustrate further the concept of cumulative exposure, assuming that a worker is exposed to respirable crystalline silica at the current PEL (i.e., about 0.100 mg/m^3 of respirable silica) every workday for 45 years (i.e., from age 20-65), his or her cumulative exposure to respirable crystalline silica would be 4.5 mg/m^3-years (0.100 mg/m^3 multiplied by 45 years). A worker exposed to the proposed PEL for 45 years would have a cumulative exposure of 2.25 mg/m^3-years. Many of the epidemiological studies evaluated in the sections that follow describe the effects of cumulative exposures within the range of cumulative exposure permitted by the current and proposed PELs.

I.A.3. Current Methods for Measuring Respirable Crystalline Silica.

This section reviews the main methodologies that OSHA, MSHA, NIOSH and similar organizations in other countries have relied upon to determine airborne concentration levels of dust or particles and the analytical methods available to evaluate silica content.

The two basic approaches for measuring airborne concentrations are sample collection with analysis and real-time, direct dynamic measurements. Either of these sample collection approaches can be used for either personal or area sampling. Sampling collection methods involve collecting particles onto a filter substrate or into a liquid medium for later analysis. Devices used to collect air samples can include inertial devices such as impactors or cyclones, which separate particles based on their size, or impingers, which pull air samples through liquid medium to capture air contaminants. Analysis of collected samples can be performed through a variety of methods, including, but not limited to: optical or electron microscopy for counting particles; X-ray diffraction (XRD); and infrared spectrophotometry. Instruments that perform direct measurements for personal sampling include optical particle counters that can provide gravimetric and particle size distribution data on a real-time basis. (For a complete discussion of sampling methods for dusts, see Ayer and Rice, 2000.)

The current OSHA convention for measuring airborne dust is to measure respirable mass with a dust sampler using a cyclone designed to be worn by the worker in the breathing zone and attached to an air pump placed on the worker's belt. Dust-laden air is pulled through a cyclone that removes the non-respirable dust (i.e., particles greater than 10 μm) and deposits respirable dust on a filter that is subsequently weighed. The cyclone is generally operated for a full work shift to yield a TWA measure of exposure to respirable dust mass, although shorter-term samples may also be taken (for example to measure exposures during a specific work task). Although there are other ways of characterizing particle size distribution, the cyclone is the device that is most commonly used to collect personal samples because its size permits it to be worn near the breathing zone, and it is relatively insensitive to orientation. By way of contrast, a horizontal elutriator, an earlier technology for collecting area samples of respirable dust, must remain horizontal and cannot be worn as a personal sampler.

In the next section, OSHA briefly describes historical methods for measuring airborne concentrations not only to show how the current measurement convention evolved, but also to illustrate the need for and the limitations of translating historical dust exposure measures to equivalent respirable dust mass, which is the current conventional exposure metric.

I.A.4. Methods Used for Collecting Dust Concentration Data for Epidemiological Evaluation.

This section outlines in more detail the methods used in gathering airborne concentration data for the epidemiological studies reviewed in the health effects section (I) and the preliminary quantitative risk assessment (Section II). The epidemiologic studies reviewed in this section present airborne concentration data from a variety of different kinds of dust measurements, which largely reflect changes in technology and industrial hygiene practices that have evolved

since the 1930's. In this section, OSHA summarizes dust measurement technologies that have been used to generate the airborne concentration data relied on by the studies.

I.A.4.a. Dust sampling techniques.

Most of the retrospective cohort studies included in OSHA's analysis span a timeframe of 40-65 years. Consequently, these studies often incorporate data collected using a number of different measurement protocols. In 1947, measurements for silica taken with felted layers of salicylic acid crystals were reported by Hatch in the industrial sand industry (Hatch et al., 1947). These were fixed-location (area), short-term samples. Also, optical particle counting devices (Konimeters) were designed to take short-term samples (also described as "snap samples") that could be collected near the worker's breathing zone. These measurements were well-suited to characterize the variability in aerosol concentrations, and Beadle used Konimeters in South African gold mines to measure dust concentrations over a series of two-minute periods (Beadle and Bradley, 1970). The use of snap samples was of limited value for determining exposures over longer periods, because a prohibitive amount of work was required to examine each sample by optical microscopy. However, as Morrow observed in 1964, dust sampling had mainly been used up to that time to evaluate dust controls, and short-term snap or "grab" samplers were useful for that purpose. These short-term approaches were suitable to depict variations in dustiness, as well as average exposures over short periods of time.

Since chronic pneumoconiosis, including silicosis, was thought to be associated with prolonged exposure to airborne dust over many years, devices that measured cumulative airborne dust concentrations over longer periods were more suitable for hazard assessments. This was the case, even though they did not provide useful information about the variability of short-term peak concentrations. In the U.S., starting in the 1950's, there was a gradual conversion from the collection of silica dust by Greenburg-Smith impingers, and later, midget impingers for respirable dust counting, to the collection of respirable samples on a filter membrane with a cyclone pre-selector for gravimetric silica analysis (Ayer and Rice, 2000). Greenburg-Smith impingers were area samplers that used dust counting techniques in the analysis. Dust-laden air was drawn at high velocity through a nozzle in a glass flask, usually containing water and impinged against a glass plate immersed in the water. Dust particles were counted and sized with an optical microscope on a Wattman reticule. Midget impingers, introduced later, could be used in explosive atmospheres because they were hand-cranked, and could be worn in the person's breathing zone. Sample times varied from 15 to 20 minutes with a midget impinger, to 2-4 hours with a Greenburg-Smith impinger (ACGIH, 1972).

At about the same time in Great Britain, there was a gradual transition from the standard thermal precipitator, followed by the long-running thermal precipitator, to respirable gravimetric measuring instruments, e.g., horizontal elutriator, in mines and in selected dusty industries (Ayer and Rice, 2000). The thermal precipitator operated at very low velocities and drew dust-laden air at rates ranging from 7 ml/minute to 1 liter/minute past a hot wire that caused the thermal deposition of particles against a cooler collection surface. An inlet elutriator was commonly used to remove the coarse particles from the air. Thermal precipitators are nearly 100 percent efficient in obtaining most particles from 0.01-5 micrometers (microns). Because sample

collection was limited in size, the thermal precipitator tended to be used as a fixed area sampler for a half or full shift of work. Typically, dust counting was done with an optical microscope using a Porton® microscope eyepiece reticule, (ACGIH 1972).

In South Africa, exposures of gold miners was extensively characterized using Konimeter snap measurements taken at 10-minute intervals throughout the work shift, as well as thermal precipitator measurements taken continuously during the shift (Page-Shipp and Harris, 1972). These intensive sampling protocols to characterize exposures over the work shift combined with an approach for estimating respirable dust mass concentration from the resulting particle count data permitted the researchers to construct one of the early exposure-response analyses for silicosis among South African miners (DuToit, 1991; Hnizdo and Sluis-Cremer, 1991; Page-Shipp, 1972). Investigators studying exposures of Canadian gold and other miners initially used Konimeter dust measurements. Over time, this was replaced with gravimetrically analyzed respirable mass sampling. In a few studies, mostly based in China and Finland, available exposure data is primarily derived from total dust measurements requiring the use of appropriate correction factors to estimate respirable dust exposures.

Investigators have devised several approaches to making optimum use of historical airborne dust concentration measurements to estimate worker exposures. Generally, these approaches have been empirical in nature, based on data collected by simultaneous, or nearly simultaneous, sampling with two (or more) devices in the same environment. The comparative data were then used to derive one (or more) conversion factor(s) or to create an algorithm so that airborne dust concentrations could be expressed in a uniform manner. This has been done, for example, by transforming particle count data measured by liquid impinger sampling to an estimate of respirable particle mass concentration. Drinker and Hatch (1954) described several complications in making this conversion and advised against making such a conversion in the absence of knowing the particle size distribution. In any case, making this conversion was a prominent feature in the development of the mass-based ACGIH TLV in 1968.

Table I-1 summarizes the selected U.S. and British studies that developed either study-specific internal conversion factors or external conversion factors used to estimate gravimetric measures of dust exposure from historic measurements (e.g., dust particle counts). Three investigators evaluated and used pre-existing external conversion factors: Rice et al. (1984) in her study of North Carolina dusty trades; Cherry et al. (1998) for the British pottery workers study; and Sanderson et al. (2000) in their study of U.S. industrial sand workers. Investigators of three other cohorts (diatomaceous earth workers, Vermont granite workers, and U.S. industrial sand workers) developed internally derived estimates. There is reasonable correspondence in the findings of U.S. investigators who have sought to derive empirical (data-based) relationships between airborne dust particle count measurements and gravimetric respirable dust measurements to estimate occupational exposures to silica. There is certainly variability between the types of dust that were evaluated in these studies, which must be considered in generalizing the findings. Most U.S. investigators developed conversion factors from concurrent impinger-based measures of particle count and measures of respirable mass from cyclone sampling. A variety of approaches were used, from calculated ratios of measurements taken side-by-side with the sampling devices being compared in laboratory exposure chambers and in

field settings, to modeling approaches that considered the influence of sampling location, type of industry, and specific process within the industry.

Table I-1 Conversion Factors (CF)Used in Select U.S. Studies and Research Converting Respirable Dust Counts Collected by Impingers in Millions of Particles Per Cubic Foot (mppcf) to a Mass Respirable Dust Equivalent in Milligrams Per Cubic Meter (mg/m3)

Study Description/ Author	CF Internal/ External	Conversion to Respirable Dust 1 mppcf = _ µg/m^3	Conversion to Respirable Silica 1 mppcf =_µg/m^3	Comment
Lab Research/ Nelson et al. 1978	Internal	0.11 0.083		Greenburg-Smith Impinger Midget impinger
Vermont Granite/ Ayer et al. 1973	Internal	0.1	1 mppcf = 0.01 mg/m^3	Reported as 10 mppcf = 0.1 mg/m^3
Vermont Granite/ Davis et al. 1983	Internal	0.075	1 mppcf = 0.0075 mg/m^3	Reanalysis using paired data from Sutton and Ayer
North Carolina Dusty Trades,. Rice et al. 1984	External	0.09		Used mean of four previous studies
Diatomaceous Earth Seixas et al. 1997	Internal	0.09 – 0.18		Station-specific factors
U.S. Industrial Sand Sanderson et al. 2000	External	0.1		
U.S. Industrial Sand Rando et al. 2001	Internal	.275 .206 - .364		Reported as 1 mppcf = 276 µg/m^3
British Pottery Cherry et al. 1998	External	0.09		Based on Rice's paper cited above

The industry-based studies of particle samples in the granite mining and processing industry (Sutton and Reno, 1968; Ayer et al., 1968; and Rice et al., 1984), and the re-calculation of these data (Davis et al., 1983), have all estimated conversions around 0.1 mg/m^3 respirable dust as equivalent to 1 million particles per cubic foot (mppcf). In laboratory studies of small diameter (0.9 µm) silica flour particles, Nelson et al. (1978) observed relationships between dust count and mass concentration of 1 mppcf = 0.11 mg/m^3 for the Greenburg-Smith impinger, and 0.088 mg/m^3 for the midget impinger. In the diatomaceous earth industry study by Seixas et al. (1997), estimated conversion factors ranged from 0.09 to 0.18 mg/m^3 per mppcf over seven departments and operations. In the industrial sand industry, Rando et al. (2001) estimated a mean conversion factor of 0.275 mg/m^3 per mppcf with a range of 0.206 – 0.364 mg/m^3 higher than those reported by other investigators.

The approach used for the South African studies did not rely on a single conversion factor; instead, their approach used the size distributions obtained from the particle counts to estimate total respirable particle surface area based on previously determined relationships between particle diameter, sampling efficiency, and particle surface area. From that, respirable particle mass was estimated.

I.A.4.b. Estimation of the percentage of silica content.

Since the 1970s, crystalline silica content of airborne respirable dust has been determined directly from the air sample used to measure exposure to respirable dust. However, historically the estimation of the percentage of silica in dust was a separate process from air sampling used to quantify employee exposure to airborne dust. XRD analysis was available in the 1940s and early 1950s for measuring crystalline silica content, but it required relatively large bulk or airborne dust samples on the order of 1 gram.

In a study of South African gold mines prior to 1958, large electronic precipitators with a sampling flow rate of 3,000 liters per minute were used to collect samples of crystalline silica-containing dust for bulk analysis by XRD (Beadle and Bradley, 1970). During the 1950s, the sensitivity of XRD improved markedly, allowing investigators to collect a 1-milligram sample (1,000 times smaller) of total dust for crystalline silica analysis. A portable battery operated pump with flow rates ranging from 2 to 10 liters per minute was developed and used by Beadle and Bradley (1970) for sample collection in the mines.

For most of the cohort studies described in this section, crystalline silica content of airborne respirable dust was estimated by XRD or infrared analysis of either airborne respirable dust samples, total dust samples, or settled dust samples. In general, use of total dust or settled dust samples tends to overstate the silica content of airborne respirable dust because crystalline silica is harder than most other minerals, and thus, resists being fragmented into respirable-sized particles. For example, Hatch et al. (1947) partially relied on XRD analysis of settled dust for U.S. industrial sand worker studies conducted from 1947 to 1955. Rando et al. (2001) elected not to use Hatch's settled dust samples because of a concern that they would overestimate the silica content of airborne respirable dust. Instead, he used more current data taken from personal and area respirable dust samples. In more recent years (since approximately the early 1970s),

laboratory methods were devised to prepare and analyze airborne respirable dust samples directly for crystalline silica content. Since then, these have been the laboratory methods of choice.

Some of the better historical characterizations of respirable dust silica content were employed in the Vermont granite studies, U.S. diatomaceous earth studies, studies of British pottery workers, and those of U.S. industrial sand workers. These four groups of studies relied on modern sampling data that characterizes both respirable gravimetric dust and the percentage of silica in the dust. The modern data was used to supplement and to serve as a reference point for historic respirable dust and silica content measurements or estimates, thus, allowing these investigators to create representative job exposure indexes.

I.B. ***Silicosis.***

Silicosis refers to a spectrum of lung diseases attributable to the inhalation of respirable particles of silicon dioxide, or silica, in crystalline form. Crystalline silica is a naturally occurring mineral, the most common form being quartz. Less frequently encountered in industry is cristobalite (Becklake, 1994; Balaan and Banks, 1992), which usually is produced by hot processes. Respirable crystalline silica particles are those that are smaller than 10 μm in diameter (Ziskind et al., 1976).

Unlike other conditions that can result from both occupational and non-occupational sources of exposure, silicosis is, with rare exception, an occupational disease. Crystalline silica exposure and silicosis have been associated with work in mining, quarrying, tunneling, sandblasting, masonry, heavy construction, foundry work, glass making, stone grinding, ceramic and pottery production, cement and concrete production, stone and cut stone and gemstone work, and work with certain materials in dental laboratories (Linch et al., 1998; Becklake, 1994; Balaan and Banks, 1992).

Silicosis most commonly occurs as a diffuse nodular pulmonary fibrosis (NIOSH, 1996). Three types of silicosis have been described: an *acute* form following intense exposure to respirable dust of high crystalline silica content for a relatively short period (i.e., a few months or years); an *accelerated* form, resulting from about 5 to 15 years of heavy exposure to respirable dusts of high crystalline silica content; and, most commonly, a chronic form that typically follows less intense exposure of usually more than 20 years (Becklake, 1994; Balaan and Banks, 1992).

Acute silicosis (sometimes referred to as “silicoproteinosis”) is a fatal pulmonary condition of rapid progression. Acute silicosis develops after exposure to very high concentrations of respirable crystalline silica and results in symptoms in a few weeks to four or five years after the initial exposure (Davis, 1996; NIOSH, 1992a, 1992b; Peters, 1986). Workers who perform occupational tasks such as sandblasting, rock drilling, quartz milling, or any other process resulting in high exposures to small particles of dust with a high quartz content are at risk for developing acute silicosis. The distinguishing feature of acute silicosis is the presence of a surfactant-like liquid in the alveoli, caused by filling of lung’s airspaces with fluid containing debris from dismembered cells of the respiratory tract and lung (Becklake, 1994; Wagner, et al.,

1993). Acute silicosis usually progresses rapidly to acute respiratory failure, typically in less than two years (Becklake, 1994; Balaan and Banks, 1992; Davis, 1996).

Less severe than acute silicosis, but often associated with unprotected dust exposure (i.e., from lack of respiratory protection), is accelerated silicosis. This disease can be seen today among sandblasters, concrete cutters, mine and tunnel drillers and workers in other occupations who work without sufficient respiratory protection and who are exposed to respirable quartz. This disease has the same symptoms as acute silicosis, which include shortness of breath (restrictive and/or obstructive defects) and production of bloody sputum. Unlike acute silicosis, accelerated silicosis is marked by silicotic nodules that are detectable on chest radiographs. Accelerated silicosis usually manifests over a period from 5 to 15 years (Becklake, 1994), but can develop in as little as 2 to 5 years if exposure to crystalline silica is intense (Davis, 1996). It is ultimately fatal, even if affected workers are removed from high silica exposures.

Chronic silicosis is the most frequently observed type of silicosis in the U.S. today. It usually requires a minimum of 10 years of employment in jobs involving exposure to crystalline silica in some of the dusty industries described above, albeit at lower concentrations of silica than those associated with development of acute or accelerated silicosis. Affected workers may have a dry chronic cough, sputum production, shortness of breath, and reduced pulmonary function. These symptoms result from airway restriction and/or obstruction caused by the development of fibrotic scarring in the alveolar sacs and the lower region of the lung. The scarring can be detected by chest x-ray or computerized tomography when the lesions become large enough to appear as visible opacities. The result is restriction of lung volumes and decreased pulmonary compliance with concomitant reduced gas transfer (Balaan and Banks, 1992). A standardized system exists to classify the opacities seen on chest radiographs (Merchant and Schwartz, 1998). The International Labor Organization (ILO) International Classification of Radiographs of the Pneumoconioses. (the ILO 1980, and the 2000 revision), is the currently accepted standard against which chest radiographs are evaluated in epidemiologic studies, for medical surveillance, and for clinical evaluation (ILO, 1980). The ILO system standardizes the description of chest x-rays with respect to the size, shape, and density of opacities, which together indicate the severity and extent of lung involvement. The density of opacities seen on chest x-ray films is described using a 12-step scale divided into four major numeric categories, from 0 to 3, where 0 indicates the absence of visible opacities and categories 1 to 3 reflect increasing profusion of opacities and a concomitant increase in severity of disease. A more detailed description of the ILO's system for classifying pneumoconiosis and surveillance criteria for identifying silicosis cases appears later in this section.

Various terms have appeared in the literature to describe the presence and severity of chronic silicosis. The term "simple" silicosis has often been used to refer to the early stages of chronic silicosis as evidenced by radiologic findings of diffuse, small, rounded opacities that appear in low density in the upper zone of the lungs (Davis, 1996; Banks, 2005). In pulmonary massive fibrosis (PMF), the radiologic findings are distinguishable from earlier stages of silicosis by the appearance of larger (>1 cm) opacities. When the large opacities becomes extensive, larger opacities can coalesce and result in a "snowstorm" appearance on chest x-ray film. Though there is general agreement on the definitions and use of the terms "accelerated" and

"acute" silicosis in the literature, such is not the case with the term "chronic" silicosis. Early stages of chronic silicosis can be referred to as either simple or nodular silicosis; later stages are referred to as either pulmonary massive fibrosis (PMF), complicated, or advanced silicosis. Though the terms "PMF" and "complicated silicosis" both refer to the later stages of chronic silicosis, they are not always synonymous, as complications of advanced stages of chronic silicosis can also include infection by mycobacteria or fungi, cor pulmonale, spontaneous pneumothorax and broncholithiasis (Becklake, 1994). Based on these definitions, the term "simple silicosis," when used by researchers and reported in this document, will be considered synonymous with chronic silicosis, absent PMF or other complications

The knowledge that silicosis is associated with certain dusty occupations has existed since antiquity. Hippocrates reported that miners developed dyspnea (shortness of breath) with exertion. In the sixteenth century, Agricola was instrumental in recognizing the relationship between exposure to rock dust and the development of dyspnea (Agricola, 1556). In the United States, the greatest death toll from silicosis occurred with the excavation of Hawk's Nest Tunnel, critical to the construction of a hydroelectric plant in West Virginia during 1930 to 1931. Approximately 5,000 workers bored through Gauley Mountain to create the tunnel; an estimated 2,500 worked inside. A subsequent study determined that silicosis claimed the lives of at least 764 workers at Hawk's Nest Tunnel (Cherniack, 1986).

Occupational cohorts exposed to silica have been studied extensively, resulting in several hundred epidemiological studies investigating silicosis morbidity or mortality, as well as other health effects. These studies have conclusively linked occupational exposure to crystalline silica-containing dust with silicosis (Davis, 1996; Becklake, 1994; NIOSH, 1974, 2002; Balaan and Banks, 1992; Banks, 2005; Wagner et al., 1993). Because the causal relationship between exposure to crystalline silica and silicosis has long been accepted in the medical community, the studies that contributed to understanding that causal link will not be discussed here.

Of greater interest to OSHA is the quantitative relationship between exposure to crystalline silica and development of silicosis. A large number of cross-sectional and retrospective studies have been conducted to evaluate this relationship. Some of these are cross-sectional studies in which radiographs taken at a point in time were examined to ascertain cases (Kreiss and Zhen, 1996; Love et al., 1999; Ng and Chan, 1994; Rosenman et al., 1996); these radiographs may have been taken as part of a health survey conducted by the investigators or represent the most recent chest x-ray available for study subjects. Other studies were designed to examine radiographs over time in an effort to determine onset of disease. Some of these studies examined primarily active, or current, workers (Hughes et al., 1998; Muir et al., 1989a, 1989b; Park et al., 2002), while others included both active and retired workers (Chen et al., 2001; Hnizdo and Sluis-Cremer, 1993; Miller et al., 1998; Buchanan et al., 2003; Steenland and Brown, 1995b). In general, these studies, particularly those that included retirees, have found radiological silicosis risk (most often defined as x-ray films classified ILO 1/0+ or 1/1+) among workers exposed near the range of cumulative exposure permitted by current exposure limits. These studies are not presented in detail here, but are discussed in section II, Preliminary Quantitative Risk Assessment.

Occupational exposure to crystalline silica continues to be widespread today in a large number of industry sectors and occupations. More detailed information on current occupational exposures will be presented later in this section in the discussion on surveillance data.

The next part of this section reviews published studies and other information that describes the tools and approaches used in both clinical evaluations and epidemiologic investigations to assess the presence and severity of silicosis. These include the use of radiography and other standardized imaging methods for detecting lung fibrosis as well as pulmonary function studies.

I.B.1. Clinical and Epidemiological Considerations in Assessing Workers at Risk of Developing Silicosis.

I.B.1.a. Clinical features of silicosis.

The clinical diagnosis of silicosis has three requisites (Balaan and Banks, 1992; Banks, 2005). The first is the recognition by the physician that silica exposure adequate to cause this disease has occurred. The second is the presence of chest radiographic abnormalities consistent with silicosis. The third is the absence of other illnesses that could resemble silicosis on chest radiograph, e.g., pulmonary fungal infection or miliary tuberculosis. Biopsy is not necessary to make a diagnosis and a diagnosis does not require that chest x-ray films be rated using the ILO system (NIOSH, 2002). In addition, an assessment of pulmonary function, though not itself necessary to confirm a diagnosis of silicosis, is important to evaluate whether the individual has impaired lung function. Assessment of impairment is based on symptoms and measurements of pulmonary function at rest, and while exercising, if indicated (Becklake, 1994).

As discussed in the introduction to this section, there are three types of silicosis: acute, accelerated, and chronic. A worker may develop any of these types, depending on the airborne levels of respirable silica in the work environment, the length of the exposure, and some physical characteristics of the respirable silica itself (NIOSH, 2002; Banks, 2005). Another consideration is whether or not the worker was provided with effective respiratory protection (Banks, 2005).

Acute silicosis is the most infrequent yet most devastating form of this disease (Abraham and Weisenfeld, 1997; CDC, 1998; Becklake, 1994; Banks, 2005). Chest radiographs reveal few silicotic nodules (NIOSH, 1996); the appearance is that of a diffuse perihilar alveolar filling process with opacities that have been described as having the appearance of “ground glass.”

Workers with acute silicosis have been reported to present with an irritative, sometime productive cough, weight loss, fatigue, and occasionally, pleuritic pain (Banks, 2005). The onset of symptoms is usually one to three years after the initial exposure, but symptoms occurring less than a year after beginning sandblasting have been reported (CDC, 1998). Serial lung function tests show progressive restriction of lung volumes and impairment of diffusing capacity. This form of silicosis has often been complicated by fulminating tuberculosis (Becklake, 1994). The invariable downhill clinical course of acute silicosis includes rapid progression to acute

respiratory failure (Becklake, 1994), usually within several years of beginning exposure (Balaan and Banks, 1992).

Accelerated silicosis is marked by irregular nodular lung fibrosis that is detectable on chest radiographs (Abraham and Weisenfeld, 1997; Becklake, 1994). Unlike simple chronic silicosis, the radiographic picture is of diffuse, small, irregular opacities, or reticulonodular opacities (Davis, 1996). Pathologic features of accelerated silicosis include the appearance of numerous nodules at various stages of development, sometimes with irregular interstitial fibrosis (Becklake, 1994).

The symptoms of accelerated silicosis are similar to those of chronic silicosis, but clinical and radiographic progression is disabling (Davis, 1996), rapid (NIOSH, 2002; Banks, 2005), and often leads to progressive massive fibrosis (Banks, 2005), severe respiratory impairment (Banks, 2005) and respiratory failure (Becklake, 1994).

Chronic (also called "classic") silicosis is the most common form of silicosis today, and can be described by the degree of radiologic chest involvement (Balaan and Banks, 1992). The hallmark of the chronic form is the silicotic islet or nodule, one of the few agent-specific lesions in pathology (Balaan and Banks, 1992). The typical presentation of chronic silicosis on chest x-ray is with upper and midzone nodular opacities that are rounded in shape; however, the lesions may be irregular and involve other zones of the lungs. Calcification of lymph nodes in a peripheral, or "eggshell" pattern is classic in silicosis, though not all chest x-rays of persons with silicosis will demonstate this (Davis, 1996; Becklake, 1994). This eggshell pattern may also be seen in sarcoidosis (Balaan and Banks, 1992). However, in addition to the differences in the clinical courses of the two diseases, described elsewhere (see Davis, 1996), silicosis is distinguished from sarcoidosis by an extensive history of exposure to silica (Davis, 1996).

The mature lesion of chronic silicosis is characterized by a cell-free and largely dust-free central area of concentrically arranged, whorled hyalinized collagen fibers, surrounded by an area of concentrically arranged collagen fibers and a more peripheral zone of randomly oriented fibers interspersed with dust-laden macrophages (Davis, 1996). Affected workers may have a dry chronic cough, sputum production, shortness of breath, and reduced pulmonary function. These symptoms result from restricted airways caused by the fibrotic scarring in the alveolar sacs and the ends of the lung tissue. The scarring can be detected from chest x-rays when the lesions become large enough to be visible opacities (Balaan and Banks, 1992).

The small rounded opacities seen in accelerated and chronic silicosis may "progress" and develop into large fibrotic masses, resulting in progressive massive fibrosis (PMF). The appearance of ILO category 2 or 3 background profusion of small opacities appears to be consistent with the histopathhological view that massive fibrosis is formed by the conglomeration of individual fibrotic nodules (Ng and Chan, 1991). These conglomerate lesions appear against a background of smaller nodules (Davis, 1996) and may obliterate bronchi and vessels and cause marked distortion of lung structure and function (Wagner et al., 1993). The result is typically restriction of lung volumes, decreased pulmonary compliance, and reduced gas transfer (Balaan and Banks, 1992). In cases involving PMF, (sometimes referred to as

complicated silicosis), death is commonly attributable to progressive respiratory insufficiency (Balaan and Banks, 1992). Once established, the fibrotic process of chronic silicosis is thought to be irreversible (Becklake, 1994). The primary risks to the worker with silicosis are progression of disease with progressive decline of lung function. Development of mycobacterial infection is also a concern. Both conditions can hasten the development of respiratory impairment (Banks, 2005). In addition to infection by mycobacteria, other complications include infection by fungi, cor pulmonale, spontaneous pneumothorax, broncholithiasis, and tracheobronchial obstruction from polypoid granuloma developing in the vicinity of egg-shell calcification in hilar nodes (Becklake, 1994).

There is no specific treatment for silicosis (Davis, 1996: Banks, 2005), though a number of treatment modalities, including whole lung lavage (washing) and administration of corticosteroids (medications that suppress inflammation, and can have serious side effects) have been tried in individual patients (Banks, 2005).

In addition to the functional impairments described here, including increased ventilatory impairment, shortness of breath, and inability to continue to perform activities of daily living, research has shown that people with silicosis advanced beyond ILO category 1 have a higher mortality rate than the general population (Infante-Rivard et al., 1991; Ng et al., 1992a; Westerholm, 1980).

Westerholm (1980) found that the life expectancy of individuals identified through a silicosis case registry in Sweden was lower than that of the general population. This registry used the Johannesburg classification scheme, which, like the ILO system, uses increasing gradations of severity of opacities. The authors did not attempt to re-classify older cases according to newer criteria, or to align the silicosis categories in this study with those of the ILO. Data are presented for two time periods, 1931 to 1948 and 1949 to 1969. In addition to severity of silicosis, tuberculosis status was also considered. Reduction of life expectancy was increased for higher stages of silicosis (category 2 and 3) and having tuberculosis. If data from just the later reporting period (1949 to 1969) are considered, median reduction in life expectancy for categories 2 and 3 was 6.5 years (95% CI = 3.5-8.5). Category 1 showed a shortening of median survival time of 3.5 years, as compared to a sample drawn from the general population (Westerholm, 1980).

Infante-Rivard et al. (1991) examined factors influencing survival of silicotic patients who received workers' compensation. Using multivariate analysis of clinical prognostic factors with the Cox proportional hazards model, the authors concluded that among this population, having complicated silicosis (large opacities), dyspnea, expectoration, abnormal breath sounds, low vital capacity, and current smoking status were all risk factors for poorer survival (Infante-Rivard et al., 1991).

Ng et al. (1992a) examined predictors of mortality in persons who had silicosis. The mortality of a cohort of 1,487 male patients with silicosis in a population-based register followed up from 1980 to 1986 was evaluated with reference to the mortality rates of the general male population. A striking excess of deaths from all causes (368 observed, SMR = 3.00) was noted.

Seventy-four percent of the deaths were due to respiratory conditions and complications either directly or indirectly related to silicosis. The risk of death was higher than expected in younger patients less than 45 years of age. Patients with simple silicosis of ILO profusion category 1 did not appear to be at increased risk of death relative to the general population. Higher degrees of profusion and conglomerate disease were associated with increased mortality. Among patients having the same degree of profusion, the presence of tuberculosis increased the mortality rate; however, increased mortality was also observed in tuberculosis-free patients. There was no evidence, however, that patients who smoked had higher mortality than silicosis patients who did not. Age at diagnosis, degree of silicotic nodule profusion, and the occurrence of tuberculosis were therefore strong predictors of increased mortality rate in patients with silicosis.

I.B.1.b. Chest radiography and other imaging techniques to assess silicosis.

Chest x-rays have been central to clinical evaluation and surveillance of dust-exposed workers. Epidemiologic studies of occupational cohorts exposed to dust rely on chest radiographs to investigate the development and progression of pneumoconiosis, including silicosis.

For many decades, the chest radiograph has been the standard approach to assessing dust diseases of the lung, being relatively simple, inexpensive, non-invasive, and safe (NIOSH, 2008a). Today, the chest radiograph, or chest x-ray, remains the primary means of determining the presence and extent of pneumoconiosis, including silicosis. As such, it is an important tool in epidemiologic investigations of silica-exposed workers, in surveillance, in clinical evaluations, and in disability determinations (Wagner et al., 1993).

However, there is a major distinction between reading and classifying radiographs for epidemiologic research and reading radiographs for clinical purposes (Wagner et al., 1993). In epidemiologic investigations, the intent is to obtain reliable data for a large group of people, and data collection is done using tightly controlled protocols, often by more than one investigator. In clinical practice, it is the individual person under investigation who is the focus of interest. Detailed medical information is usually elicited by physicians working singly, and making their own decisions to medically evaluate the patient. The ultimate objective of a clinical evaluation is to learn all that is necessary to diagnose and treat that particular individual.

Because of the susceptibility of silicosis patients to tuberculosis, miners and other silica-exposed workers were the subject of chest radiographic studies starting in the in the 1920s (Merchant and Schwartz, 1998). As early as 1930, the need for a standardized approach to classifying the opacities viewed on chest radiographs was recognized, and led to improvements that over time developed into the International Labor Organization (ILO) International Classification of Radiographs of the Pneumoconioses (Merchant and Schwartz, 1998). As noted above, the ILO 1980, and the 2000 revision, is the currently accepted standard against which chest radiographs are evaluated in epidemiologic studies, for medical surveillance, and for clinical evaluation (ILO, 1980).

NIOSH describes the classification system as follows:

> The Classification system includes the Guidelines and two sets of standard films. The standard films represent different types and severity of abnormalities and are used for comparison to subject films during the classification process. The system is oriented towards describing the nature and extent of features associated with the different pneumoconioses, including silicosis. It deals with parenchymal abnormalities (small and large opacities), pleural changes, and other features associated, or sometimes confused, with occupational lung disease.
>
> In the present manifestation of the ILO system, readers are first asked to grade film quality. They are then asked to categorize small opacities according to shape and size. The size of small round opacities is characterized as p (up to 1.5 mm), q (1.5-3 mm), or r (3-10 mm). Irregular small opacities are classified by width as s, t, or u (same sizes as for small rounded opacities). Profusion (frequency) of small opacities is classified on a 4-point major category scale (0 – 3), with each major category divided into three [subcategories], giving a 12-point scale between 0/- and 3/+. Large opacities are defined as any opacity greater than 1 cm that is present in a film. Large opacities are classified as category A (for one or more large opacities not exceeding a combined diameter of 5 cm), category B (large opacities with combined diameter greater than 5 cm but not exceeding the equivalent of the right upper zone), or category C (bigger than B). Pleural abnormalities are also assessed with respect to location, width, extent, and degree of calcification. Finally, other abnormal features of the chest radiograph can be commented upon (ILO 2002). (NIOSH, 2008a).

Although the ILO system provided a standardized approach for classifying and describing pneumoconioses seen on radiographs, there were, prior to the early 1970s, issues surrounding the inconsistent application of the ILO system and its use by physicians not having proper training. NIOSH responded by initiating the B Reader Certification Program to train and certify licensed physicians in the use of the ILO Classification System. The B Reader Program tests the ability of a reader to classify a sample set of radiographs and certifies only those who achieve a certain level of proficiency. The B Reader Program is intended to ensure the accuracy of ILO readings regarding the presence of pneumoconiosis. NIOSH's B Reader Program began in 1974, although it was not until 1978 that the certification exam was given widely (Merchant and Schwartz, 1998; NIOSH 2008a). NIOSH plays a major role in administering the B reader program and is continually updating the program to account for advances in medicine and technology.

Assuming that the quality of chest radiographs is adequate, of great importance in assessing the ability of chest radiography to detect silicosis are sensitivity, specificity, and concordance (agreement between readers). Sensitivity refers to the frequency with which radiographs detect silicosis in persons who have silicosis and specificity refers to the frequency with which radiographs indicate absence of silicosis in persons without the disease. Studies that evaluated the ability of chest radiography to detect silicosis (i.e., sensitivity) have used various methodologies, but are essentially of two types: 1) those that compared radiological findings

with pathological evidence, and 2) those that compared findings of chest radiographs to those of computed tomography (CT) scans, or other imaging techniques.

Because pathological findings are the most definitive for silicosis, findings on biopsy and autopsy provide the best comparison for determining sensitivity and specificity of chest imaging. Unfortunately, there is no non-invasive technique for detecting silicosis that can serve as a "gold standard" against which other diagnostic approaches can be compared.

Hnizdo et al. (1993) evaluated the sensitivity, specificity and predictive value of radiography by correlating radiological and pathological (autopsy) findings of silicosis. The study used three readers and defined a profusion score of 1/1 as positive for silicosis. Sensitivity was defined as the probability of a positive radiological reading (ILO category $\geq$ 1/1) given that silicotic nodules were found in the lungs at autopsy. Specificity was defined as the probability of a negative radiological reading (ILO category < 1/1) given that no, or only an insignificant number of silicotic nodules were found at autopsy. The average sensitivity values were low for each of the three readers (0.39, 0.37, and 0.24), whereas the average specificity values were high (0.99, 0.97, and 0.98). For all readers, the proportion of true positive readings (i.e., the sensitivity) increased with the extent of silicosis found at autopsy. Two of the readers had similar sensitivity and specificity values, while the third had a lower average sensitivity value, but the same specificity value.

Thus, radiography was consistently found in this study to yield a high degree of specificity (very few false positives), but low sensitivity (negative chest x-ray, with silicosis actually present), suggesting that the use of radiography to assess presence and progression of silicosis is a relatively crude tool and underestimates the true prevalence of silicosis in populations exposed to crystalline silica.

To address the low sensitivity of chest x-rays for detecting silicosis, Hnizdo et al. (1993) recommended that radiographs consistent with an ILO category of 0/1 or greater be considered indicative of silicosis among workers exposed to a high concentration of silica-containing dust. In like manner, to maintain high specificity, chest x-rays classified as category 1/0 or 1/1 should be considered as a positive diagnosis of silicosis. This recommendation underscores the importance of taking an accurate occupational history, including information on exposures to crystalline silica, and obtaining any available exposure monitoring data to augment the history.

Other studies reported similar findings. Craighead and Vallyathan (1980) examined post-mortem lung tissue from 15 Vermont granite workers, and found silica-associated lesions in all workers, despite the failure of radiological studies to reveal evidence of pneumoconiosis. Rosenman et al. (1997) also compared the ability (or sensitivity) of radiologic methods to detect cases of silicosis. In a state-based surveillance system, 577 individuals were identified as having silicosis by radiologic methods. An additional nineteen (3.3%) had biopsy evidence of silicosis but normal radiographs.

As with most medical determinations, radiographic classifications are subject to accuracy and precision considerations. Accuracy is defined as the ability of a measurement to reflect the

true degree of underlying abnormality. Precision reflects the extent to which a measurement is consistent across repeated determinations. Both criteria are important – a measurement technique should preferably be both accurate and precise.

Inter- and intra-reader variability in chest radiography has existed since chest radiography was first used to identify and classify pneumoconiosis (Fletcher and Oldham, 1949). Inter-reader variability occurs when different readers disagree on a classification. Intra-reader variability occurs when a reader classifies a given radiograph differently on different occasions.

Inter-reader variation consists of two components: systematic differences and random variability. Systematic variation between readers, in which one reader persistently reports more or less abnormality than another, is related to bias. Bias can be reduced by blinding the readers to any information concerning the radiographs being classified that can consciously or unconsciously influence their classifications, for example knowledge of exposure. Reducing bias, along with instituting concurrent quality control measures, increases the accuracy of the measurement.

Both accuracy and precision in film classification is gained through the use of summary measures based on independent and unbiased classifications of multiple different readers who classify the films independently (that is without other readers being present and without knowledge of other readers' classifications). Summary classifications derived from the independent classifications are more precise than any single individual classification. Valid summarization methods include the use of median classifications or properly-designed consensus measures.

In a study of a silica-exposed occupational cohort within a general population, three NIOSH-certified B readers independently classified chest radiographs for 124 subjects without personal identifiers and in random order (Kreiss and Zhen, 1996). Silicosis cases were defined as those cases with a mean radiologic profusion of small opacities of $\geq$ 1/0 using the 1980 ILO classification. The authors used the Kappa statistic to evaluate the concordance (agreement) between pairs of B readers, using a 1/0 profusion criterion for abnormality, with values of 0.70 ($p < 0.0001$) for the first and second readers, 0.66 ($p < 0.0001$) for the first and third readers, and 0.58 ($p < 0.0001$) for the second and third readers. (When the two measurements agree only at the chance level, the value of kappa is zero; when the two measurements agree perfectly, the value of kappa is one.) The Kappa statistics for abnormality using the 1/1 criterion were 0.80, 0.75, and 0.75, respectively.

Newer imaging technologies with both research and clinical applications include computed tomography, and high resolution tomography. Computed tomography (CT) of the chest represents an important advance that may substantially improve our ability to noninvasively identify and quantify pleural and paranchymal (lung tissue) lesions, as in silicosis, or may add other important information when it comes to diagnosis. High-resolution computed tomography (HRCT) uses thinner image slices and a different reconstruction algorithm to improve spatial resolution over CT.

Two older studies that compared CT and HRCT with chest x-rays for identifying silicosis did not find CT or HRCT to be a more sensitive diagnostic tool than chest x-rays. However, several more recent studies and reviews have suggested that HRCT may be superior to chest x-ray in the early detection of silicosis and the identification of progressive massive fibrosis (PMF).

One of the older studies (Bégin et al., 1987a) also found that the CT scan did not identify more cases of minimal paranchymal disease than did chest x-ray films. However, CT scan did identify significantly more coalescence and/or large opacities in 33 percent of patients who were thought to have simple silicosis based on chest x-ray.

In the second older study, Talini et al. (1995) studied 27 subjects with varying degrees of silicosis who underwent chest x-ray and pulmonary function testing to compare the utility of HRCT with chest x-ray in the diagnosis and assessment of the severity of silicosis. The authors used the major ILO categories (i.e., 0, 1, 2, or 3) to categorize the chest x-ray films; the HRCT images were graded according to a standardized system developed by the authors, based on the profusion of parenchymal (lung tissue) opacities, and also with a visual scoring system based on estimating the percentage of overall area that showed emphysematous or nodular changes. Although the systems used to score both chest x-rays and HRCT images were based on four categories of increasing severity of changes in the lung, it is unclear to what extent the categories are actually comparable to the four ILO categories that describe profusion. According to the authors, there are no standard ILO-type films for use in classifying the extent of pneumoconiosis in the HRCT images. When comparing the agreement between two readers on the categories of parenchymal opacities on chest x-rays and HRCT, the authors found that concordance (agreement) between readers was better with HRCT than for chest x-rays (Cohen's *k* statistic: 0.49 *vs.* 0.29 respectively). However, the concordance between the two different imaging methods, chest x-ray and HRCT, was fairly low; only 10 of 27 subjects were classified as the same profusion category for both chest x-ray and HRCT. Eight subjects were classified as category 0 by chest x-ray, but only two of these eight were classified as category 0 by HRCT, suggesting improved sensitivity. However, five additional subjects were classified in the category 0 by HRCT, but category 1 or higher for chest x-ray. For category 1, a similar pattern was observed. For the higher profusion categories (3 and 4), HRCT identified twice as many (4 vs. 2) subjects as did chest x-ray. Thus, there was no consistent pattern that would suggest HRCT had higher sensitivity than chest radiography for detecting silicosis.

No relation was found between pulmonary function studies and profusion of parenchymal opacities as assessed by chest x-ray, except for a reduction of maximal flow at 50 percent of FVC in the highest profusion category. On the contrary, the profusion of opacities detected by HRCT correlated reasonably well with indices of airway obstruction and diffusion capacity. In particular, subjects classified in the highest profusion category by HRCT exhibited lower values of FEV_1, expiratory flows, and diffusion capacity than did subjects classified as category 0 or 1. Multiple logistic regression analyses between pulmonary function studies and HRCT categories showed that the relationship was not explained by smoking history or symptoms of chronic bronchitis.

Talini et al. (1995) concluded that, in the absence of a gold standard for the diagnosis of silicosis, (i.e., examination of lung tissue, obtained by necropsy or biopsy) it is difficult to determine which technique more accurately detected early paranchymal involvement in silicosis. The authors pointed to the greater concurrence among the readers when rating HRCT images compared to chest x-ray films, despite the absence of ILO-type standard films for HRCT images. In addition, the presence of a significant correlation between HRCT profusion categories and pulmonary function decrements seemed to indicate that HRCT was a better predictor of disease than chest x-ray. However, the data showed that HRCT was not a more sensitive tool for identifying early stages of silicosis, but the authors believed it could be useful to identify those silicotics more likely to have pulmonary impairment.

Sun et al. (2008) studied the value of HRCT as compared to x-ray in the diagnosis of small opacities and complications of silicosis in 90 mine machinery manufacturing workers in China. The authors also briefly reviewed previous studies. The authors believed that previous research had indicated that HRCT is more sensitive than chest x-ray in detecting lung parenchymal changes suggestive of silicosis and early confluence of small opacities in the lung, but that HRCT was not currently accepted as a diagnostic tool for the detection of the disease. In the present study, Sun et al. found that HRCT results led to the diagnosis of silicosis in subjects who originally were not diagnosed with silicosis based on chest x-ray. In other subjects previously diagnosed with silicosis by chest x-ray, use of HRCT revealed a higher degree of profusion of small opacities. The numbers of small opacities in HRCT were significantly higher than those seen in x-ray in all lung zones ($p < 0.01$). A statistically significant increase in the detectability of bulla, emphysema, pleural, mediastinal, and hilar changes was also observed ($p < 0.05$). Sun et al. (2008) concluded that HRCT has potential diagnostic value for silicosis, especially in the early stage.

Lopes et al. (2008) studied 44 non-smoking patients with silicosis and without a history of tuberculosis in an effort to correlate HRCT parameters with respiratory function parameters and to compare the HRCT findings with the chest x-ray findings. As in the Sun et al. (2008) study above, HRCT identified more cases of silicosis than x-ray. There were four patients who were classified as category 0 based on x-ray and as category 1 based on HRCT. For large opacities, there was concordance between the two methods in 70.5 percent of the cases. HRCT also identified PMF in 33 patients as compared to 23 patients by x-ray. Seventy-five percent of the patients in this study had large opacities (HRCT findings) and there was a progressive decrease in pulmonary function in parallel with increases in the extent of damage (HRCT classification). This was not the case among patients with small opacities only. The authors concluded that an HRCT finding of large opacities can be an important indicator of severity of silicosis. The authors also concluded that HRCT is superior to x-ray in the diagnosis of silicosis, both for the early detection of the initial phases of the disease and for the identification of PMF.

A review of recent studies of the use of HRCT for diagnosis and grading of silicosis and other pneumoconioses was conducted by Blum et al. (2008). The authors noted that HRCT has been acknowledged as the gold standard in the noninvasive diagnosis of pneumoconiosis, providing essential visual information far beyond x-ray, predominately in the early stages of disease. The authors reported that, in 2005, an international expert panel harmonized several

national HRCT classifications of occupational and environmental thoracic diseases and published the harmonized system in book format combined with digital reference films.

Blum et al.'s. (2008) review also highlighted the following findings:

- PMF and emphysema indicies, as detected by HRCT, were significantly correlated with measured lung function decrements;
- In an investigation of the role of expiratory HRCT in estimating the obstructive impairment in patients with silicosis, the extent of emphysema and air trapping correlated well with lung function impairment consistent with emphysema, while other radiological patterns did not;
- Pleural disease was observed in previous CT studies of subjects with autopsy-proved silicosis; and
- In the early detection of silicosis, branching centrilobular structures are a useful HRCT feature besides nodules because they showed a statistically significant correlation with restrictive lung function losses.

Blum et al. concluded that HRCT provides access to a higher diagnostic level in dust-induced occupational lung diseases and that, in comparison to x-ray, several studies demonstrated a superiority of HRCT in predicting clinical impairment due to occupational lung diseases.

I.B.1.c. Pulmonary function testing (PFT).

Although not essential for the diagnosis of silicosis, lung function tests are used to assess the degree of impairment caused by exposure to crystalline silica. Standard practice guidelines for administering and interpreting pulmonary function studies are available from the American Thoracic Society (ATS) (Miller et al., 2005) and the American College of Occupational and Environmental Medicine (ACOEM) (ACOEM, 2004) and are summarized here. The most common pulmonary function test, spirometry, measures how quickly and how much air can be expired from the lungs after a maximal inspiration. The individual blows into a device called a spirometer. The most common measurements reported from a spirometry test are the forced vital capacity (FVC), the forced expiratory volume in one second (FEV_1), and the FEV_1/FVC ratio. Although some clinicians use the mean forced expiratory flow between 25 percent and 75 percent of the FVC ($FEF_{25-75\%}$) as an indicator of small airways disease, ATS recommends caution in this practice due to the high variability of the measurement and its dependency on the test subject's level of expiratory effort.

More detailed measurement of lung function can be performed with other pulmonary function tests. In some circumstances, measurement of absolute lung volumes is required for specific diagnoses. There are three possible measurement techniques for determining absolute lung volumes: 1) body plethsymography, 2) nitrogen washout, and 3) helium dilution. Although

there are several indices that are either measured or calculated for lung volume assessment, the most important include the following:

- The functional residual capacity (FRC) is the volume of gas remaining in the lung at end-expiration after tidal breathing;
- Residual volume (RV) is the volume of gas remaining in the lung after a maximal expiration;
- Total lung capacity (TLC) refers to the volume of gas in the lungs after maximal inspiration; and
- Vital capacity (VC) is the volume change between full inspiration and complete expiration.

Lung diffusing (DL) capacity is another test that provides information about the ability of the lungs to exchange gas across the lung (alveolus) and blood (capillary) interface. The principle measurement, carbon monoxide uptake by the lung (DL_{co}), reflects the gas exchange properties of those regions of the lung that are ventilated. The subject inhales some gas containing a very small quantity of carbon monoxide, holds his breath for 10 seconds, then rapidly exhales. The single exhaled gas is analyzed to determine how much carbon monoxide was absorbed during the breath. DL_{co} may be elevated or reduced, depending on the underlying disease. Individuals with interstitial lung diseases, such as silicosis, may have a reduced DL_{co}, depending on the severity of the disease.

Interpretation of pulmonary function results for individual patients is based on comparisons to reference (predicted) values from populations of healthy, non-smoking individuals having similar anthropometric (age, sex, height) and ethnic characteristics as the patient. Reference values define the upper and lower limits of the normal range. For each lung measurement index, values below the 5^{th} percentile of the distribution of values for the reference population have traditionally been considered to be below the normal range. However, as discussed below, "normality" is an elusive concept when discussing pulmonary function because of a high degree of individual variation (Becklake, 1994)

When lung function tests were first introduced in the 1940s and 1950s, emphasis was put on the profile of functional impairment, leading to widespread use of the terms *obstructive defect* and *restrictive defect* (Becklake, 1994). Spirometry is useful for determining whether lung function impairment has an obstructive, restrictive, or mixed pattern, but spirometry alone cannot diagnose specific diseases. Obstructive lung disease is characterized by decreased forced expiratory volumes with respect to FVC (or FEV/FVC ratio), of hyperinflation, and/or of air trapping reflected in increases in functional residual capacity (FRC) and residual volume (RV), with or without gas exchange impairment. An obstructive impairment, airway narrowing during exhalation, shows a disproportionate reduction in maximal flow rate compared to the total volume exhaled. This is reflected by an FEV_1/FVC ratio that falls below the 5^{th} percentile. Restrictive impairments do not allow the lungs to fully expand. A restrictive impairment would

be demonstrated by a normal FEV_1/FVC ratio accompanied by a reduction in TLC below the 5^{th} percentile. A reduced VC alone would not be indicative of restrictive disease. Mixed ventilatory impairment is defined by the presence of obstructive and restrictive patterns. A mixed impairment is characterized by both the FEV_1/FVC ratio and TLC below their relative 5^{th} percentile values. The terms obstructive and restrictive to describe respiratory disorders are useful when disease is obviously present, but is less helpful when using lung function tests to evaluate earlier stages of disease. Becklake (1994) suggested the following reasons for this. First, a clear profile of restriction is seldom demonstrated in the early stages of pneumoconiosis, whereas in the later stages, relatively cursory testing (e.g., measurement of FVC or TLC) may be all that is required to characterize the impairment. Second, interpretation of results in an individual is complicated by the need to define what is normal. As mentioned above, this is usually done by the use of reference or predicted values for a population; however, published prediction formulas vary considerably due primarily to differences in the characteristics of the subjects examined to generate the various predicted values. Thus, no one set of prediction equations is likely to be applicable to all laboratories, in all circumstances, and for all populations (Becklake, 1994).

Traditionally, an individual's measured lung function has been compared with a "predicted" value, *i.e.*, the average expected for an asymptomatic non-smoker of the subject's age, height, race/ethnicity, and sex. Many sources of predicted values have been derived from studies of asymptomatic non-smoking populations, and some applications require the use of specific sets of prediction equations. In the occupational setting, many healthy workers are tested periodically, not because they have abnormal lung function, but to monitor their response to potentially harmful occupational exposures. Because of their health, working populations usually have higher levels of pulmonary function than clinic populations, and many workers have lung function that is above average, *i.e.*, greater than 100 percent of predicted. Such individuals may lose their lung function at an excessive rate *but still remain in the normal range* throughout their working lifetime and into retirement. Remaining in the normal range does not indicate respiratory health, since their function may drop from the top to the bottom of the normal range, but these individuals must lose large fractions of their lung function before they will fall below the normal range. For these workers, the widespread practice of repeatedly comparing serial test results with the traditional normal range may not detect serious pulmonary function deterioration. For this reason, longitudinal evaluation that compares current measured values with previously measured values, "using the subject as his/her own control," is needed especially for this group (ACOEM, 2004). In addition, the inter-individual variation discussed above (Becklake, 1994) makes it difficult to detect abnormality cross-sectionally.

Although the lung impairment associated with silicosis is more frequently reported as restrictive in nature, it is not clear that this is always the case. Studies report finding both restrictive and obstructive lung function decrements in workers exposed to silica. It is not clear whether functional impairments differ at various stages of silicosis (e.g., reduction in capacity (restrictive) that is associated with fibrosis earlier in the process, and an “obstructive” pattern later) or is a “mixed” type of pulmonary impairment.

In addition to what is known about the clinical presentation of silicosis and what is learned through epidemiologic investigations, surveillance systems for silicosis, though incomplete, continue to provide information on the extent of silicosis present in the U.S. today. Many individuals with silicosis were initially identified through hospital records or other health care providers. Through some surveillance programs implemented at the state level, silicosis cases are confirmed and information is collected on each case's occupation and history of employment to obtain industry specific data on silicosis prevalence. The next part of this section reviews existing silicosis surveillance systems and the data those systems produce.

I.B.2. Review of Surveillance Data.

According to the National Institute for Occupational Safety and Health (NIOSH), "Occupational respiratory disease surveillance is the ongoing, systematic collection, analysis, and dissemination of health and hazard data to monitor the extent and severity of occupationally-related lung disease and related workplace exposures for use in public health education and in disease prevention" (NIOSH, 2008b). Mortality and morbidity data for lung diseases that are caused predominantly by work exposures are included in NIOSH's *Work-Related Lung Disease Surveillance System*. The surveillance information is used for establishing priorities, for investigation and intervention, and for tracking progress toward elimination of preventable disease (NIOSH, 1997).

This section presents a discussion of the surveillance systems that currently report silicosis mortality and morbidity data, along with the data reported through those systems, with a focus on the more recent data. A discussion of the literature on underreporting of surveillance data specifically related to silicosis concludes this section.

In general, surveillance methods can be divided into four categories: passive, active, sentinel, and special systems. In general, passive and active systems are based on conditions that are reportable to health jurisdictions. Sentinel systems and special systems are usually designed to obtain information that is not generally available to health departments.

Passive surveillance is the most common form of surveillance and relies on standardized reporting forms or cards provided by or available through the state or local health departments. These completed forms are returned to the health department when cases of disease or deaths are detected. The term "passive" is used to convey the idea that health authorities take no action while waiting for report forms to be submitted. Additionally, case reports received by the public health authority may require further action to ensure completeness and proper case classification.

In contrast, a*ctive surveillance* involves outreach by the public authority, such as regular telephone calls or visits to laboratories, hospitals, and providers to stimulate reporting of specific conditions or events and thus may capture more cases than passive surveillance systems.

Sentinel surveillance involves the collection of case data from only part of the total population (from a sample of providers) to learn something about the larger population, such as trends in diseases and mortality. *Special systems* are occasionally designed and implemented to

generate surveillance information that is not possible to acquire by any of the other systems already mentioned.

Based on these definitions, the silicosis surveillance systems described here are all of the passive type. Because passive surveillance systems depend upon health practitioners (1) being aware that there is a reporting requirement for a particular condition or event, and (2) being diligent in both recognizing and reporting cases, the actual prevalence of diseases may be higher than is suggested by the surveillance data. There is no national surveillance program that accurately and completely collects mortality data associated with silicosis for the entire U.S.

The most comprehensive and current source of surveillance data in the U.S. related to occupational lung diseases, including silicosis, is NIOSH's *Work-Related Lung Disease (WoRLD) Surveillance System*; the *WoRLD Surveillance Report* is complied from the most recent data from the *WoRLD System*. The seventh and most current edition was published in 2008 (NIOSH, 2008c). Updates to the *(WoRLD) Surveillance System* can be found online (eWoRLD). Data contained in the eWoRLD surveillance system originate from various publications reports, data files and tabulations provided by various sources including Department of Labor (DOL), and the National Center for Health Statistics (NCHS).

The CDC also publishes the *Morbidity and Mortality Weekly Report*, which reports on provisional data based on weekly reports to CDC by state health departments, and the *CDC Surveillance Summaries*, which provide a means for CDC programs to disseminate surveillance findings, permitting detailed interpretation of trends and patterns based on those findings (CDC, 2006a). NIOSH also published the *Worker Health Chartbook* (NIOSH, 2004), a compilation of occupational injury and illness surveillance data from some of the same sources discussed here.

The following sections review statistics describing silicosis mortality and morbidity indicators of silicosis.

I.B.2.a. Silicosis mortality.

Since 1968, NIOSH has obtained mortality data from the National Center for Health Statistics (NCHS) for various respiratory conditions, including silicosis, coded according to the International Classification of Diseases (ICD). Because each death record includes codes for up to 20 conditions (underlying and contributing causes) listed on the death certificate, deaths involving silicosis can be thought of as deaths "from silicosis" or "with silicosis" (i.e., though not related to the immediate cause-of-death, silicosis was present at the time of death). Other data on death certificates include age, race, sex, and state and county of residence at time of death. In addition, usual industry and occupation codes are available for decedents from a selected list of states, but only for 1985–1999 (NIOSH, 2004, 2008c).

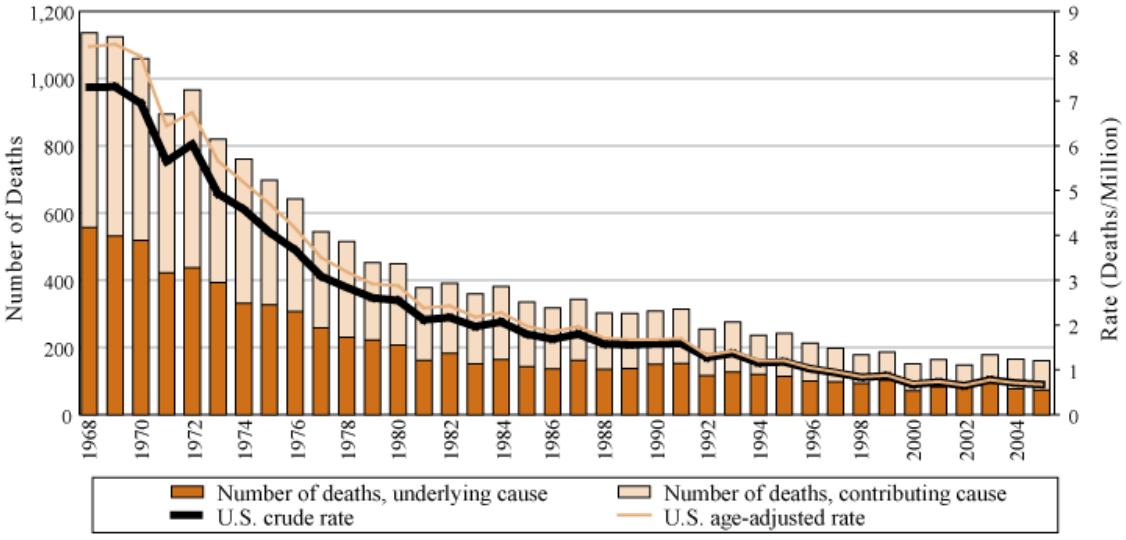
National statistics on mortality associated with occupational lung diseases are compiled in the *National Occupational Respiratory Mortality System (NORMS*, available on the Internet at http://webappa.cdc.gov/ords/norms.html*)*, a searchable database administered by the National

Institute for Occupational Safety and Health (NIOSH). The source of these data is death certificates reported to state vital statistics offices, which are collected by the NCHS.

In a recent review of statistics specific to silicosis mortality, MMWR Report *Silicosis Mortality, Prevention, and Control — United States, 1968–2002* (CDC, 2005), NIOSH identified silicosis deaths from 1968 to 2002, and included all deaths for which an ICD code for silicosis was listed as either the underlying or contributing cause of death. Death rates (per million persons aged ≥15 years) were age-adjusted to the 2000 U.S. standard population. Codes for usual occupation or industry were available for each year 1985 -1999 for up to 26 states (CDC, 2005).

During 1968 to 2002, silicosis was recorded as an underlying or contributing cause of death on 16,305 death certificates; of these, a total of 15,944 (98 percent) deaths occurred in males (CDC, 2005). From 1968 to 2002, the number of silicosis deaths decreased from 1,157 (8.91 per million persons aged ≥15 years) to 148 (0.66 per million), corresponding to a 93-percent decline in the overall mortality rate. The racial distribution of persons who died from silicosis was approximately 88 percent (14,310 decedents) white, 12 percent (1,925) black, and less than one percent (70) other. Since 1996, on average, almost 31 silicosis-related deaths per year have been recorded among persons aged 15 to 64 years (NIOSH, 2008c). In its most recent WoRLD Report (NIOSH, 2008c), NIOSH reported that the number of silicosis deaths in 2003, 2004, and 2005 were 179, 166, and 161, respectively, slightly higher than that reported in 2002. The number of silicosis deaths identified each year has remained fairly constant since the late 1990's. Figure I-1 depicts the change in the number of silicosis deaths identified since 1968.

Figure I-1. Number of silicosis deaths and age-adjusted mortality rate, U.S. residents age 15 years and older, 1968-2005



Source: NIOSH, 2008c

The findings reported by CDC (2005) and NIOSH (2008c) indicate a decline in silicosis mortality during the time period 1968 to 2005. NIOSH cited two main factors that were likely responsible for the declining trend in silicosis mortality. First, many of the deaths in the early part of the study period occurred among persons whose main exposure to crystalline silica dust probably occurred before introduction of national standards for silica dust exposure established by OSHA and the Mine Safety and Health Administration (MSHA) (i.e., permissible exposure limits (PELs). These regulatory limits, coupled with other recommendations, such as that by NIOSH in 1974 (which issued a recommended exposure limit (REL) to respirable crystalline silica of 0.05 mg/m^3), have likely led to reduced silica dust exposure since the 1970s. NIOSH also stated that ancillary preventive measures (e.g., use of respiratory protection, hazard communication, and recordkeeping and reporting of occupational illnesses) where practiced, might have contributed to a reduction of personal exposures to respirable crystalline silica. The second major factor identified by NIOSH as contributing to a reduction in silicosis mortality relates to declining employment in heavy industries (e.g., foundries) where silica exposure was prevalent (CDC, 2005). Declining employment in industries with high exposure to silica would reduce the number of people at risk for developing silicosis, as well as the rate of silicosis mortality within the U.S. population. Although the factors described by NIOSH are reasonable explanations for the steep reduction in silicosis-related mortality, it should be emphasized that the surveillance data are insufficient for the analysis of the residual risk associated with current occupational exposure limits for crystalline silica. Analyses designed to explore this question must make use of appropriate exposure-response data, as is presented in OSHA's Preliminary Quantitative Risk Assessment (Section II).

NIOSH also identified the following limitations to the findings in the MMWR Report (NIOSH, 2004). First, accuracy of the coding of usual industry and occupation on death certificates was not verifiable because individual work histories are not listed on death certificates. Second, codes for usual industry and occupation were available only for the period 1985 to 1999 for 26 states; thus, these data are not nationally representative. Twenty-four states do not provide decedents' employment data to NCHS. Third, the state of residence at death is not always the state in which decedents' exposures occurred. Fourth, no exposure information is listed on death certificates. Therefore, no silica exposure-response relationship was evaluated. Finally, physicians might have misclassified or underreported silicosis deaths. These limitations apply to the use of death certificates as a source of mortality surveillance data in general, and do not reflect any particular limitation of the use death certificates for silicosis mortality specifically. While the 1970s saw a precipitous drop in the number of silicosis deaths as recorded on death certificates, reductions occurring in the 1980s and later appear more modest. (See Figure I-1.) To compare the percent reduction in the number of deaths over time, OSHA queried the NORMS database (http://webappa.cdc.gov/ords/norms.html) for the total number of decedents age 15 and older with any mention of silicosis coded on the death certificate (i.e., silicosis as underlying or contributing cause of death), for all races and both sexes. The total number of relevant deaths per each 5-year interval during the years 1970–2004 was generated by NORMS. OSHA then calculated the percent change from each 5-year interval to the next, for comparison purposes. These data are presented in Table I-2, which shows that the largest reduction (36 percent) occurred from the early 1970's (1970-1974) to the later 1970's (1975-

1979). The smallest reduction occurred from the 1985-1989 to the early 1990's (13 percent). From the last half of the 1990's to the 2000-2004 interval, the reduction was 20 percent.

Table I-2. Total Number of Deaths with Silicosis Mentioned on Death Certificate, (U.S. residents, age 15 and older, all races, both sexes) 1970-2004.

Years	Total number of Silicosis Deaths	Percent Change (Reduction)
1970-1974	4,263	
1975-1979	2,711	36%
1980-1984	1,958	28%
1985-1989	1,601	22%
1990-1994	1,389	13%
1995-1999	1,018	27%
2000-2004	809	20%
*NORMS database (http://webappa.cdc.gov/ords/norms.html)		

NIOSH has also reported silicosis mortality data by state (NIOSH, 2008c) for the years 1996-2005. Although larger numbers of silicosis deaths are concentrated in some states (e.g., Pennsylvania, the highest, with 228 over this period), at least one death with silicosis was reported to have occurred in each of the fifty states, plus the District of Columbia. Table I-3 shows the number of silicosis deaths in each state for U.S. residents age 15 and over, for the years 1996 to 2005.

Although the number of deaths from silicosis overall has declined since 1968, the number of silicosis associated deaths reported among persons aged 15 to 44 had not declined substantially prior to 1995 (CDC 1998). NIOSH reported results from an analysis of the age of silicosis-related decedents for the years 1968 to 1994, noting that: "(A)mong young persons (i.e., aged 15-44 years), deaths from silicosis declined less [than overall]." Young silicosis decedents resided in 38 states and the District of Columbia; the majority of the deaths (150 (72.5 percent) of the "young" decedents) were aged 35 to 44 years; 40 (19.3 percent) were aged 25 to 34 years; and 17 (8.2 percent) were aged 15 to 24 years. For the years 1968 to 2003, 234 of the silicosis deaths were among persons aged 15 to 44 (NORMS). Of the 59 young silicosis decedents who died between 1985 and 1994, a total of 25 (42.4 percent) died in a year for which their state of residence provided decedents' employment information to NCHS. Construction and manufacturing were coded most frequently as the usual industry (28.0 percent each); no deaths were attributed to mining (CDC, 1998). It is plausible that the deaths of some of these young workers were due to acute silicosis, but data is not available to distinguish between acute and chronic silicosis cases.

One measure of the impact of silicosis-related mortality is the number of years of potential life lost (YPLL), which is calculated both to life expectancy and to age 65. While YPLL to life expectancy represents a loss of years from the overall life span, YPLL to age 65 may be considered a loss of years from a working life (NIOSH, 2003). Between 1996 and 2005,

Table I-3. Number of silicosis deaths by state, U.S. residents age 15 and FDMS Docket Manager/Agency Administrator Trainingover, 1996-2005.

STATE	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	TOTAL
Alabama	3	1	8	4	2	1	3	4	2	3	**31**
Alaska	1	-	-	-	1	-	-	-	-	-	**2**
Arizona	3	3	3	4	1	3	3	8	2	4	**34**
Arkansas	1	2	2	3	2	-	1	1	1	1	**14**
California	13	5	4	6	8	9	4	6	7	8	**70**
Colorado	10	7	6	7	4	3	7	10	5	10	**69**
Connecticut	3	1	4	1	1	3	1	2	-	-	**16**
Delaware	1	1	-	1	1	-	-	-	1	-	**5**
District of Columbia	-	1	-	-	-	-	1	-	-	-	**2**
Florida	5	6	6	5	1	3	7	7	6	4	**50**
Georgia	4	4	3	2	2	1	-	3	3	4	**26**
Hawaii	-	-	-	-	-	-	1	-	-	-	**1**
Idaho	3	2	1	-	-	3	-	2	2	3	**16**
Illinois	7	8	7	5	5	8	4	7	2	2	**55**
Indiana	2	5	5	5	8	4	3	3	2	1	**38**
Iowa	1	4	4	1	1	4	-	-	-	2	**17**
Kansas	-	1	1	1	-	-	-	-	1	-	**4**
Kentucky	3	4	5	2	6	4	3	2	3	4	**36**
Louisiana	2	2	1	5	1	4	4	3	1	4	**27**
Maine	1	-	-	1	-	-	1	1	-	-	**4**
Maryland	4	1	3	5	2	-	6	1	3	1	**26**
Massachusetts	2	5	3	1	2	3	1	-	-	1	**18**
Michigan	16	5	9	6	8	4	4	4	9	7	**72**
Minnesota	6	5	-	4	3	6	1	3	7	5	**40**
Mississippi	1	3	1	2	1	1	2	3	3	2	**19**
Missouri	3	5	3	3	2	2	3	1	4	3	**29**
Montana	2	1	1	2	2	2	1	1	-	1	**13**
Nebraska	1	-	-	1	-	-	-	1	-	1	**4**
Nevada	-	1	-	-	1	-	1	-	2	1	**6**
New Hampshire	-	2	-	-	-	-	-	1	1	1	**5**
New Jersey	3	4	4	3	3	5	2	6	3	3	**36**
New Mexico	1	5	2	2	1	2	3	3	2	2	**23**
New York	10	6	8	8	9	4	10	4	10	9	**78**
North Carolina	6	9	5	6	6	5	1	4	6	7	**55**
North Dakota	1	-	-	-	-	-	-	-	-	-	**1**
Ohio	16	12	16	23	15	15	14	17	12	16	**156**
Oklahoma	-	1	-	5	1	1	-	1	1	2	**12**
Oregon	2	-	1	5	2	3	1	1	5	5	**25**
Pennsylvania	38	33	24	20	20	24	18	21	16	14	**228**
Rhode Island	2	3	-	2	-	1	-	2	3	1	**14**
South Carolina	3	2	1	2	3	5	-	1	1	1	**19**
South Dakota	1	1	-	1	2	-	1	1	-	-	**7**
Tennessee	2	3	5	3	-	4	2	4	4	4	**31**
Texas	9	11	8	12	6	8	14	15	12	7	**102**
Utah	-	3	3	1	2	6	4	2	1	4	**26**
Vermont	1	2	2	1	1	1	-	1	1	1	**11**
Virginia	2	3	6	1	4	4	1	5	7	-	**33**
Washington	2	2	4	3	2	1	2	3	2	1	**22**
West Virginia	6	6	5	6	4	1	6	4	1	1	**40**
Wisconsin	10	6	4	6	6	6	7	8	12	10	**75**
Wyoming	-	1	-	-	-	-	-	2	-	-	**3**
TOTAL	**213**	**198**	**178**	**187**	**152**	**164**	**148**	**179**	**166**	**161**	**1,746**

a total of 1,746 deaths resulted in a total of 20,235 YPLL, with an average of 11.6 YPLL to life expectancy due to silicosis mortality among U.S. workers. For the same period, among 307 decedents who died before age 65, there were 3,045 YPPL to age 65, with an average of 9.9 YPPL to age 65 (NIOSH, 2007).

Another statistical measure of mortality reported in the WoRLD Report (NIOSH, 2008c) is the proportionate mortality ratio (PMR). The PMR is defined as the observed number of deaths due to the condition of interest within a specified industry/occupation, divided by an expected number of deaths calculated as the total number of deaths in the specified industry or occupation multiplied by the proportion of all deaths across all industries or occupations that were caused by the condition of interest. Though the PMR does not reflect the risk of dying from or with silicosis, it is useful in indicating the relative importance of silicosis compared to other causes of death among workers in an industry sector (Lilienfeld and Lilienfeld, 1980). A PMR greater than 1.0 indicates that there were more deaths associated with the condition in a specified occupation or industry than would be expected under an assumption that the cause-specific mortality rate in the industry is the same as across all industry sectors (NIOSH, NORMS).

PMRs by usual industry for 1990-1999 indicate that workers in industries known and expected to have high silica exposures were more likely to die from silicosis than would be predicted based on the occurrence of silicosis mortaltity across all industries combined. Historically, these industries have included metal mining (PMR = 41.70), miscellaneous nonmetal mineral and stone products (PMR = 30.72), pottery and related products (PMR = 29.35), nonmetal mining and quarrying (PMR = 29.27), iron and steel foundries (PMR = 21.14), structural clay products (PMR = 19.72), fabricated metal products (PMR = 5.71), blast furnace and steelworks (PMR = 3.19), and construction (PMR = 1.26) (NIOSH, 2008c). A PMR of 1.26 for construction indicates that workers in this industry were 26 percent more likely to die from silicosis than were workers across all industries combined.

For those states (up to 23 at any time) for which industry and occupation codes from death certificates met NCHS quality criteria for “usual industry” and “usual occupation” during the 1990-1999 reporting period, Table I-4 shows the number of silicosis deaths reported among workers in the industries most frequently recorded on death certificates for U.S. residents age 15 and over. For the years 1990-1999 (most recent data available), a total of 118 deaths with silicosis were reported among construction workers, the largest number of silicosis-related deaths found for any industry sector (NIOSH, 2008c). This represented 13.4 percent of the 880 silicosis-related deaths identified for which usual industry and occupation were recorded.

Some of the death certificates captured in NORMS include information coded for occupation. OSHA queried NORMS for the number of silicosis deaths for the ten occupations most frequently mentioned on death certificates and evaluated the data output. The numbers of silicosis deaths recorded at the level of detail of the three-digit occupation code are very small (e.g., the highest number occurs in mining machine operators (138 deaths), next highest is laborers, except construction (84 deaths), and following that is managers and administrators (34

Table I-4. Silicosis: Most frequently recorded industries on death certificate, U.S. residents age 15 and over, selected states and years, 1990-1999

CIC	Industry	Number of Deaths	Percent
060	Construction	118	13.4
040	Metal mining	86	9.8
041	Coal mining	69	7.8
270	Blast furnaces, steelworks, rolling and finishing mills	51	5.8
050	Nonmetallic mining and quarrying, except fuel	48	5.5
271	Iron and steel foundries	48	5.5
262	Miscellaneous nonmetallic minerals and stone products	44	5.0
392	Not specified manufacturing industries	33	3.8
331	Machinery, except electrical, n.e.c.	23	2.6
252	Structural clay products	20	2.3
	All other industries	317	36
	Industry not reported	23	2.6
	Total	880	100
CIC – Census Industry Code n.e.c. – not elsewhere classified SOURCE: National Center for Health Statistics multiple cause of death data. NIOSH 2008c, Table 3-6, p. 62			

deaths)). All of the other specified occupations listed have 32 or fewer deaths. The occupational category with the largest number of deaths is "All other occupations," with 422, almost half of the total number of deaths. The small number of states reporting industry and occupation codes from death certificates that met National Center for Health Statistics quality criteria, (e.g., 19 states in 1999), is a major factor in the resulting small numbers of deaths coded for specific occupations. The small size of the data base limits its utility.

Table I-4 shows that for the years 1990 through 1999, the most frequently recorded industry on death certificates mentioning silicosis was construction (118 deaths). Linch et al. (1998) examined OSHA enforcement data for the years 1979-1995, (from OSHA's Integrated Management Information System (IMIS)), and found that some of the highest exposures to respirable crystalline silica in recent years occurred in construction (masonry, heavy construction, and painting), iron and steel foundries (casting), and in metal services (sandblasting, grinding, or buffing of metal parts). Exposures were estimated at concentrations of at least 1, 2, 5, and 10 times the NIOSH Recommended Exposure Limit (REL) of 0.05 mg/m^3. The study found that industries with exposures at least 10 times the REL were: masonry, stonework, tile setting, and plastering; heavy construction, except highway and street

construction; and painting and paper hanging. The industry that was found to have the highest percentage of workers exposed to at least the NIOSH REL was the cut stone and stone products industry.

OSHA compiled more recent IMIS data and identified high rates of noncompliance with OSHA standards, with the non-compliance rate being somewhat higher in construction compared to general industry. OSHA enforcement data contained in IMIS between 1997 and 2009 (Table I-5) indicate that 19 percent of silica samples from construction industry and 15 percent for general industry were at least three times the OSHA permissible exposure level (PEL). For general industry and construction, about two-thirds of the silica samples contained in IMIS during inspections in general industry were in compliance with the PEL, while only 58 percent of the samples collected in construction were in compliance.

Because of the long latency period of chronic silicosis (i.e., the interval between beginning of exposure to silica and the onset of disease), the deaths that have occurred in the recent past may be due to exposures that occurred decades ago, so looking at ore current exposures may predict future trends in silicosis mortality.

Table I-5. Number and Percent of Time-Weighted Average (TWA) Exposure Respirable Silica Samples for Construction and General Industry, Compared to the OSHA PEL (OSHA IMIS* January 1, 1997–December 31, 2009)

Exposure (severity relative to the PEL)	Construction		Other than construction	
	No. of samples	Percent	No. of samples	Percent
<1 PEL	972	66%	3,174	67%
1 x PEL to < 2 x PEL	135	9%	576	12%
2 x PEL to < 3 x PEL	80	5%	261	6%
≥ 3 x PEL and higher(3+)	283	19%	707	15%
Total # of samples	1,470		4,718	

*Integrated Management Information System: enforcement database maintained by OSHA, unpublished data

In summary, the CDC reported a 93 percent decline in mortality associated with silicosis from 1968 to 2002 (CDC, 2005), and referred to a decline in exposures over that time period as one likely factor for the dramatic decline in these deaths. The largest percent reduction occurred in the 1970s, from the first half of the 1970s to the second half. For the years 1995 to 2004, and for a total of 320 deaths and 2,810 YPPL to age 65, an average of 8.8 YPPL to age 65 was lost for each silicosis death. Geographically, though deaths with silicosis tend to be concentrated in a few regions of the country, all fifty states identified at least one silicosis-related death on death certificates in the 10-year period 1996 to 2005, the last year for which data are available. Despite the reductions in mortality associated with silicosis, silicosis continues to be identified

on death certificates as an underlying or contributing cause of death, with higher mortality seen in specific industries.

In the states that provide data on the usual industry of decedents, the most frequently reported industry (1990 to 1999) is construction. OSHA IMIS data for 1992 to 2002 show that exposures to respirable silica are higher in construction than in industries other than construction (primarily general industry). As long as exposure to crystalline silica remains high, silicosis mortality risk is expected to remain higher than average in those industry sectors (e.g., construction) and occupations where significant exposures to crystalline silica continue to occur today.

I.B.2.b. Silicosis morbidity.

With the exception of the NIOSH Coal Workers' X-Ray Surveillance Program, no ongoing national surveillance systems exist for occupational respiratory disease morbidity. Conventional sources of occupational injury and illness data were judged inadequate for measuring the prevalence of work-related respiratory diseases. For example, the BLS annual Survey of Occupational Injuries and Illnesses, which relies on employers' injury and illness logs for its data, has long been known to under-report incidences of diseases with long latency periods, such as silicosis, since such diseases are often not recognized or reported by employers.

To improve collection of data on occupational diseases, NIOSH, in association with state health departments, initiated targeted provider-reporting systems, called SENSOR, (Sentinel Event Notification System for Occupational Risks) in 1987. These SENSOR systems built on the experience and capacity that were already present in state health and labor departments (Baker, 1989).

SENSOR addressed a number of limitations of previously-existing provider-reporting systems, such as lack of epidemiologic case definitions, lack of formal, defined networks of sentinel providers with specific responsibility for reporting selected conditions, and lack of expert guidance. As part of this initiative, NIOSH recommended that each participating state target a select list of work-related conditions that were significant problems in the state and that would be appropriate for surveillance under the SENSOR model. NIOSH also developed a list of work-related conditions of public health importance. Of the initial 10 states participating in the SENSOR program in 1987, 4 (Michigan, New Jersey, Ohio, and Wisconsin) identified silicosis as a condition targeted for surveillance. In 1992 these four states were granted additional five-year cooperative agreements, and three other states (Illinois, North Carolina, and Texas) were also awarded SENSOR cooperative agreements to establish similar surveillance systems. During the third SENSOR funding cycle, 1997 to 2002, Ohio and New Jersey were funded for a third five-year cycle, and Michigan, though not funded, continued to participate and collaborate. Two of the original silicosis states (Michigan and New Jersey) continue surveillance for silicosis today. In addition to the SENSOR states, several states funded by NIOSH under various cooperative agreements to either develop model state-based surveillance systems, called Expanded Programs, or to develop new state-based surveillance programs, called Fundamental Programs, chose to focus at least some of their efforts on surveillance for silicosis using the

SENSOR model (see http://grants1.nih.gov/grants/guide/rfa-files/RFA-OH-02-007.html.). Both California and New Mexico were funded during 2002 to 2005 to conduct surveillance for silicosis.

Summary statistics from these states are compiled and published by NIOSH in electronic format at eWoRLD (http://www2a.cdc.gov/drds/WorldReportData/) and in the hard copy WoRLD Surveillance Report (http://www.cdc.gov/niosh/docs/2008-143/pdfs/2008-143a-iv.pdf). The electronic on-line system and the corresponding WoRLD Report are the most comprehensive compilation of surveillance data related to indicators of silicosis morbidity in the U.S. today.

The CDC/NIOSH encourages all states to collect and report silicosis cases and provides the following reporting guidelines for the purpose of surveillance:

> State health departments should encourage physicians, including radiologists and pathologists, as well as other health-care professionals, to report all diagnosed or suspected cases of silicosis. These reports should include persons with: a physician's provisional or working diagnosis of silicosis, OR a chest radiograph interpreted as consistent with silicosis, OR pathologic findings consistent with silicosis (CDC, 2006a).

The CDC/NIOSH has established the following silica case definition for surveillance purposes: "The following criteria were established for the purpose of defining a case of silicosis: history of occupational exposure to airborne silica dust and either or both of the following: a chest radiograph or other imaging technique interpreted as consistent with silicosis; pathologic findings characteristic of silicosis."

The CDC/NIOSH provides supplemental information, informing the reader that silicosis cases can be classified as nodular or acute. Chest radiographs or other images are interpreted as consistent with nodular silicosis if they have small opacity profusion categories of 1/0 or greater, as classified by a NIOSH-certified "B" reader under the ILO system. (The ILO classification system and the NIOSH "B" reader program are described above.) If the largest opacity is >1 cm in diameter, progressive massive fibrosis [PMF] is present. A bilateral alveolar filling pattern is characteristic of acute silicosis and may be followed by rapid development of bilateral small or large opacities.

Pathologic findings characteristic of silicosis consist of fibrotic nodules with a concentric "onion-skinned" arrangement of collagen fibers, central hyalinization, and a cellular peripheral zone with lightly birefringent particles seen under polarized light. In acute silicosis, microscopic pathology shows a periodic acid-Schiff positive alveolar exudate (alveolar lipoproteinosis) and a cellular infiltrate in the alveolar walls.

For the reporting period 1993-2002, the last year for which data are available, three states (Michigan, New Jersey and Ohio) recorded 879 cases of silicosis. Hospital discharge records represent the primary ascertainment sources for all three states (see Table I-6). It should be noted

that hospital discharge records most likely include cases of acute silicosis or advanced chronic silicosis. It is unlikely that, in cases with radiographic diagnoses of ILO category 1/0, there would be a need for hospitalization. Ascertainment sources for case identification have remained relatively constant over the years, with hospital reports being the primary source, followed by physician reports, and death certificates (NIOSH 1999, 2008c). Another source of data is workers' compensation case data. Demographic, work history, and medical information used for case confirmation and description were obtained through a combination of the initial case ascertainment source, a review of medical records, and follow-up telephone interview with the reported cases or their surviving next-of-kin.

Table I-6. Silicosis: Number of cases by ascertainment source and state, 1993-2002

Source	Michigan		New Jersey		Ohio		Total	
	No.	%	No.	%	No.	%	No.	%
Health care professional report	108	23.2	2	1.5	13	4.7	123	14.0
Hospital discharge data	312	67.1	127	94.1	234	83.9	673	76.6
Death certificate data	10	2.2	2	1.5	9	3.2	21	2.4
Workers' compensation files	35	7.5	-	-	19	6.8	54	6.1
Other	-	-	4	3.0	4	1.4	8	1.0
TOTAL	465	100	135	100	279	100	879	100

Source: NIOSH, 2008c

Confirmation of a silicosis case would depend upon a record of a chest x-ray or pathology findings consistent with silicosis and evidence that the worker was exposed to silica. If no evidence of occupational exposure to silica is found in the existing records, either the patient or surviving family member can be interviewed to obtain an occupational history.

In addition to its *WoRLD Reports*, the CDC publishes periodic updates of silicosis surveillance, including trends and case clusters in its *Morbidity and Mortality Weekly Reports*. MMWRs are widely distributed and read by public health practitioners. Cases of silicosis are reported to CDC by state health departments and can be compiled by the CDC across a number of states for a specific reporting period (either a single year or a number of years and by year of case ascertainment or case confirmation) for publication. For example, one publication, CDC, 1997a, reported 256 cases of silicosis that were ascertained (those reported and those confirmed) between January 1 and December 31, 1993 in seven states. Another, CDC, 1993, reported on 430 cases of silicosis reported by four states (249 cases for Michigan, 89 for New Jersey, 42 for

Ohio, and 50 for Wisconsin) for the years 1987 to 1990. Clusters of cases published are typically observed in the same occupation and/or with similar exposures. Clusters of cases of silicosis have been reported to CDC by state health departments and published in the MMWR for sandblasters (Texas) (CDC, 1990), workers involved in abrasive blasting (Ohio) (CDC, 1997b) and dental laboratory technicians (five states) (CDC, 2004).

Another indicator of morbidity associated with silicosis is the number of persons who were hospitalized because of silicosis or who had silicosis when hospitalized for other reasons. The WoRLD Report (NIOSH, 2008c) presents estimated numbers of hospital discharges that have been abstracted from National Hospital Discharge Survey (NHDS) reports published by the National Center for Health Statistics (NCHS) (see Table I-7). The NHDS, conducted annually by NCHS, collects data on the use of short-stay non- Federal hospitals in the United States. In recent years, data have been abstracted from approximately 270,000 records from about 500 hospitals (NIOSH, 2008c). One limitation of NHDS data is that they represent number of discharges, not the number of patients (NIOSH, 2008c). Some workers are hospitalized more than once for pneumoconiosis, and these secondary hospitalizations cannot be excluded (CSTE, 2005). In addition, the NCHS information is available only nationally and by region, but not by state. Furthermore, the NHDS relies on the completeness of hospital medical records, and findings can be influenced by diagnostic practices (NIOSH, 2008c).

The Council of State and Territorial Epidemiologists (CSTE), in collaboration with NIOSH, has published state-level statistics on pneumoconiosis hospitalizations. CSTE's statistics also rely on data from the National Hospital Discharge Survey (NHDS) (CSTE, 2005). Table I-8 shows the number of hospital discharges of persons with silicosis and other or unspecified pneumoconiosis for thirteen states for the year 2000. The total number of hospital discharges for the U.S. is estimated by the NCHS from the NHDS.

State-based hospital discharge data is a useful population-based surveillance data source for quantifying the prevalence of pneumoconiosis, including silicosis, even though only a small proportion of individuals with pneumoconiosis may be hospitalized for that condition in any given year. These data show that in the year 2000, 1,128 silicosis-related hospitalizations occurred indicating that silicosis continues to be a significant health issue and impacts our health care delivery system in the U.S. Additionally, some of the 952 hospitalizations reported to occur with "other or unspecified pneumoconiosis" may have been due to silicosis (CSTE, 2005).

Table I-7. Estimated number of silicosis-related discharges from short-stay non-federal hospitals

Year	Number of Discharges
1970	6,000
1971	7,000
1972	6,000
1973	5,000
1974	4,000
1975	4,000
1976	5,000
1977	4,000
1978	2,000
1979	3,000
1980	1,000
1981	2,000
1982	3,000
1983	2,000
1984	2,000
1985	3,000
1986	3,000
1987	3,000
1988	3,000
1989	2,000
1990	3,000
1991	4,000
1992	3,000
1993	1,000
1994	3,000
1995	3,000
1996	4,000
1997	3,000
1998	1,000
1999	1,000
2000	1,000
2001	300
2002	2,000
2003	1,000
2004	1,000

Source: NIOSH (2008c)

Table I-8. Number of Hospitalizations from or with Silicosis and Other/Unspecified Pneumoconiosis, by State and U.S., 2000

	CA	CT	MA	ME	MI	NC	NE	NJ	NM	NY	OR	WA	WI	US
Silicosis	67	21	25	6	106	64	<5	47	15	117	18	19	54	1,128
Other and unspecified pneumoconiosis	53	5	18	<5	17	63	<5	22	<10	45	<5	6	<5	952

Data Sources: Number of hospitalizations per state: State hospital discharge data. Estimated Number of hospitalizations in the U.S.: National Hospital Discharge. Survey Population Statistics used to calculate rates: Census Bureau Year 2000 U.S. Standard Population.

Source: CSTE, 2005

I.B.2.c. Underreporting of surveillance data.

In this section, OSHA reviews studies that attempt to estimate the degree of silicosis-related morbidity and mortality after accounting for underreporting. In the absence of *active* surveillance systems for silicosis, passive surveillance, which depends upon the health care community to generate records is likely to underestimate cases of silicosis in the U.S. (Froines et al., 1989). In clinical settings, occupational diseases, including silicosis, are generally under-recognized and underreported. Physicians play the main role in case-based disease surveillance by virtue of their unique role in recognizing and diagnosing diseases, but most primary care physicians do not take occupational histories (Goldman and Peters, 1981; Rutstein et al., 1983). In addition to the lack of information about exposure histories, difficulty in recognizing occupational illnesses that have long latency periods, like silicosis, contributes to under-recognition and underreporting by health care providers. Recognizing a history of occupational exposure to dust containing respirable silica is critical in the identification and reporting of cases of silicosis. Furthermore, as described above, state-based silicosis surveillance programs rely heavily on hospital discharge data, which will not capture cases where there are early radiographic signs of silicosis (i.e., an x-ray classified as ILO 1/0) absent symptoms that would otherwise trigger a hospital visit.

Identifying silicosis as a cause of death requires that the physician has a readable chest x-ray or appropriate tissue specimen and then recognizes x-ray changes or pathology evidence as being consistent with silicosis. Because of the limitations discussed above, physicians often miss silicosis as a cause of death, resulting in misclassification and underreporting. Furthermore, if the silicosis is recognized at death, and the decedent resides in one of the states that codes usual industry and occupation on the death certificate, the state of residence at death may not be the state in which decedents' exposures occurred, also resulting in a misclassification error. Inability to verify the coding of usual industry and occupation is another potential limitation of the use of death certificates. Codes for usual industry and occupation are available only for up to 26 states

for the period 1985 to 1999; thus, these data might not be nationally representative. If usual industry and occupation are not recorded, no exposure information is listed on death certificates; therefore, no silica exposure-response relationship can be evaluated.

OSHA identified only one study that attempted to evaluate underreporting of silicosis mortality. Goodwin et al. (2003) estimated, through radiological confirmation, the prevalence of unrecognized silicosis in a group of decedents presumed to be occupationally exposed to silica, but whose causes of death were identified as respiratory diseases other than silicosis. In order to asses whether silicosis had been overlooked and under-diagnosed by physicians, the authors looked at x-rays of decedents whose underlying cause of death was listed as tuberculosis, cor pulmonale, chronic bronchitis, emphysema, or chronic airway obstruction, and whose usual industry was listed as mining, construction, plastics, soaps, glass, cement, concrete, structural clay, pottery, miscellaneous mineral/stone, blast furnaces, foundries, primary metals, or shipbuilding and repair.

Any decedent found to have evidence of silicosis with a profusion score of 1/0 was considered to be a missed diagnosis. Of the 177 individuals who met study criteria, radiographic evidence of silicosis was found in 15 (8.5%). The authors concluded that silicosis goes undetected even when the state administers a case-based surveillance system.[1] The strength of this study is its use of existing data from death certificates, hospital records including chest x-rays, and the state silicosis registry to estimate the extent of undetected silicosis in one state.

OSHA identified two published papers that estimated the extent of previously undetected silicosis morbidity. The first of these, Windau et al. (1991), reported on the effort of four states (California, New Jersey, New York and Wisconsin) to collect hospital discharge data (from short-term, acute, non-federal hospitals) and compared the ability of hospital discharge records to identify cases of occupational lung diseases (including silicosis) with the BLS employer-based system. The second study, Rosenman et al. (2003), used data from death certificates and the Michigan-based silicosis surveillance system, along with capture-recapture analysis to derive national estimates of newly-recognized cases of silicosis in the U.S.

Windau et al. (1991) identified seven ICD-9 codes for diseases widely recognized to be work-related, including silicosis ("pneumoconiosis due to silica or other silicates") and "pneumoconiosis due to other organic dust." They then searched hospital discharge records, noting those codes on either primary or secondary diagnosis fields, indicating the presence of the condition at the time of hospitalization (secondary field), even though it may not have been the primary reason for the hospitalization (primary field). For pneumoconiosis due to silica or silicates, the number of cases reported by state appears in Table I-9.

[1] This study used data collected from hospitals in New Jersey, which administers a case-based surveillance system.

Table I-9. No. of Cases of Silicosis Identified Through Hospital Discharge Records (Windau et al., 1991)			
States	Years		
	1980-83	1984	1985
Wisconsin	96		
California		132	
New Jersey		77	82
New York			122
Total	96	209	204
Source: adapted from Table 3, Windau et al., 1991			

In Wisconsin, silicosis was the most prevalent of the seven occupational lung diseases reported. Data from New York specified the fields where the diagnoses of interest were captured. Of the 122 hospitalizations with "pneumoconiosis due to silica or other silicates" listed as a diagnosis, only 20 of these listed silicosis as the primary diagnosis; the others listed silicosis in the secondary field, indicating the presence of the condition at the time of hospitalization, even though it was not the primary reason for the hospitalization.

By comparison, almost half (99/200) of the hospitalizations with extrinsic allergic alveolitis and respiratory conditions due to chemical fumes and vapors were captured in the primary diagnosis field. The reasons for the difference in the categorization of these two occupational conditions as they are listed in hospital discharge records are probably related to the longer latency and more chronic nature of silicosis. In addition to the long latency of silicosis, this is consistent with death associated with silicosis often being due to cor pulmonale or obstructive lung disease and other late-stage complications of silicosis progression, which would be listed in the "immediate" or primary cause of death field, with silicosis coded in secondary fields.

The authors compared the hospital discharge data from the states to data from the two BLS data-collection systems that gather information on occupational injuries and illnesses (the Annual Survey of Occupational Injuries and Illnesses and the Supplementary Data System (SDS)). The Annual Survey is a sample survey of about 280,000 private sector establishments nationwide. Sampled employers are required to report all new occupational illnesses and qualifying occupational injuries for the survey year. States participating in the SDS provide injury and illness information from state workers' compensation reports, which reflect cases that result in death or disability.

For the purpose of comparing the Windau et al. (1991) data with the BLS data, the Windau data for only one year (1985) are being considered here, since the Windau data report results for different states for different years, and data from both systems are reported only for 1985. More silicosis cases were captured from the hospital discharge data from two states reporting in 1985 (204 cases) than were identified from the SDS data for 23 states (128 cases). The 1985 BLS survey data did not report silicosis cases but did report a total of 1,700 cases of pneumoconiosis. By comparison, the total number of cases of pneumoconiosis reported in the

SDS system in 1985 was 1,191 (for 23 states). However, hospital discharge data from 4 states reported 2,910 cases (data are for California, 1984; New Jersey, 1985; New York, 1985; and Wisconsin, 1980-1983 (averaged for the four years, based on estimates)), or more than twice the number reported from the SDS system for 23 states, and one-and-a-half times the number of pneumoconiosis cases estimated from the BLS national survey (Windau et al., 1991).

Hopital discharge data, although more comprehensive than either the BLS or SDS system, still fail to capture all cases since these data identify only those cases in which the person has been hospitalized, either for the disease of interest or for another condition. On the other hand, the data reflect the number of hospitalizations, not individuals with silicosis, and it is possible that some persons with silicosis are hospitalized more than once during any specific year. Nevertheless, the findings by Windau et al. (1991) show that the incidence of silicosis cases, as determined from hospital discharge records, is far greater than what would be suggested by either the BLS survey or the SDS system.

The only attempt to derive a national estimate of the annual incidence of new cases of silicosis in the U.S. was published by Rosenman et al. (2003). These researchers used data from death certificates and the Michigan state-based surveillance system along with capture-recapture analysis to account for sources of under-reporting. The starting point for the analysis was death certificates for the years 1987 to 1996, which included 2,787 deaths nationwide where silicosis was listed as either an underlying or contributing cause of death. Of these, 130 were identified as having occurred in Michigan (NIOSH, 1999). The number of cases identified from the Michigan surveillance system where silicosis was indicated on the death certificate was 110. The authors explained that the difference was "presumed to be secondary to differences between coding by the National Center for Health Statistics and that done by nosologists at the Michigan Department of Community Health." For this analysis, the 110 deaths identified by Michigan were used.

The next step was to determine how many of the silicosis deaths reported in Michigan could be confirmed. By applying the diagnostic criteria established for surveillance (i.e., a history of exposure to silica, and either a chest radiograph interpretation showing rounded opacities of 1/0 or greater profusion as per the ILO classification system for pneumoconiosis, or a biopsy report of lung tissue showing fibrosis consistent with silicosis), the authors determined that 85 (or 77.27 percent) of the deaths could be confirmed as silicosis cases. Applying this proportion to the 2,787 silicosis-related deaths in the U.S., the authors estimated that there would be 2,154 confirmed silicosis deaths in the U.S. between 1987 and 1996.

The authors then identified living individuals in Michigan with silicosis from one of the non-death-certificate sources (i.e. hospitals, physicians' reports, and workers' compensation) over the same time period. Cases for which there was a death certificate between 1987 and 1996 and that identified silicosis as a cause of death were excluded to avoid double-counting of cases. The presence of silicosis in these living cases was confirmed using the same criteria that were applied to the deceased cases. In all, 547 confirmed cases were identified. Based on the confirmed silicosis cases from Michigan, the ratio of living to deceased cases was calculated (547 divided by 85 = 6.4), and applied to the estimated national number of confirmed silicosis

deaths (2,154) to yield a national estimate of 13,872 silicosis cases believed to have occurred between 1987 and 1996, or an average of 1,387 per year. According to the authors, this is the estimated number of living silicosis cases that would have been reported if there had been a nationwide surveillance system for silicosis similar to that administered by Michigan.

The investigators used the Michigan surveillance data in a capture-recapture analysis to account for cases that were likely missed by the surveillance program and to derive an overall estimate of the annual number of new silicosis cases that occur in the U.S. This analysis assumes that all silicosis cases have an equal chance of being detected by any one of the data sources used in the surveillance program (i.e., hospital discharge reports, physicians' reports, or workers' compensation claims). Log-linear regression models were used to control for several possible interactions between the three data sources, and a range in the estimate of the total number of new cases in Michigan was derived from the models judged to be the best fit for the data according to criteria based on the likelihood ratio statistic.

From this analysis, the investigators estimated the total number of living silicosis cases in Michigan to range from 1,339 to 2,800, or between 2.45 and 5.12 times the actual number of cases identified from surveillance activities. Assuming that the extent of underreporting is the same nationwide, the authors estimated that between 33,986 and 71,025 (2.45 or 5.12 times 13,872) silicosis cases occurred in the U.S. for the years 1987-1996, or approximately 3,600-7,300 new cases per year. The analysis conducted by Rosenman et al. suggests that silicosis morbidity statistics arising from state-based surveillance programs are under-reported by at least a factor of 2.5 and possibly by as high a factor as 5. In their study, Rosenman et al. (2003) cite an abstract by Geidenberger and Socie (1997), who also used capture-recapture analysis with Ohio data and estimated that the number of actual cases was 3.03-3.18 times the number identified, which is in close agreement to the Rosenman et al. (2003) study.

Surveillance systems for silicosis mortality and morbidity in the U.S. have been reviewed. There is no comprehensive, reliable surveillance system for silicosis in the U.S. (i.e., there is no a system that captures either all deaths associated with silicosis or all new cases of silicosis). Mortality data coded for silicosis have been collected by the National Center for Health Statistics, and are made available in an electronic format by NIOSH in its NORMS database. Silicosis mortality is reported to have declined dramatically since the 1970s, although deaths either from or with silicosis still occur today.

Though existing systems are passive and incomplete, cases of silicosis continue to be reported, where surveillance systems exist. State-based silicosis surveillance systems have provided more detailed information on a limited number of cases. Both silicosis mortality and morbidity statistics derived from surveillance efforts likely under-report the true extent of disease. The one published analysis (Rosenman et al., 2003) of silicosis morbidity and mortality that accounted for under-reporting estimated that 3,600-7,300 new cases of silicosis occur each year (based on 1989 to 1998 data) in the U.S. This estimate is about 2.5 to 5 times higher than the actual number of silicosis cases identified from state-based surveillance efforts.

I.B.3. Progression of Silicosis and Its Associated Impairment.

The scientific literature describing the relationships between exposure to crystalline silica and silicosis is vast and has been reviewed in textbooks and by many authors of scientific review papers (Davis, 1996; Becklake, 1994; NIOSH, 2002). That exposure to crystalline silica is the only known cause of silicosis, and that silicosis is with rare exception exclusively an occupational disease, is without dispute. However, there continues to be much scientific discussion concerning the relationship between magnitude of exposure and silicosis risk, of the clinical significance of early radiological signs of silicosis, and the potential for exposure to increase the risk of pulmonary function decrements associated with the development of chronic obstructive lung disease (COPD). In reviewing the literature on crystalline silica, silicosis, and other non-malignant respiratory effects, OSHA identified four principal areas of emphasis necessary to inform the Agency's development of an effective revised standard for crystalline silica. These are:

- The factors that affect the progression of silicosis to more advanced stages and the clinical significance of disease progression;

- The relationship between pulmonary function decrements and early radiological signs of silicosis;

- The evidence describing the relationships between exposure to crystalline silica and pulmonary function decrements and/or development of COPD where radiological signs of silicosis are largely absent; and

- The quantitative relationship between exposure to crystalline silica and silicosis risk.

The first two areas are discussed immediately below. The literature describing development of COPD and pulmonary function decrements that are not generally associated with the presence of radiological findings of silicosis is discussed below in section I.D., Other Non-Malignant Respiratory Diseases. Finally, several epidemiological studies conducted in several industry sectors have found positive relationships between cumulative exposure to respirable crystalline silica and silicosis; many of these studies described quantitative exposure-response relationships for silicosis morbidity and mortality, as well as for COPD mortality. These are summarized and discussed in Section II, OSHA's Preliminary Quantitative Risk Assessment.

I.B.3.a. Factors influencing radiological progression of silicosis.

Numerous epidemiological studies have demonstrated, and it is widely accepted, that exposure to respirable crystalline silica of sufficient intensity and duration elevates the risk for developing silicosis. Researchers have made numerous attempts to quantitatively relate the risk of silicosis to silica exposure, and OSHA discusses the studies that provide quantitative estimates of the risk of developing silicosis in Section II, Preliminary Quantitative Risk Assessment. This current section will evaluate the published literature that informs us about the progression of silicosis, i.e., the factors that affect the progression of silicosis once it has been established.

As seen on chest x-ray films, progression is typically described as an increase in profusion, often but not always according to the ILO scale, although it can also refer to an increase in the size of opacities. Progression of silicosis has also been described in terms of increasing functional impairment. In this section, OSHA presents an evaluation of studies that have examined the relationship between exposure to crystalline silica and progression of silicosis as determined by radiography, pulmonary function studies, or both. Specifically, this section reviews scientific literature relevant to the question of which factors influence disease progression and how radiologic progression relates to progression of functional impairment.

Two broad types of epidemiological studies are reviewed in this section. These include studies that describe the prevalence of a particular end point in an exposed population at a single point in time (cross-sectional) and studies that have followed an exposed population forward over time (prospective). Some cross-sectional studies also employed a "follow-back" feature to obtain information on how silicosis developed over time in an exposed cohort. Prospective studies that follow the exposed cohort over a long period of time with periodic examinations can provide the best information on factors affecting the development and progression of silicosis, which has a latency period from 10 to 30 years after first exposure (Weissman and Wagner, 2005). Studies that follow the cohort after retirement or other event signifying the end of silica exposure can inform us of what happens with regard to disease progression in the absence of further silica exposure. Because silica is a "progressive" disease, all cases seen in a higher category of profusion (e.g., ILO category 3) have "progressed" from the previous category (category 2). It is also the case that each worker identified with advanced silicosis was considered to have acquired simple silicosis at an earlier point in time.

Hughes et al. (1982) studied sandblasters with silicosis in a longitudinal study that included chest x-rays and pulmonary function studies. Estimates of respirable silica concentrations were assigned to each job held by a worker, then combined with job histories to produce estimates of total cumulative silica exposure and average silica dust concentration for each person, though cumulative exposures were not presented in the published paper.

Employment in blasting ranged from 1 to 32 years, with a mean of 11.3 years. Estimated average respirable silica concentrations ranged from a low of 0.25 mg/m^3 (for five participants who had been exclusively bystanders) to 10 mg/m^3, with a geometric mean of 1.98 mg/m^3. Ten persons were exposed to mean concentrations of 1.25 mg/m^3 or less respirable silica, 40 were exposed to concentrations of respirable silica between 1.25 and 3.0 mg/m^3, and 10 were exposed to mean concentration of more than three mg/m^3respirable silica. Eleven participants had died since entering the study and eight death certificates were located. For seven, respiratory failure (or equivalent) was listed as a primary or contributing cause of death, while only three specified silicosis as a cause of death. Sixty-one of the 83 original participants returned for at least one follow-up visit. Follow-up ranged from one to seven years.

Criteria for inclusion (and thus for the definition of silicosis) in this study were a majority reading (by three readers) of small opacities of 1/1 or greater, involvement of both lungs, and a history of exposure in sandblasting operations. Agreement among the three readers was good: for final stages of disease (simple or complicated), the three readers completely agreed for 81

percent of the cases. For evidence of progression, there was complete agreement for 70 percent of those with serial films. Length of follow-up was five to 32 years, with a mean of 13 years.

Of the 60 persons with serial chest x-rays available, 38 (63 percent) were judged to have x-ray evidence of disease progression between initial and latest films. In general, the longer the time between serial films, the more likely it was that progression had occurred. Those with larger opacities and/or certain indicators of complication on the ILO scale on initial x-ray had a higher probability of progression than those with only small opacities. Seventy-two percent of those with complicated silicosis and 52 percent of those with simple silicosis exhibited evidence of progression. Of the 10 individuals in the lowest exposure group ($\leq$ 1.25 mg/m^3), 50 percent (5) progressed; of the 40 persons in the mid-exposure group (1.25-3.0 mg/m^3), 59 percent progressed; and all 10 of those in the highest exposure group (> 3.0 mg/m^3) progressed. Though the sample sizes are small, this study demonstrates a clear exposure-response relationship between silica exposure concentration and rate of progression of silicosis.

To determine the importance of multiple explanatory variables on the probability of radiological progression, step-wise logistic regressions were performed in which the following variables were considered: length of time between films, cigarette smoking (ever or never), pack-years of cigarette use, age at initial film, age at initial employment in sandblasting experience, lag time from initial experience, race, initial stage of disease (by chest x-ray), duration of sandblasting exposure and average silica dust concentration during exposure. The probability of x-ray progression was significantly related to the length of time between films, duration and concentration of exposure, initial disease state, race, and age at initial film. After adjusting for the other variables, those with complicated silicosis initially had a higher probability of progressing than those in the simple stage, and blacks had a higher probability than whites. Similarly, the probability of progression increased with increasing length of time between films, years of sandblasting employment and average silica dust concentration. Thus, both components of cumulative exposure, duration and concentration, were related to the likelihood of progression. The coefficient of age was negative; thus, among men who are comparable for all other variables, older men had a lower probability of progression than younger ones.

The exposures of these sandblasters were considerably higher than those found in general today. Most had ceased working by the late 1960s or early 1970s. Nevertheless, numerous cases occurred among young men with only a few years of recent sandblasting experience, and the authors reported that five cases had been exposed only as bystanders. For bystanders, exposure to respirable silica was estimated to be 0.25 mg/m^3, well within the range of that experienced by other workers today.

Ng et al. (1987a) identified a small group (n = 81) of granite quarry workers in Singapore with silicosis who had been followed at a pneumoconiosis clinic and were still alive at the time of their study. Subjects had been diagnosed with silicosis in the 1960s and 1970s. The authors followed the radiologic progression and changes in lung function and attempted to identify likely determining factors related to disease progression. This study made use of historical data while, at the same time, benefited from 10 years of follow-up.

The authors used historical particle count measurements made in the 1950s and 1960s, and results of a gravimetric survey done in 1982 to estimate respirable crystalline silica exposures. Cumulative lifetime exposure to silica and average quartz concentration were calculated from estimates of jobs and calendar-year-specific silica concentrations and duration of exposure in each job. On average, the cumulative respirable quartz exposure was 11.3 mg/m^3-years. The mean length of exposure was 23.4 years, and the mean respirable silica concentration to which they had been exposed was 0.48 mg/m^3.

Of the initial group, 52 were no longer working, 11 quit shortly after the initial exam, and 19 remained working for varying lengths of time. Serial radiographs were available for 73 individuals. Follow-up chest x-rays were done between two and ten years during 1975 to 1985. None of these workers used respiratory protection prior to 1975. All but 11 were no longer exposed at the start of the study; these eleven continued to work for 4 more years.

At the start of the study, 53 (73 percent) exhibited radiologically simple silicosis, while 20 (27 percent) had complicated disease. Of the 73 for whom serial radiographs were available, 35 (48 percent) showed radiological evidence of progression over the follow-up period ranged from 2 to 10 years, mean 7.2 years). From the original radiological state of disease, 24 of 53 men (45 percent) who had simple silicosis and 11 of 20 (55 percent) men who had complicated disease showed evidence of progression. Those with simple silicosis at the start of the study had lower cumulative respirable silica exposures (11 mg/m^3-years) than those with complicated silicosis (12.7 mg/m^3-years).

In this study, simple silicosis was defined as having only small opacities (rounded or irregular), and complicated if small opacities were present together with large opacities or one or more signs of other complications. Complications included tuberculosis, pleural thickening, and emphysema. These authors defined progression as an increase of two or more ILO subcategories or one step in the size of opacities between the initial and most recent films, or a change from small to large opacities.

Stepwise logistic multiple regression was used to examine the relationships between radiological progression and several possible determining factors, including age at initial examination, initial radiologic category (simple or complicated), smoking history, interval between initial and most recent radiograph, age at first exposure, average dust concentration, and duration of exposure. The authors reported that the probability of radiologic progression was most strongly determined by the average dust concentration, though it was not a statistically significant variable in the model. The authors did not include cumulative exposure as a variable in the regression analysis.

These investigators also found that radiologic progression of silicosis was associated with reduced pulmonary function; these findings are discussed in Section I.B.4 below. In addition, the estimated exposures are uncertain due to the need to estimate exposures from particle count data.

Lee et al. (2001) studied what appears to be a similar cohort of granite quarry workers in Singapore, investigating predictive risk factors for progression by comparing an initial and the most recent radiographs of 141 granite workers diagnosed with silicosis. Although this study was reported as covering a longer period of time (17 years) than that of Ng et al. (1987a), with the period of follow-up varying from 2 to 17 years, the reported mean length of follow-up (7.5 years) was the same as in the earlier study.

Silicosis has been a legally notifiable occupational disease since 1970 in Singapore, and annual chest x-ray films have been required for all granite quarry workers since 1972. Physicians are required to report suspected cases of silicosis, which are then confirmed on the basis of chest radiographs of ILO profusion grade of at least 1/1, a definite history of occupational exposure to silica, and exclusion of other causes of radiological opacities. Once identified, cases are followed up every 3 years with a chest film and a questionnaire. Of the 260 cases of silicosis identified, 141 who had available serial chest x-ray films of acceptable quality were selected for study.

Progression was defined as an increase of two or more steps (sub-categories) in the ILO 12-point scale of radiological profusion of small opacities or a one step in the size of small or large opacities or the development of large opacities not previously present. Agreement between at least two of the three readers was required.

All study participants had worked in granite quarries where exposure to silica was considered high. The study reported that historical measurements of dust in granite quarries in Singapore taken from 1973 to 1987 found exposure to total dust ranged from 0.83 to 3.07 mg/m^3 with a mean exposure duration of 27.3 (4-50) years; however, duration of exposure was the only exposure variable included in the regression model.

Logistic multiple regression was used to examine the relationship between radiological progression and several possible predictive factors, including age at initial chest radiography, initial radiological category, smoking history, interval between initial and most recent chest radiograph, duration of exposure to silica dust, history of pulmonary tuberculosis, and the duration (or length of time) since exposure ended at the time of the most recent chest radiograph.

Overall, 52 (37 percent) of this cohort showed evidence of progression. From the initial state of the disease, 24 (31.6 percent) of those with radiological profusion category 1, 15 (37.5 percent) with category 2 and 13 (52 percent) of those classified with complicated silicosis (including all 7 with category 3) showed evidence of radiological progression during the follow-up period.

Among those with simple silicosis, 36 (31 percent) had an increase in profusion of small opacities, 18 (15.5 percent) had an increase in size of small opacities, and 19 (16.4 percent) had developed large opacities. Nine (22.5 percent) diagnosed with category 2 who had simple silicosis and 10 (13.2 percent) with category 1 simple silicosis developed large opacities. Among those with complicated silicosis, 11 (44 percent) had an increase in size of large opacities, and 5 (20 percent) had an increase in profusion of small opacities, and 5 (20 percent)

had an increase in size of small opacities. Multiple logistic regression analysis of risk factors showed that the probability of radiologic progression was statistically significantly determined by the presence of large opacities in the initial chest x-ray film ($p = 0.01$) and the interval between the two chest radiographs ($p = 0.001$).

Due to the longer period of follow-up, the authors were able to estimate a 20-percent increase in odds of progression (by one sub-category of profusion) for every year of follow-up; however, there was some evidence that radiological progression might slow over longer periods following the end of exposure. Although the results were of borderline statistical significance, for those for whom exposure to silica had ceased, there was a 7-percent reduced likelihood of progression for every year following termination of exposure to silica up to the time of the most recent chest x-ray. Also of borderline statistical significance, there was an increased likelihood of silicosis progression when TB was present.

Ogawa et al. (2003) also studied a population whose exposure to silica had ceased. They reported on two groups of whetstone cutters (200 and 75 men) followed up to 40 years and 15 years, respectively, after cessation of exposure. The smaller group of men were recipients of disability compensation. Of these, 68 were followed until the end of the study. Although no exposure data were available for this population, the authors reported that the whetstone cut by this cohort was approximately 50 percent quartz. Assuming that silicosis prevalence in the cohort was 42 and 65 percent after 15 and 25 years of service (by averaging prevalences from duration ranges), respectively, and applying these figures to an exposure-response curve from data presented by other authors on a different population, exposure concentrations of silica dust were estimated by Ogawa et al. (2003) to be approximately 0.53 mg/m^3 silica for 15 years or 0.40 mg/m^3 silica for 25 years of exposure. Ogawa et al. (2003) stated that this was equivalent to about 0.9 mg/m^3 total dust. Duration of service was the only exposure variable analyzed in the study.

Between 1952 and 1956, at the first examination, 16 percent of the cohort had radiographic evidence of silicosis. At the third examination, in 1995, after exposure had ceased, 64 percent had silicosis. For workers whose initial x-ray film was classified as ILO categories 1 through 3, the rate of progression over a 15-year period was 50 percent or more. Longer duration of service and higher category of chest x-ray at the previous examination were the factors that were most strongly associated with progression. During this same 40-year period of follow-up, more than half of the 200 workers died due to various diseases, including 29 cases of silicosis (which included 9 cases of silicotuberculosis) and 6 cases of lung cancer.

Carneiro et al. (2006) also compared clinical and radiologic outcomes between silicotic gold miners whose exposure to silica had ceased and those for whom exposure continued after diagnosis. Among the 83 miners, 44 had continued exposure to silica after being diagnosed with silicosis. Continuation of silica exposure was associated with advanced silicosis (ILO category 3, OR = 6.42, 95% CI = 1.20-34.27), presence of coalescence and/or large opacities (OR = 3.85, CI = 1.07-13.93), and TB (OR = 4.61, CI = 1.14-18.71). Because this was a retrospective study, no information was available about the course of radiological progression, i.e. the initial classification of cases that were later determined to be advanced.

Miller et al. (1998) studied men who had worked at a Scottish colliery (coal mine) during the 1970s, until it closed in 1981. Unlike other coal miner cohorts, these workers were exposed to higher-than-usual quartz levels (greater than 10 percent freshly-cut quartz) in one of two seams that operated for a period of time in the 1970s. This study presented more detailed quantitative exposure data compared to many other epidemiological studies reviewed in this section because of a pneumoconiosis field research program that was started in the U.K. in the early 1950s. The data collection program lasted for over 30 years, was based on regular examination of the workforce at selected collieries, and included detailed descriptions of the working environments, including extensive dust sampling and mineral compositional analysis, and regular recording of how long each man spent working in those environments.

The program at this particular colliery began in 1954 and continued until the colliery closed in 1981. Respiratory health surveys included chest radiography (performed on-site) and a questionnaire that included smoking habits and (for the 1990/91 follow-up survey only) occupational history since leaving the colliery. The study reviewed the data from the six respiratory health surveys, the first in 1954, and the last in 1978. Additionally, attempts were made to contact all living members of the colliery cohort. Of 1,032 men not identified as deceased, 547 received a chest x-ray along with the survey. Methods used to collect data for the follow-up study survey in 1990/91 were based on the earlier surveys, so that results could be compared.

For each study participant, the radiograph from the 1990/91 follow-up survey, plus any radiograph taken in the 1974 or 1978 survey were read. If these were not available, then the film taken in 1970 was used. Each of the three radiograph readers read and classified the follow-up radiograph independently, then compared the follow-up with the earlier films. The readers were allowed to revise the classification of the follow-up radiograph based on viewing the earlier films. The median classification from the three readers was used for the analysis. All classifications were according to the ILO system.

Respirable dust concentrations were measured at the colliery from 1954 until its closure in 1981. Dust samples were analyzed for quartz, and mean and maximum exposure to respirable quartz was estimated for each individual for each time period between respiratory health surveys. The authors combined the respirable quartz concentrations with the records of time worked to estimate individual cumulative exposures. The authors reported that for the time period covering approximately 1964 to 1980, the mean cumulative exposure to respirable quartz was 3.15 gram-hours/m^3 (ghm^3), and the maximum cumulative exposure was 14.4 ghm^3. These exposures are equivalent to 1.8 mg/m^3 –years and 8.3 mg/m^3–years respectively, assuming 1,740 hours worked per year over the 15-year time period. These cumulative exposure values correspond to mean concentrations of respirable quartz of 0.12 mg/m^3 and 0.55 mg/m^3, respectively. However, between 1971 and 1976, workers experienced unusually high concentrations of respirable quartz in one of the two coal seams in which the miners worked. For some occupations, quarterly mean quartz concentrations ranged from 1 to 3 mg/m^3, and for a brief period, concentrations exceeded 10 mg/m^3 for one job. Overall, quarterly mean respirable quartz concentrations exceeded 1 mg/m^3 more than 10 percent of the time.

Based on the median of the three readers' results on profusion of small opacities, 203 men (38 percent) showed progression of at least one sub-category on the ILO 12-point scale, between the time of the surveys conducted in the 1970s to the follow-up in 1990-1991. Progression of one sub-category was found in 75 cases (14 percent), and of two sub-categories in 55 cases (10 percent). A total of 158 men (29 percent) had profusion scored at least 1/0, and 47 (8.6 percent) at least 2/1 at the follow-up survey. Large opacities were recorded as present by at least two readers for 14 (2.6 percent) of the men. Profusion of small opacities was strongly related to exposures experienced in the 1970s, and more strongly for quartz than for the non-quartz fraction of the dust.

Of the 547 workers included in the study, the last chest x-ray taken while still working was classified in major category 0 for 504 workers; of these, 20 percent had progressed to the 1/0 category within 15 years of follow-up, though this transition is probably more specifically identified as "onset" of radiological silicosis, rather than progression (Hessel et al., 1988). Table I-10 shows radiologic progression for those workers whose last working chest x-ray was in the major category 0. The data presented in the paper do not permit an analysis of the rate of progression for the remaining 36 workers whose last chest film while working was classified in the major category 1 or higher. Most progression occurred after exposure ended. The best single predictor of the risk of small opacities at a profusion of 2/1+ was reported to be concentration of respirable quartz.

Table I-10. Number and percent of British coal workers exhibiting chest x-ray abnormalities at follow-up, where the last x-ray taken while working was classified 0/0 or 0/1.

Results of follow-up x-ray, 1990-91	
ILO category	No. of workers (%)
0/0, 0/1	382 (76%)
1/0, 1/1, 1/2	97 (20%)
2/1, 2/2, 2/3	21 (4%)
3/1, 3/2, 3/3	4 (0.8%)
Total	504 (100%) (rounded)

Source: Miller et al., 1998

Yang et al. (2006) examined silicosis progression in a retrospective cohort study of 33,640 Chinese workers exposed to silica in tungsten and tin mines and pottery factories. All subjects had worked for at least one year from 1972 to 1974 and were followed from the first year of exposure to 1994. Although no information was given on time period of work or year of first exposure, information was provided that some silicosis cases were diagnosed prior to 1960. Exposure information was also not provided. Diagnosis was made based on readings by at least two of three radiologists according to a Chinese national classification system. The classes included suspected cases (0^+), stage I, II, and III silicosis, corresponding to profusion category

0/1, 1, 2, and 3, respectively, of the ILO classification system. Only stages I-III were considered to be silicosis for the purposes of this study.

It was reported that, at the end of the follow-up period (1994), among the 33,640 dust-exposed workers, 24,202 (71.9 percent) of the workers were retired or deceased and 7266 (21.6 percent) were still working. In the cohort, 20,660 (61.4 percent) dust-exposed workers had no silicosis, 5060 (15.0 percent) were suspected cases, and 7920 (23.5 percent) had silicosis. Of those with silicosis, 45.3, 42.2, and 12.5 percent had stages I, II, and III, respectively. The mean latency from the year of first exposure to stage I silicosis was 22.9 years and the fifth percentile was 8.6 years. Of the cases of stage I silicosis, 52.2 percent were diagnosed after silica exposure had ceased. The time interval from the ceasing of silica exposure to the time of first diagnosis of silicosis was 9.1 years and the fifth percentile was 1.8 years.

The time interval of silicosis progression was about 5.1 years from 0^+ to stage I, 4.1 years (fifth percentile 1.0 years) from stage I to stage II, and 6.8 years (fifth percentile 1.3 years) from stage II to stage III. The progression rates for 0^+ to stage I, stage I to stage II, and stage II to stage III were 48.7, 48.2, and 18.5 percent, respectively. Median survival time (i.e., the interval from the year of diagnosis to death) of stage I silicosis in tungsten mines, tin mines, and pottery factories was 21.2, 26.7, and 18.3 years, respectively. However, the survival time of 25 percent of stage I silicosis was 28.4 to 32.6 years. For those diagnosed at a later stage, the survival time was shorter. For example, the survival time for stage III was 6.8 years.

Yang et al. (2006) concluded that, while the disease course for silicosis was relatively long, it progresses quickly once established. Also, they concluded that it was necessary to handle the cases of 0^+ as if they had silicosis, by taking measures such as removing them from exposure, giving them medical examinations every year, and treating them as silicosis patients, because of their progression rate (48.7 percent) and their quick progression (5.1 years) to stage I.

Thus, some studies have shown evidence of radiologic progression of silicosis after exposure to silica has ceased (Miller et al., 1998; Ng et al., 1987a; Yang et al., 2006). Hessel et al. (1988) were also interested in the question of how continued exposure to silica after onset of silicosis affected the progression of the disease. The objectives of their study were: 1) to describe/quantify the progression of silicosis in South African gold miners; 2) to determine the effect of exposure to silica dust on progression; and 3) to compare the silica dust exposures of those who developed progressive massive fibrosis (PMF) with those who did not.

In South Africa, the Medical Bureau for Occupational Diseases is responsible for monitoring the health of miners. This includes conducting pre-employment examinations, as well as annual, benefit and periodic exams for the purpose of determining eligibility for compensation due to silicosis. Miners with silicosis receive compensation but can continue to work in dust.

Historical radiographic records were available for the potential cases from benefit records and records of periodic medical exams. These records were searched and five films were selected for each case, one record representing an initial chest x-ray, three taken over specified

time periods, and the most recent available film. Cases were identified as those with acceptable films for which two of three readers agreed that silicosis (at least 1/0) was present during the period 1967-1971, for a total of 631 subjects. Radiographs were coded on a scale from 1 to 10, with each subcategory in the ILO classification scheme representing a sequential number (e.g., 0/0, 0/1, 1/0 represented by 1, 2, and 3 respectively). On average, the men were nearly 67 years old at the time of their last chest x-ray and had been exposed to mine dust for an average of 31.7 years.

Exposure levels for high, moderate and low-dust occupations were defined as 0.97, 0.48 and 0.24 mg/m^3 respirable crystalline silica, respectively. Cumulative silica exposures were calculated as the number of shifts worked at each occupation multiplied by the mean silica dust exposure experienced in that occupation, expressed in mg/m^3-shifts. Exposure estimates were based on measurements of respirable particle counts and estimated quartz content of bulk material.

The main focus of this study was to look at the effect of continued silica exposure on progression of silicosis and compare those who continued to have exposure after onset with those whose exposure had ceased following onset. Overall, 92.4 percent of the silicotics progressed at least one category on the author's scale (or one ILO subcategory). The average annual progression rate was 0.2 minor ILO categories per year. The average length of follow-up was 14.2 years resulting in an average change over the follow-up period of 2.8 minor categories. Silicotics exposed to silica after onset of disease were only somewhat more likely to progress (94.6 percent) than those not exposed after onset (88.3 percent), and this difference was not statistically significant after controlling for year of birth and age at onset.

The younger silicotics experienced a higher rate of progression than older ones. The older silicotics began with a higher degree of profusion on their initial or earliest x-ray than did younger silicotics, and workers in all age groups reached nearly the same level of profusion by the time the last radiograph was taken. However, it cannot be concluded from these data that the rate of progression decreases with age or that the rate of progression slows as the disease progresses, since this observation may also reflect faster-progressing contemporaries of the older silicotics having left the industry, changes in film technique and quality over time, or the fact that the date of the last radiograph was not fixed by the investigators but was instead based on the miner's willingness to travel to the facility and have the examination. In addition, the authors speculated that workers experiencing slower progression may have continued to come in for examinations longer than the workers experiencing more rapid progression for reasons related in part to progression of the disease.

The authors also found that the rate of progression declined with increasing initial profusion score. For a person whose x-ray film is scored as major category 3, the ability to progress is limited. However, the authors found this trend to be evident for workers whose initial film was classified as having category 2 profusion. The authors noted that the group that started at category 0 in 1957 progressed at a greater rate than the other groups, 2.4 minor categories during the 10-year period, compared to an average of 2.0 minor categories for those whose initial x-ray showed evidence of silicosis.

The authors stated that cumulative silica dust exposure showed a positive, significant association with the rate of progression after controlling for covariates. When cumulative silica dust exposure prior to and subsequent to onset were separated, it was found that exposure after onset of silicosis was statistically significantly associated with the rate of progression ($p < 0.0001$) while exposure prior to onset was not.

The silicotics who developed PMF were similar to those who did not develop PMF for year of birth, year of first exposure, overall cumulative dust exposure and cumulative dust exposure up to onset of silicosis. PMF cases experienced earlier onset of silicosis and higher cumulative exposures after onset compared to non-PMF cases. Cumulative exposure after onset remained a statistically significant predictor of PMF when age at onset was controlled for ($p = 0.015$).

To summarize, various investigators identified a number of factors that are associated with an increased probability of progression. These include: 1) degree of profusion seen on initial films, with higher degrees of profusion associated with lower rates of progression (Hughes et al., 1982; Lee et al., 2001); 2) increasing length of time between films (Hughes et al., 1982; Lee et al., 2001); and 3) race (Hughes et al., 1982). In addition, older men experienced lower rates of progression than did younger ones (Hessel et al., 1988; Hughes et al., 1982).

Similarly, the probability of progression increased with years of employment in silica-exposed occupations (Hughes et al., 1982; Ogawa et al., 2003) and average silica dust concentration (Hughes et al., 1982; Miller et al., 1998; Ng et al., 1987a). Studies that included estimates of cumulative exposure found this exposure variable also was associated with progression (Hessel et al., 1988; Hughes et al., 1982; Miller et al., 1998; Ng et al., 1987a). OSHA notes that the mining cohort studied by Miller et al. (1998) was exposed to high episodic exposures of crystalline silica that periodically exceeded 1 mg/m^3, and those high peak exposures could have contributed to the silicosis progression (Buchanan et al., 2003). (See section II for a detailed discussion of the cumulative dose as the appropriate exposure metric for silicosis and the evidence of a dose-rate effect.)

At least three studies (Hessel et al., 1988; Miller et al., 1998; Yang et al., 2006) examined the extent to which silicosis progressed after cessation of exposure. These studies consistently found evidence of progression absent continued exposure. Silicotics who continued to be exposed to silica after onset were only somewhat more likely to progress (94.6 percent progressed) than those not exposed (88.3 percent progressed) (Hessel et al., 1988).

I.B.3.b. Relationship of progression to pulmonary function impairments.

This section discusses epidemiological literature that examines the relationship between progressive changes observed on radiographs and corresponding declines in lung-function parameters. Studies that report results of pulmonary function studies along with chest x-ray results attempt to correlate functional decrements with radiographic changes, both effects of exposure to respirable silica. Some of the studies that evaluated pulmonary impairment in

individuals with silicosis also attempted to characterize the functional impairment as restrictive, obstructive, or mixed. Some studies also attempted to distinguish between the impairment associated with silicosis and that related to chronic obstructive pulmonary disease (COPD), primarily emphysema.

In a 1992 study, Ng and Chan investigated the effects of simple silicosis on lung function, noting that "(T)here is no doubt that silica exposure is associated in a dose-related manner with the radiological responses that denote silicosis, and that silicosis in an advanced stage denoted by large opacities (massive fibrosis) is associated with significant lung function impairment, usually of an obstructive and/or restrictive type." The Ng and Chan (1992) study subjects were current and past workers in two granite quarries who were members of a cohort defined when all active workers were first given annual radiologic examinations at the start of a medical surveillance program in 1967, were employed for at least one year between 1967 and 1985, and were initially without silicosis. All the current (n = 206, 91 percent response) and past workers (n = 132, representing 61 percent of survivors, or 49 percent of all past workers in the cohort) with or without silicosis were given a questionnaire interview, chest x-ray, and lung function test.

Detailed work histories were obtained and used to estimate individual cumulative exposure to respirable quartz based on quarry- and job-specific measurements of past exposures, as in an earlier companion paper, Ng et al. (1987a). Cumulative exposure to granite dust was also estimated. Pulmonary function studies and chest x-rays were performed on all the subjects according to standard procedures. A case was identified when at least 2 of the 3 readers classified the film as 1/1 or greater by ILO convention.

The lung function values between groups of subjects with and without radiological opacities were compared with statistical adjustment for age, height, cigarette-years smoked and cumulative exposure (log-transformed) using analysis of covariance. "Cigarette-years" is defined as the number of cigarettes smoked per year multiplied by the number of years the individual smoked. Multiple linear regression techniques were also used to estimate the independent effects of cumulative exposure to respirable silica or total dust and radiological opacities on lung function of the study subjects. A total of 320 subjects were available for study. Irregular and rounded small opacities with a minimum radiological profusion of 0/1 were present in 79 (25 percent) and 60 (19 percent) subjects, respectively, and large opacities were present in 10 (3 percent) subjects.

Compared to subjects without radiological opacities (category 0/0), subjects with rounded opacities (indicative of silicosis) had lower values for FEV_1 ($p < 0.05$) and FVC ($p < 0.10$). After adjusting for age, height, cigarette-years, and cumulative silica exposure, the adjusted values in subjects with category 1 profusion were not statistically significantly different from those with profusion 0/0. However, these were statistically significantly lower for ILO profusion categories 2 and 3 of small rounded opacities ($p < 0.01$). As expected, highly significant reductions in FEV_1, FVC, and FEV_1/FVC were noted in subjects with large opacities. These investigators studied lung function by ILO silicosis category; there was no unexposed control group in this study, nor did the authors compare the values to population-based predicted values.

The category 0 group was exposed to a geometric mean of 0.69 mg/m^3/yr (GSD 7.5 mg/m^3/yr) respirable silica. This study also included workers who had resigned or retired.

In multiple regression analyses, in which cumulative respirable silica exposure or profusion of small opacities were entered separately as explanatory variables, each of these individual factors were significantly associated with decrements in FEV_1 and FVC. The authors concluded that chronic simple silicosis, except that classified as profusion category 1, is associated with significant lung function impairment. The authors of this study concluded that lung function loss in silicotics was attributable to fibrotic disease.

In an earlier paper that was discussed in the progression section, Ng et al. (1987a) identified a small group (n=81) of granite quarry workers in Singapore with silicosis who had been followed at a pneumoconiosis clinic and were still alive at the time of the study. The authors followed the radiologic progression and changes in lung function and attempted to identify likely determining factors related to disease progression in a group of workers who had silicosis.

Subjects had been diagnosed with silicosis in the 1960s and 1970s. Follow-up chest x-rays and pulmonary function testing was done between two and ten years during 1975 to 1985. Lung function was reduced in men who had complicated disease. For example, FVC in men with complicated disease was about 13 percent below predicted values whereas for those with simple silicosis, FVC was only about 4 percent below predicted values. The mean rate of decline in FEV in one second and FVC were 79 ml./year and 75 ml./year, respectively, in men who had simple silicosis and 84 ml./year and 88 ml./year, respectively, in those who had complicated disease.

In both groups (men with simple silicosis and those with complicated disease), those who showed radiologic evidence of disease progression had significantly greater rates of decline in lung function than those who did not show such progression. These differences were highly statistically significant after adjusting for small differences in baseline ventilatory capacity, age, and smoking habits. Those showing evidence of disease progression experienced mean rates of decline in FEV_1 and FVC of 97 and 95 ml./year, respectively, compared to 64 and 59 ml./year, respectively, among those not showing evidence of progression.

Bégin et al. (1988) also found a correlation between decreased lung function (FVC and the ratio of FEV_1/FVC) and increases in profusion of opacities. They studied 94 long-term (more than 20 years) silica-exposed workers in the granite industry or in foundries in Quebec using computerized tomography (CT scanning) of the chest, chest x-rays and pulmonary function testing. Chest radiographs were assessed and categorized using the ILO method; CT scans were also categorized by degree of severity graded on a 4-point scale of increasing severity that was derived by the investigators.

The subjects were divided into four subsets based on chest x-ray and CT scan of the thorax: group 1 consisted of 21 subjects who did not meet the criteria for silicosis (category 0 chest x-ray and CT scan); group 2 consisted of 28 subjects with simple silicosis (category 1 on

both chest x-ray and CT scan); group 3 consisted of 18 subjects with simple silicosis (category 1 on chest x-ray, but with coalescence or conglomeration or both seen only on CT scan). Group 4 consisted of 27 workers with complicated silicosis on chest x-ray and CT scan of the thorax.

Lung volumes were significantly reduced, but only in the group exhibiting the highest degree of profusion (group 4) ($p < 0.05$). Lung compliance, diffusion capacity, and the rest-exercise $P(A\text{-}a)O_2$ gradient were reduced among workers whose images were graded group 3 or group 4 ($p < 0.05$). Expiratory flow rates were significantly reduced for those in groups 2, 3 and 4, with the lowest values among those in group 4. The expiratory flow rates among those in group 3 were significantly lower than for those in group 2. Therefore, this study demonstrated increasing impairment with higher imaging categories (3 and 4), as expected, but also impairment (significantly reduced expiratory flow rates) among persons with more moderate pulmonary fibrosis (group 2).

Moore et al. (1988) also found chronic silicosis to be associated with significant lung function loss, especially among workers with chest x-rays classified as ILO profusion categories 2 and 3. For those classified as category 1, lung function was not diminished.

Cowie (1998) compared findings on chest x-rays and pulmonary function studies in 242 gold miners to those obtained 4.5 years earlier. At follow-up, 32 were no longer working underground. A total of 202 men exhibited silicosis on their follow-up chest radiograph (183 on the initial chest radiograph): 40 (78 on the initial radiograph) with category 1 profusion; 120 (73) with category 2; and 42 (32) with category 3 nodule profusion. He found that silicotics progressed one subcategory on chest x-rays (e.g., from 2/1 to 2/2), and that lung function declined in excess of what was expected for age, and more rapidly in men with silicosis than those without. Annual loss of FEV_1 was 37 ml. in those without silicosis, 57 ml. in those with category 1 profusion, 100 ml. in those with category 2, and 128 ml. with category 3 nodule profusion. These changes remained statistically significant after controlling for age, original lung function, and smoking habits. A similar pattern was noted for FVC.

This study (Cowie, 1998) examined the progression of silicosis in a short period of time (4.5 years) in gold miners exposed to silica. In addition to the 24 ml./yr. decrements expected due to aging, this study found an additional loss of 8 ml. of FEV_1 per year would be expected from continued exposure to dust in the mines. The author reported that the men with silicosis suffered a loss of FEV_1, which exceeded the loss in men without silicosis on entry by 210 ml. over the follow-up period of 4.5 years. However, no exposure information was presented by the author, limiting the conclusions that can be drawn from this study.

An earlier cross-sectional study by these authors (Cowie and Mabena, 1991) examined 1,197 black underground gold miners who had silicosis and were still working. Each worker was assigned to an exposure group (high, medium or low), based on knowledge of occupations, physical demand of the job, and years underground in the gold mine. No industrial hygiene measurements were obtained. Of those with silicosis, 50 percent were in ILO category 1, 44 percent in category 2, and 6 percent in category 3. There were only small differences in the dust exposure, smoking and the years underground by category of silicosis. Silicosis (analyzed as a

continuous variable) was associated with reductions in FVC, $FEV_{1,}$ FEV_1/FVC, and DL_{co} values, and these relationships persisted after controlling for duration and intensity of exposure and smoking. The cross-sectional design of this study did not permit comparisons over time. This study did not include true controls; the men without silicosis on chest radiograph (category 0) were also underground miners, with 28 percent in the "high dust" exposure category, 53 percent in the "medium dust" and 19 percent in the "low dust" category.

Other investigators have reported that exposure to crystalline silica is also associated with pulmonary function decrements or airflow obstruction absent, or independent of, radiological evidence of silicosis. Although this may reflect the insensitivity of radiologic tools for detecting silicosis, such findings are consistent with epidemiological and pathological studies that suggest that exposure to silica dust is associated with chronic obstructive pulmonary disease (COPD), in the absence of radiological signs of silicosis. Section V.D reviews the evidence that exposure to crystalline silica increases the risk of COPD and pulmonary impairment absent radiological signs of silicosis. The following section briefly discusses several studies that found pulmonary impairment independent of radiological signs of silicosis in workers exposed to silica.

Several studies have reported finding no correlation between decrements in lung function parameters and degree of nodular profusion seen on chest x-rays. Hughes et al. (1982) studied a representative sample of 83 silicotic sandblasters, 61 of whom were followed for one to seven years. A multiple regression analysis showed that the annual reductions in FVC, FEV_1 and DL_{co} were related to average silica concentrations but not duration of exposure, smoking, stage of silicosis, or time from initial exposure. This same study (Hughes et al., 1982) also found a high prevalence of respiratory symptoms in this population on initial interview (88 percent with lower respiratory symptoms, 26 percent with chronic bronchitis, 88 percent with some level of dyspnea and reduced pulmonary function on initial testing).

Ng et al. (1987b) studied respiratory symptoms, radiographic changes and lung function in a cross-sectional survey of 218 male gemstone workers in Hong Kong. Cutters and carvers were exposed to average respirable quartz concentrations of 60 and 30 $\mu g/m^3$, respectively. Workers in grinding/polishing and buffing jobs were exposed to average respirable quartz concentrations of 100 and 160 $\mu g/m^3$, respectively. Silica flour with quartz content often exceeding 90 percent was commonly used as an abrasive. All workers had chest x-rays classified as either Category 0 or 1 for silicosis. The FEV_1 and FVC values were not associated with radiographic category of silicosis after adjustment for years of employment. The authors concluded that there was an independent effect of respirable dust exposure on FVC, but silicosis graded as less than category 2 had no effect on lung function after dust exposure was accounted for.

In a population of 61 gold miners, Wiles et al. (1992) also found that radiographic silicosis was not associated with lung function decrements. Sixty-one South African gold miners with radiographic silicosis were matched with 61 miners without radiographic silicosis for age, date of beginning work, cumulative dust exposure, and smoking. They were all currently employed and had attended compulsory medical examinations in 1984-1985. The lung function of the 20 cases in ILO category 1 was not statistically different from that of the referents, and

there were no differences between the referents and those with category 2 or 3 silicosis. Wiles et al. raised the possibility that, in previous studies, two separate effects of exposure to silica have been demonstrated; one effect being the exposure-response relationship between cumulative exposure to respirable silica and silicosis, the other perhaps a dose-response relationship between cumulative silica dust exposure and reduced lung function due to airflow limitation separate from silicosis. They also noted, however, that those who were still working and had silicosis may not have been representative of all those with silicosis.

In a re-analysis and follow-up of an earlier study, Hnizdo (1992) found that silicosis was not a significant predictor of lung function, except for FEV_1 for non-smokers.

Wang et al. (1997) observed that silica-exposed workers (both nonsmokers, and smokers), even those without radiographic evidence of silicosis, had decreased spirometric parameters and diffusing capacity (DL_{CO}). Pulmonary function was further decreased in the presence of silicosis, even those with mild to moderate (ILO categories 1 and 2). The authors concluded that functional abnormalities precede radiographic changes of silicosis.

Workers exposed to silica and who have silicosis and impaired lung function may also have COPD, primarily emphysema. A number of studies have addressed the question of whether co-existing emphysema could account for the reduced lung function seen in those with silicosis.

Kinsella et al. (1990) compared lung function and computed tomography (CT) findings in silicotics (both smokers and non-smokers) to determine whether the presence of emphysema in silicosis was secondary or independent to the development of progressive massive fibrosis (PMF). Their data suggested that silicosis, in the absence of PMF, does not cause significant emphysema, and in the presence of both, it is primarily the degree of emphysema rather than the degree of silicosis that determines the level of pulmonary function.

The authors concluded that the degree of emphysema was the predominant independent predictor of pulmonary function impairment, and the degree of silicosis was an independent predictor only for carbon monoxide diffusing capacity. In order to evaluate the independent effects of cigarette smoking on individuals with silicosis, the authors also compared lung function in smokers with silicosis and nonsmokers with silicosis. Among subjects who did not have evidence of PMF, smokers had worse emphysema than did non-smokers. The authors stated that this was not surprising since cigarette smoking causes emphysema. In patients with more severe silicosis (PMF), the degree of emphysema in smokers and non-smokers was not statistically different. The authors reported that their findings suggest that silicosis did not cause significant emphysemas in the absence of PMF and that it is primarily the degree of emphysema rather than silicosis that determined the level of pulmonary function in subjects who showed evidence of both diseases.

In a follow-up to a previous study (Cowie and Mabena, 1991), Cowie et al. (1993) studied a sample of gold miners who were found to have abnormal lung function, including airflow obstruction and reduced diffusing capacity. A sample of 70 men from a cohort of older

miners with and without silicosis was examined, using CT, lung function tests and routine chest radiography, to determine whether emphysema accounted for these abnormalities.

On the basis of the chest x-ray findings, 55 of the men had silicosis. A total of 48 men had emphysema on examination by CT. Emphysema was present in 5 of the 15 men without silicosis and in 45 of the 55 with silicosis. Diffuse emphysema was present in 2 men without silicosis (14 percent) and in 25 men with silicosis (45 percent). The proportion of men with diffuse emphysema increased from 14 percent in those with ILO category 0 nodule profusion to 46 percent in those with category 1, 48 percent in those with category 2, and 67 percent in those with category 3. Lung function tests showed changes associated with silicosis that could be explained by the associated emphysema.

The authors noted that in the 1991 study of the same population of men working underground in gold mines, a relationship between the presence and degree of simple, chronic silicosis and airflow limitation was observed. This finding persisted after smoking and duration of exposure to the underground mine environment were controlled for, both factors having been associated with airflow limitation.

These authors also commented on the low sensitivity of CT scans for detecting silicosis. They reported finding an association between silicosis and emphysema but were unable to determine whether silicosis causes emphysema or whether both are caused by exposure to crystalline silica or some other factor. However, the authors concluded that in this population, silicosis, as seen on chest x-ray, served as a marker for emphysema and for lung function decrements in excess of that found in men from the same working environment who did not have silicosis.

Bégin et al. (1995) studied the prevalence of emphysema in workers with simple silicosis and asbestosis and in workers exposed to silica and asbestos, but without the pneumoconioses. The study population consisted of 207 workers evaluated at the Quebec Workman Compensation Board and who had a radiographic reading of pneumoconiosis in the category 0 or 1 of the ILO scale, as well as 5 (total) healthy volunteer control subjects. Emphysema was detected, typed, and graded on high-resolution CT scans independently by three experienced readers. Age, work experience and industry, smoking habits, and pulmonary function test results were analyzed for possible associations. The subjects were 58 to 60 years of age and were exposed to mineral dusts for 25 to 27 years; 31 were lifetime non-smokers and the others were either former- or current smokers. Ninety-six workers were from primary and 111 from secondary industries and did not differ otherwise in any parameter.

The three readers were in agreement regarding the extent of pneumoconiosis and emphysema seen on CT scan for 68 percent and 63 percent (respectively) of the cases. Among lifetime non-smokers, emphysema was seen in 1 of 20 subjects without pneumoconiosis but in 8 of 11 patients with pneumoconiosis. In smokers without pneumoconiosis, emphysema was present in 55 percent of patients with silica exposure, but only in 29 percent of patients with asbestos exposure ($p = 0.04$). Regression analyses documented that age, smoking, exposure type, and presence of pneumoconiosis were significant contributing factors for emphysema. In the

workers without pneumoconiosis, age, smoking, and exposure to silica were significant contributing factors.

Regression and contingency analyses relating emphysema and lung function tests showed that emphysema related best to reductions in FEV1/FVC ratio, maximal midexpiratory flow (MMEF), and DCO. Patients with emphysema had decreases in FEV1/FVC ratio (8 percent, $p = 0.001$) and DCO (8 percent, $p = 0.001$) that were statistically significant compared with the patients without emphysema. In subjects exposed to silica without silicosis, this study found no emphysema in lifetime non-smokers but a 55-percent prevalence of emphysema in smokers. This higher prevalence of emphysema in smokers with silica exposure but without silicosis was associated with lung dysfunction. These authors (Bégin et al., 1995) found a statistically significant excess of emphysema on CT scans, associated with lung dysfunction, in Workers Compensation Board-referred subjects with category 0 or 1 pneumoconiosis. Prevalence of emphysema was increased in those with pneumoconiosis and in smokers with silica exposure. In lifetime non-smokers, emphysema was present only in those individuals with pneumoconiosis. Simple mineral dust exposure, in the absence of smoking, pneumoconiosis, or both did not increase the prevalence of emphysema, as did silica exposure. The authors concluded that, in this population of workers, there was a significant excess of emphysema, associated with lung dysfunction, in those with silicosis (ILO category 1) and in smokers with silica exposure. Among nonsmokers exposed to silica, only those with silicosis had emphysema. They concluded that their data supported the concept of an association of emphysema, silicosis, and reduced lung function.

Gamble et al. (2004) reviewed the relevant studies on the correlation between radiographic silicosis and reduced lung function by grouping studies by design (i.e., cross-sectional, prospective, case-referent, and case series) and by considering the extent to which the studies attempted to control for smoking, dust exposure, and emphysema, factors that can confound the association between silicosis and lung function. The authors concluded that the data suggested a weak association between lung function (mainly obstruction) and dust exposure, although some studies reviewed had only crude measures of exposure available. In general, the lung function of those with radiographic silicosis in ILO category 1 was indistinguishable from those in category 0. Those in category 2 had small reductions in lung function relative to those with category 0 and little difference in the prevalence of emphysema. There were slightly greater decrements in lung function with category 3 and more significant reductions with progressive massive fibrosis. Emphysema was related to the presence of higher categories of nodular profusion, as well as to smoking. Gamble et al. (2004) believed that silica exposure was often inadequately controlled in studies examining silicosis and lung function.

Regarding the role of emphysema in silicosis, Gamble et al. (2004) concluded that there is little evidence that silicosis is related to development of emphysema in the absence of PMF. Because silicosis and emphysema were evaluated simultaneously in cross-sectional studies, it was impossible to discern temporal sequence. These authors pointed to the findings of Kinsella et al. (1990), who found emphysema in areas of the lung both with and without fibrosis, which led them to conclude that there is another factor that determines susceptibility to both PMF and emphysema.

Gamble et al. (2004) reviewed studies that adjusted for emphysema in addition to smoking and dust exposure and concluded that, in studies in which information on both silicosis and emphysema were available, reduced lung function was more strongly associated with emphysema than with silicosis.

In conclusion, an association between pulmonary function decrements and ILO category 2 or 3 background profusion of small opacities was reported in several studies and appears to be consistent with the histopathological view that massive fibrosis is formed by the conglomeration of individual fibrotic nodules (Ng and Chan, 1992). Emphysema may also play a role in reducing lung function in workers with higher grades of silicosis. Pulmonary function decrements have not been reported in some studies among workers with silicosis scored as ILO category 1. However, a number of other studies have documented declines in pulmonary function in persons exposed to silica and whose radiograph readings are in the major ILO category 1 (i.e.1/0, 1/1, 1/2), or even before changes were seen on chest x-ray (Bégin et al., 1988; Cowie, 1998; Cowie and Mabena, 1991; Ng et al., 1987a; Wang et al., 1997).

The literature reviewed above, most convincingly those studies with longitudinal follow-up of the cohorts, supports a finding of decreased lung function with progression of radiological silicosis, independent of emphysema. Also, evidence of functional impairment prior to radiological evidence of silicosis, and the low sensitivity of radiography, particularly in detecting early silicosis, supports a finding that exposure to silica impairs lung function in at least some individuals at an earlier point in time than can be detected on chest radiograph.

I.B.4. Pulmonary Tuberculosis.

As silicosis progresses, it may be complicated by severe mycobacterial infections, the most common of which is tuberculosis (TB). The most common site for TB infection is the pulmonary (or respiratory) tract. For the purposes of this section, "TB" refers to pulmonary TB. In workers exposed to silica, TB occurs most frequently when the macrophages are overwhelmed by silica dust and are unable to kill the infectious organism *Mycobacterium tuberculosis* (NIOSH, 2002). The risk of developing TB infection is higher in silicotics than non-silicotics (Balmes, 1990; Cowie, 1994; Hnizdo and Murray, 1998; Kleinschmidt and Churchyard, 1997; and Murray et al., 1996). There also is evidence that exposure to silica increases the risk for pulmonary tuberculosis, independent of the presence of silicosis (Cowie, 1994; Hnizdo and Murray, 1998; teWaterNaude et al., 2006).

The association between silicosis and the increased risk of TB has been firmly established by the results of multiple epidemiologic studies conducted prior to the 1990s (Balmes, 1990; Murray et al., 1996). Later studies strengthened support and added precision and detail.

Two studies of South African gold miners who were exposed to silica also included analyses of TB prevalence. Cowie (1994) found that miners with silicosis had an almost three-fold incidence of TB (relative risk for TB 2.8 (95% CI, 1.9 to 4.1)) compared to non-silicotic

workers of similar age from similar home and work environments. The incidence of TB increased with increasing severity of silicosis. The miners without silicosis were also observed to have a three-fold increase in TB incidence compared to the general population of the same race. This may have been influenced by silica exposure, however, differences in these populations, including age, gender, and level of TB surveillance make it difficult to assess.

In the other study of South African miners, which was a retrospective study (Kleinschmidt and Churchyard, 1997), the incidence rate ratio of TB for miners with silicosis was compared to miners without silicosis (1.54 (95% CI, 1.00 to 2.37)). For workers in occupations with high dust exposure, such as drilling, the incidence of TB was twice that of workers in less dusty jobs, including surface and maintenance workers.

A third study of South African gold miners, a prospective study (Hnizdo and Murray, 1998), was designed to investigate specifically whether silica dust, on its own, without the presence of silicosis, is associated with an increased risk of TB, and if so, whether the risk is dose-related. This study also looked at the chronological sequence between the development of pulmonary TB and silicosis after the end of exposure to silica.

Hnizdo and Murray (1998) followed the cohort of 2255 white South African gold miners for 24 to 27 years, for the incidence of pulmonary TB. During the follow-up period, 1592 (71%) died. Of these, 1296 (81%) had a necropsy done to determine the presence of silicosis and pulmonary TB. The investigators studied the incidence of pulmonary TB in the cohort relative to cumulative dust exposure and the onset of silicosis. For the whole cohort, the factors associated with increased pulmonary TB were cumulative exposure to dust (mg/m^3.yr) (adjusted rate ratio 1.07; 95% CI, 1.04 to 1.10), silicosis diagnosed radiologically (3.96 (2.59 to 6.06)) and tobacco pack-years (102 (101 to 103)). The rate ratio (RR) for pulmonary TB increased with increasing quartiles of cumulative exposure to dust 1.0, 1.51 (0.78 to 2.91), 2.35 (1.28 to 4.32), and 3.22 (1.75 to 5.9). In miners who did not have silicosis, the adjusted RR (for pulmonary TB and cumulative exposure was 1.10 (95% CI, 1.06 to 1.13), and increased with quartiles of exposure.

The authors concluded that exposure to silica dust is a risk factor for the development of TB in the absence of silicosis, even after exposure to silica ends. The risk of TB increases with the prevalence of silicosis, and in miners without radiological silicosis, with quartiles of exposure to dust. The severity of silicosis diagnosed at necropsy was associated with increasing risk of TB, even if the silicosis had not been diagnosed radiologically. The diagnosis of TB was on average 7.6 years after the end of exposure to dust. The onset of radiological silicosis preceded the diagnosis of TB in 92% of the cases with TB who had silicosis.

Charalambous et al. (2001) conducted a case series study of 15 South African gold miners exposed to silica who presented with TB. Radiological evidence of tuberculosis remained in 87 percent and 53 percent at 2 and 6 months after treatment. The authors noted that it is generally accepted that the response to modern TB regimens is rapid and complete resolution is achieved in most cases. The authors concluded that the combination of previous silica exposure and TB appeared to have resulted in a more negative outcome (pronounced response and potentially incomplete radiological resolution of TB) than exposure to TB alone.

Sherson and Lander (1990) studied male foundry workers in Denmark to address the question of whether workers exposed to silica but without silicosis are at a greater risk for TB than those with silicosis. They found that workers with silicosis had a 10-fold increase in prevalence rate of TB as compared to a period and age-standardized population of men in Denmark. Non-silicotic workers with at least 25 years of employment also had a significant, 3-fold increased incidence rate. The authors discussed possible factors that might explain this finding: difficulty in diagnosing early silicosis, lack of smoking histories, and social factors such as housing status, alcoholism, and diabetes could not be evaluated. Percent of foreign workers was similar to that of the general population. The authors concluded that their findings, in view of the considerable evidence from epidemiologic and animal studies, suggested that silica dust exposure, even in the absence of radiographically apparent silicosis, may be responsible for an increased TB risk. They opined that it therefore may be reasonable to maintain a tuberculosis surveillance program for silica-exposed workers in spite of diminishing silicosis prevalences.

A study of small-scale pottery workers in India also examined the associations of silica exposure, silicosis, and tuberculosis. Saiyed et al. (1995) studied the prevalence of silicosis and tuberculosis in 292 workers in eight small-scale potteries. The overall prevalence of both diseases was equal at 15.07 percent. The prevalence of TB increased with severity of silicosis. The stone grinding and glaze spraying departments, which had higher levels of airborne dusts, also showed a higher prevalence of silicosis and TB. The packing department, which had the lowest levels of airborne dust with low free silica content, showed the lowest prevalence of silicosis and TB.

In the U.S., two studies of silica exposure and TB used occupational mortality data to conduct a proportionate mortality study of persons with TB by occupation for 1979 through 1990 (CDC, 1997b; Chen et al., 1997). Although the study design did not control for confounding, it identified six occupational groups with potential exposure to silica that had age-adjusted proportionate mortality ratios (PMRs) for TB that were statistically significant at the 95% confidence level or greater than 200. The data are broken out by race. The groups with the highest PMRs include mixing or blending machine operator (black) (376, 95% CI, 122 to 878); roofers (white) (290, 95% CI, 106 to 630); mining machine operator (white) (276, 95% CI, 207 to 360); grinding, abrading, buffing or polishing machine operator (white) (265, 95% CI, 107 to 547); brick and stone mason (white) (213, 95% CI, 110 to 371) and (black) (159, 95% CI, 80 to 285).

Chen et al. (1997) conducted a case-control study (8,740 cases; 83,338 controls) with U.S. National Occupational Mortality Surveillance (NOMS) (a precursor to NORMS) data for 1983-1992. The potential for silica exposure was categorized as “high,” “intermediate,” and “low or no,” based on data from the National Occupational Exposure Survey (NOES) and the National Occupational Health Survey of Mining (NOHSM) (NIOSH). This study found that decedents with high potential for exposure to silica and no documentation of silicosis on the death certificate had a 30-percent greater odds of mortality from TB than decedents with no potential exposure to silica after adjustment by logistic regression for age, sex, race, socioeconomic status, potential exposure to active TB, and the presence of silicosis or other

pneumoconioses (OR = 1.3; CI, 1.14 to 1.48). The results also suggest an exposure-response relationship between silica exposure (in the absence of silicosis) and death from TB.

Findings of a study by Calvert et al. (2003) were consistent with those of previous studies showing an increased incidence of pulmonary TB among nonsilicotic workers with long-term crystalline silica exposure. In this study using almost five million death certificates, cases with underlying and contributory causes of death from TB were compared to matched controls with other causes of death. The potential for silica exposure was determined by three senior industrial hygienists who conducted independent assessments. Silica exposure categories were defined as low/no, medium, high, and super-high. Decedents in the super-high category had a significantly increased risk for TB. In addition, a significant trend of increasing risk of TB with increasing silica exposure was observed. Analyses were also conducted in which the disease cases with concomitant silicosis and their associated controls were excluded. These exclusions made little difference in the findings. Both the presence of silicosis and exposure to silica have been shown to increase the risk of tuberculosis.

A study by teWaterNaude et al. (2006) of the prevalence of pulmonary tuberculosis (PTB) in South African gold miners also found that, even in the absence of silicosis, PTB was significantly associated with dust and silica exposure. In this study, 520 gold miners were assessed at one time point for a history of PTB, smoking habits, and past chest illness. Each miner was given a chest x-ray at that time point. A complete job history was obtained and length of service and exposure measurements were used to calculate cumulative respirable dust and quartz exposures for each miner. For non-silicotics, there was significant increasing trend for prevalence of PTB with increasing quintile of cumulative respirable quartz exposure. Since it was not a confounder in their data, the authors believed that radiologic silicosis was most likely just a marker for substantial silica exposure.

Studies on the mechanisms of disease development for silicotuberculosis and diseases caused by silica were summarized by Ding et al. (2002). In discussing silicotuberculosis the authors noted that it is well documented that exposure to silica can lead to impaired cell-mediated immunity. Reduced numbers of T-cells, increased numbers of B-cells, and alterations of serum immunoglobulin levels have been observed in workers with silicosis.

According to Ng and Chan (1991), silicosis and TB act synergistically to increase fibrotic scar tissue (leading to massive fibrosis) or to enhance susceptibility to active mycobacterial infection. Lung fibrosis is common to both diseases and both diseases decrease the ability of alveolar macrophages to aid in the clearance of dust or infectious particles.

Pulmonary tuberculosis is a widely known complication of chronic silicosis. There is ample evidence that exposure to silica, even without the presence of silicosis, increases the risk for pulmonary TB.

I.B.5. Preliminary Conclusions: Silicosis and Disease Progression.

Silicosis is a progressive disease affecting the lungs, in some cases progressing to complications resulting in disability and death. Progression of fibrosis indicative of silicosis can be observed using chest radiography and computed tomography, though neither technique will detect the presence of silica-induced lung fibrosis in all affected individuals, particularly in early stages. However, both imaging techniques are specific enough that they are reliable indicators of silicosis, once it is detected. Pulmonary function studies are useful in documenting the types of functional impairment associated with silicosis, which may be mild in the beginning.

A restrictive pattern of airflow limitation, though it initially may be mild, typically appears early in the development of silicosis. If symptoms (primarily shortness of breath with exertion) are present, they usually result from restricted airways from the fibrotic scarring in the alveolar sacs and the ends of the lung tissue. The scarring can be detected from chest x-rays when the lesions become large enough to be visible opacities. By the time opacities have coalesced, as viewed on chest x-ray or CT scan, and silicosis has advanced to the "complicated" stage, it is associated with significant loss of lung volumes, gas exchange function, and increased airflow obstruction. For the silicotic, this means dyspnea (difficulty breathing), perhaps while attempting to complete the most simple activities of daily living, and the possibility of a shorter life span than without silicosis.

Individuals with complicated silicosis exhibited reduced median survival time as compared with the general population (Infante-Rivard et al., 1991; Ng et al., 1992a; Westerholm, 1980). Data compiled from the National Occupational Respiratory System (NORMS) database indicate that for persons for whom silicosis is identified as a cause of death, an average of 11.8 years of potential life are lost. Additional predictors of increased mortality in patients with silicosis included age at diagnosis (younger than age 45 years) and the presence of TB (higher mortality with TB) (Ng et al., 1992a; Westerholm, 1980). Those with complicated silicosis (large opacities) (Westerholm, 1980) or who exhibit dyspnea, expectoration, abnormal breath sounds or low vital capacity as well as silicotics who are current smokers have a much poorer survival (Infante-Rivard et al., 1991).

When attempting to draw conclusions from the body of literature reviewed here describing silicosis progression, the largest constraint is the lack of accurate and detailed exposure data. Of the studies reviewed here, four studies (Hughes et al., 1982; Hessel et al., 1988; Miller et al., 1998; Ng et al., 1987a) included exposure data that were based on either current or historical measurements of respirable quartz. The exposure variables most strongly associated in these studies with progression of silicosis was cumulative respirable quartz (or silica) exposure (Hessel et al., 1988; Hughes et al., 1982; Miller et al., 1998; Ng et al., 1987a), though both average concentration of respirable silica (Hughes et al., 1982; Ng et al., 1987a) and duration of employment in dusty jobs have also been found to be associated with the progression of silicosis (Hughes et al., 1982; Ogawa et al., 2003).

The study reflecting average exposures most similar to current exposure conditions is that of Miller et al. (1998), which followed a group of 547 British coal miners in 1990-1991 to evaluate chest x-ray changes that had occurred after the mines closed in 1981. Between 1964 and 1978, mean and maximum cumulative exposures to respirable quartz were estimated to be

1.8 and 8.3 mg/m^3-years, respectively, corresponding to average concentrations of 0.12 and 0.55 mg/m^3, respectively, over the 15-year sampling period. However, between 1971 and 1976, workers experienced unusually high concentrations of respirable quartz in one of the two coal seams in which the miners worked. Buchanan et al. (2003), in a reanalysis of the Miller et al. (1998) study has shown that short-term exposures to high (>2 mg/m^3) concentrations of silica can have an effect 3 times as great as a cumulative equivalent longer-term exposure to lower levels.

The Miller et al. (1998) study also provided ILO chest x-ray categories for its participants, and included workers whose last chest x-ray while they were working was recorded as either 0/0 or 0/1. Among the 504 workers whose last chest x-ray was classified as ILO 0/0 or 0/1, 20 percent had experienced onset of silicosis (i.e., chest x-ray was classified as ILO 1/0 by the time of follow up in 1990-1991), and 4.8 percent progressed to at least category 2. However, there are no data available to continue following the progression of this group because there have been no follow-up surveys of this cohort since 1991.

The cohorts followed in the other three studies (Hessel et al., 1988; Hughes et al., 1982; Ng et al., 1987a) were comprised of silicotics (i.e., individuals already diagnosed with silicosis that were followed further to evaluate disease progression). These studies also reflect exposures of workers to higher average concentrations of respirable quartz than was the case in the Miller et al. (1998) study.

With the exception of studies with highly detailed silica exposure measurements and individual's exposure times (Buchanan et al., 2003), when exposures are very high, it is difficult to extrapolate study findings with respect to the extent and rate of disease progression, except in a very general sense. Some general findings from this body of literature follow. Regarding the risk of progression of silicosis (defined as changes in chest x-ray), there is strong evidence for the following findings. First, size of opacities on initial radiograph is a determinant for further progression. Individuals with large opacities on initial chest radiograph have a higher probability of progression to chronic silicosis than those with small opacities (Hughes et al., 1982; Lee, et al., 2001; Ogawa et al., 2003). Second, although silicotics exposed after onset of disease are more likely to progress than those not exposed (Hessel et al., 1988), once silicosis has been detected there remains a likelihood of progression in the absence of additional exposure to silica (Hessel et al., 1988; Miller et al., 1998; Ogawa, et al., 2003; Yang et al., 2006). Silica exposure, measured as either average concentration (Hughes et al., 1982) or cumulative exposure (Hessel et al., 1988; Hughes et al., 1982; Miller et al., 1998; Ng et al., 1987a) is the variable that has most strongly been reported to be related to progression of silicosis.

Additionally, there is some evidence in the literature that the probability of progression is likely to decline over time following the end of the exposure, although this observation may also reflect a survivor effect (Hughes et al., 1982; Lee et al., 2001). In addition, of borderline significance was the association of TB with increased likelihood of silicosis progression (Lee et al., 2001).

Some studies estimated rates of progression as either the number in a cohort who progressed compared to the total number in the cohort (i.e., as a percentage of the cohort), or as the number of sub-categories per year on the ILO scale that cohort members were observed to have progressed. Data from these studies have shown that:

- For a mean respirable silica exposure of 0.48 mg/m^3, 45 percent of those with simple silicosis progressed over a mean of 7.2 years, yielding an annual rate of progression of 6.2 percent of the cohort (Ng et al., 1987a);

- At an average respirable silica exposure of 0.12 mg/m^3, but with high periodic exposures to freshly fractured silica, of those who had a 0/0 or 0/1 chest x-ray, 29 percent progressed (to at least a 1/0 x-ray) in a follow-up period averaging 16 years (Miller et al., 1998), yielding an average annual progression of almost 2 percent. Additionally, much of this progression most likely occurred after exposures ceased, since the mine had closed some 9 years prior to follow-up;

- For a mean respirable silica exposure of a 0.98 mg/m^3, sandblasters progressed at an overall rate of 65 percent in a mean of 11.3 years (Hughes et al., 1982), yielding an average annual progression rate of approximately 6 percent;

- Among South African goldminers, 92 percent progressed in 14 years. (Hessel et al., 1988). Exposures of high, medium, and low exposure groups were 0.97, 0.48, and 0.24 mg/m^3, respectively; and

- Chinese mine and factory workers categorized as "suspected" silicosis cases i.e., 0/1, had a progression rate to stage I of 48.7 percent and the interval was about 5.1 years (Yang et al., 2006).

Two studies (Miller et al., 1998; Ng et al., 1987a) provide the information most relevant to current conditions. The range (0.12 to 0.48 mg/m^3) is relatively narrow and falls within the range of exposures of particular interest to OSHA, because current enforcement data indicate that exposures in this range or not much lower are common today, especially in construction and foundries, and sandblasting operations. Both of these studies reported progression in terms of percentage of workers whose chest x-ray categories progress, and their results are close (2 percent to 6 percent). Based on these data, one can estimate an annual progression rate of 2-6 percent for this exposure range. This means that every year, provided sufficient time has elapsed since beginning of exposure to account for latency, approximately 2 to 6 percent of workers exposed to respirable silica dust in the range of 0.12 to 0.48 mg/m^3 are expected to progress at least 1 sub-category on the ILO scale (as noted by Hessel et al. (1988), the transition from major category 0 to the 1/0 category is probably more specifically identified as "onset" of radiological silicosis, rather than progression).

The following studies provide higher estimates, based on higher historical exposures, and are provided for comparison:

- In a population of gold miners, a 20 percent increased odds of progression was found for every year of follow-up. In 4.5 years, silicotics progressed one subcategory on chest x-rays (i.e., from 2/1 to 2/2), for an annual progression rate of 0.22 subcategories/year (Cowie, 1998) (which is very close to the rate of progression found by Hessel et al., 1988 of 2.4 minor categories in 10 years); and

- For a mean exposure of 1.4 mg/m^3 total granite dust for 7.5 years, the overall rate of progression was 37 percent, for an annual rate of 0.2 categories if large opacities were present on initial radiograph (Lee et al., 2001).

Regarding the relationship between progression of reduced lung function and its correlation with chest x-ray changes, there is strong evidence in the literature for the finding that lung function deteriorates more rapidly in workers exposed to silica, especially those with silicosis, than what is expected from a normal aging process (Cowie et al., 1998; Hughes et al., 1982; Malmberg et al., 1993; Ng and Chan, 1992). The rates of decline in lung function were significantly greater in men whose disease showed evidence of radiologic progression after adjusting for differences in age, smoking, and baseline value of lung function. Excessive loss of lung function was noted in relation to progression of chest x-ray changes (Bégin et. al., 1987a; Cowie 1998; Ng and Chan, 1992; Ng et al., 1987a). Additionally, the deterioration of lung function seen on average exceeds that in smokers (Hughes et al., 1982).

Two studies attempted to correlate x-ray changes with functional decrements (progression) and had sufficient data to compare both chest x-rays and PFTs for the same workers for at least two distinct points in time (Cowie, 1998; Ng and Chan, 1992). Both studies found statistically significant decrements that exceed the expected values for those men with chest x-rays consistent with ILO category 2 and 3, and the second study found statistically significant decrements starting with ILO profusion category 1. Both studies observed deterioration in lung function in proportion to the degree of silicosis. Both of these studies included a profusion 0/0 group for comparison, but neither study included an unexposed comparison group. Other studies (Ng et al., 1987a; Wang et al., 1997) suggested that measurable changes in pulmonary functions are evident well before the changes seen on chest x-ray.

Left unresolved after this review is the question of whether or not there is a relationship between silicosis and emphysema, in the absence of PMF. The evidence presented here is equivocal. Some studies suggest that emphysema is associated with dust exposure and PMF. Others suggest that emphysema can be a complication of silicosis, even at its earliest stages.

In the next subsection, OSHA presents its discussion of the epidemiologic investigations that have described lung cancer mortality in workers exposed to crystalline silica. First OSHA reviews cohort and case control studies of exposed workers, then discusses of large pooled and national registry studies. This is followed by a review of studies of lung cancer mortality among workers with silicosis.

I.C. *Carcinogenic Effects of Silica (Cancer of the Lung and Other Sites).*

I.C.1. Introduction.

There has been extensive epidemiological and toxicological study about whether respirable crystalline silica dust is a risk factor for lung cancer mortality among exposed workers. In 1997, IARC concluded that "crystalline silica inhaled in the form of quartz or cristobalite from occupational sources *is carcinogenic to humans (Group I)*." The working group noted there was "*sufficient evidence*" in both the epidemiologic studies and animal data to support these conclusions (IARC 1997, p.210-Italics in original). In its review, IARC considered more than 40 lung cancer studies (both cohort and case-control) among silica-exposed workers and among workers diagnosed with silicosis (silicotics). IARC based its overall finding on studies of nine occupational cohorts that IARC considered to be the least influenced by confounding factors, as well as selected studies of registered silicotics with lung cancer. Most of these studies reported finding an excess lung cancer risk in occupationally exposed populations. While acknowledging some inconsistency in the studies, IARC stated that "… in view of the relatively large number of epidemiological studies that have been undertaken and, given the wide range of populations and exposure circumstances studied, some non-uniformity of results would be expected" (IARC 1997, p. 208). IARC also noted that some studies demonstrated increasing risk gradients (positive exposure-response trends) in relation to cumulative silica exposure, duration of exposure, and/or radiographic-diagnosed silicosis, and that "… these observed associations could not be explained by confounding or other biases" (IARC, 1997, p. 208).

IARC's 1997 lung cancer review included many occupational and case-control studies within many industrial sectors. In four of these industrial sectors, IARC identified nine occupational studies considered to be the least confounded or biased. These four industrial sectors and the nine study cohorts were:

1. Stone Quarrying and Granite Works (three studies)
    --Danish stone industry workers;
    --Vermont granite shed and quarry workers;
    --U.S. crushed stone industry workers;
2. Metal Ore Mining (one study)
    --U.S. gold miners;
3. Ceramics, Pottery and Refractory Material (four studies)
    --United Kingdom pottery workers;
    --Chinese pottery workers;
    --Chinese refractory brick workers;
    --Italian refractory brick workers;
4. Diatomaceous Earth (one study)
    --U.S. diatomaceous earth workers.

No foundry studies were selected as the least confounded studies by the IARC panel, because foundry workers are generally exposed to multiple occupational carcinogens, (e.g., PAHs, aromatic amines and metals).

Relying largely on the same information as IARC, the U.S. National Toxicology Program (NTP) also concluded that respirable crystalline silica is a known human carcinogen (NTP, 2000). The National Institute for Occupational Safety and Health (NIOSH) (2002) also reviewed the health effects of occupational exposure to respirable crystalline silica and stated "NIOSH has reviewed the studies considered by IARC and American Thoracic Society (ATS), and NIOSH concurs with the conclusions of IARC (1997) and ATS (1997)."

Since the IARC panel review, a number of the studies initially reviewed by IARC have been updated with the benefit of additional mortality follow-up, or IARC has supplemented the original research by conducting a nested case-control study, or improving upon the quantification and analysis of exposure data. Also, new research has been conducted in other industrial sectors, including the industrial sand industry, the silicon carbide industry, and the construction industry.

OSHA has made every attempt to be as inclusive in its review of the literature pertaining to health effects associated with silica exposure as possible. In this section, OSHA presents its review of epidemiologic studies, including those contained in IARC and NIOSH reviews. To identify relevant literature published subsequent to these reviews, OSHA conducted literature searches and relied on other published reviews. The most comprehensive and thorough of these were by Steenland et al. (2001a), Mannetje et al. (2002a, b), Birk et al. (2003), HSE (2003) and Pelucchi et al. (2006). OSHA reviewed other seminal papers including: Finkelstein (2000), McDonald et al., (2001), Checkoway and Franzblau (2000), Hessel et al. (1990, 2000), Soutar et al. (2000), Steenland (2005b), and Stayner (2007). In addition, OSHA has evaluated selected studies and six meta-analyses that investigated lung cancer mortality among workers who developed silicosis. OSHA's review also includes the pooled multi-center analyses conducted by Steenland et al. (2001a), and Mannejte et al. (2002a), a pooled, multi-centered European Union case-control study (Cassidy et al., 2007), as well as two large national registry studies (Calvert et al., 2003; Pukkala et al., 2005). Table I-11 lists approximately 60 epidemiological that have been reviewed by OSHA. This table summarizes the design, properties, and findings from the studies presented in this health effects section, and is organized by industrial sector, cohort or study population, author(s), and year of publication. This literature base reflects the study of more than 30 occupational cohorts in a wide range of industries.

OSHA's evaluation of the cancer literature reflects a weight-of-evidence approach where studies are given greater weight and consideration when they include a robust number of workers in the study population; have adequate length of follow-up since onset of exposure; have sufficient power to detect modest increases in lung cancer incidence and mortality; use quantitative exposure data of sufficient quality to minimize serious misclassification of exposure; evaluate exposure-response relationships between exposure to silica and lung cancer; and consider confounding factors including smoking and exposure to other carcinogens. The studies meeting these criteria were considered to be most reliable for evaluating whether exposure to crystalline silica increases the risk of lung cancer. Where studies provided adequate data on exposures and lung cancer response, they were further examined in the quantitative risk assessment detailed in Section II (Preliminary Quantitative Risk Assessment).

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
Granite and stone quarrying and processing						
Danish stone workers	Cohort study of incident cases in Danish registries. N = 2,071 (1,081 stonecutters, 990 unskilled workers)	Mass concentration of respirable crystalline silica and particle count taken between 1948 and 1980: median exposures 0.16mg/m^3 for road material industry; 0.05mg/m^3 for stone cutting industry; 0.26mg/m^3 for stone crushing industry	44 cases among stone cutters, 24 among unskilled workers	SIR 2.00 (CI 1.49-2.69) for stonecutters, 1.81 (CI 1.16-2.70) for unskilled; SIR for highest subgroup of stonecutters was 8.08 (CI 1.16-2.70)	Smoking data not available. Stone workers not exposed to other carcinogens.	Guénel et al., 1989a, 1989b
U.S. (Vermont) granite shed and quarry workers –	Proportional mortality study. N = 969, 1 yr. min. employment from 1952-1978.	From 1924-1966, particle counts of respirable particles with conversion to mass: 0.075mg/m^3 per mppcf. From 1970-1976, mass concentration of respirable crystalline silica.	62	PMR 120 (90-105)	PMR increased with cumulative exposure for silicosis and TB, but not for lung cancer.	Davis et al., 1983
	Cohort study. N = 5,414 employed at least 1 year between 1950 and 1982.	Exposure data not used in analysis.	53 deaths among those hired before 1930; 43 deaths among those hired after 1940.	SMR 129 for pre-1930 hires (not stat. sig.); SMR 95 for post-1940 hires (not stat. sig). SMR 181 (stat. sig) for shed workers hired before 1930 and with long tenure and latency.	Dust controls employed between 1938 and 1940 with continuing improvement afterwards.	Costello and Graham, 1988

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
	Cohort study (update of Costello and Graham, 1988). N = 5,414 employed at least 1 year between 1950 and 1982. Followed through 1996.	Exposure data not used in analysis.	91 deaths among those hired before 1940; 120 deaths among those hired after 1940.	SMR 118 overall (stat.sig.). SMR 126 for pre-1940 hires (stat. sig.). SMR 113 for post-1940 hires (not stat. sig.). SMRs stat. sig. elevated for both pre- and post-1940 shed worker hires.	Higher SMRs for workers who smoking habits could be confirmed. SMRs were elevated for silicosis and TB, but most deaths occurred among pre-1940 hires.	Graham et al., 2004
	Cohort study. N = 5,414 employed at least 1 year between 1950 and 1982. Followed through 1994.	From 1924-1966, particle counts of respirable particles with conversion to mass: 0.075mg/m^3 per mppcf. From 1970-1976, mass concentration of respirable crystalline silica. Mean cumulative exposure was 2.1 mg/m^3-yrs (SD = 3.8).	201 overall	SMR 117 ($p < 0.05$) overall. SMRs were 77, 98, 126, 125, 133, 147, 170, and 116 respectively for increasing exposure groups.	Found a positive exposure-response relationship based on Poisson regression.	Attfield and Costello, 2004
U.S. crushed stone	Cohort study. N = 3,246, employed at least 1 year between 1940-1980. Follow-up from 1979-1981.	Geometric mean concentration of respirable particles (α-Quartz component): 0.6mg/m^3 for granite operations, 0.4 mg/m^3 for trapwork and limestone operations.	51	SMR 129 (CI 96-170) overall. SMR 150 (CI 95-225) for limestone workers and 335 (CI 134-690) for granite workers.	Not exposed to other carcinogens. Only counted deaths where work histories could be confirmed.	Costello et al., 1995

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
Finnish granite workers	Cohort and nested case-control studies. N = 1,026, follow up from 1972-1981, extended to 1985 (Koskella et al., 1990) and 1989 (Koskella et al., 1994).	Personal sampling data collected from 1970-1972 included total and respirable dust and respirable silica sampling. Average silica concentrations ranged form 0.3-4.9 mg/m^3.	31 through 1989.	Through 1989, SMR 140 (CI 98-193). For workers in two regions where silica content of rock was highest, SMRs were 126 (CI 71-208) and 211 (CI 120-342), respectively.	Smoking habits similar to other Finnish occupational groups. Minimal work-related exposures to other carcinogens.	Koskela et al., 1987, 1990, 1994
Refractory brick industry						
Chinese refractory brick workers	Cohort study N = 6,266 workers employed before 1962. Follow up through 1985.	No exposure data presented.	610	SRR 1.49 ($p < 0.01$) overall and 2.10 ($p < 0.01$) for silicotics.	No statistically significant excess cancer risk among non-silicotics.	Dong et al., 1995
	Case-control study. Cases worked 10 years or more and were diagnosed between 1987-1993.	No exposure data presented.	40	OR 2.9 (CI 1.4-5.9) for workers with 15 or more years of work.	Possible confounding by asbestos exposure.	Xu et al., 1996b
Italian refractory brick workers	Cohort study. N = 231 workers employed as of Jan. 1 1960. Follow up through 1979.	No exposure data presented.	11	SMR 183 (CI 91-327)	No asbestos exposure; PAH levels were considered to be minimal.	Puntoni et al., 1988

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
	Cohort study. N = 1,022 workers employed at least 6 months between 1954-1977 (included population studied by Puntoni et al., 1988). Follow up through 1986.	No exposure data presented.	28	SMR 151 (CI 100-218) overall. SMR 177 (CI 103-284) among workers hired prior to introduction of dust controls; SMR 123 (61-220) among workers hired afterwards.	No asbestos exposure; PAH levels were considered to be minimal.	Merlo et al., 1991
Gold mining						
South African (white) gold miners	Case-control study. N = 133 cases selected between Jan. 1979 and Oct. 1983. Two controls per case.	Occupations grouped into four levels of dustiness.	133	No association with silica exposure index, duration of employment, or number of shifts worked in high dust.	ORs for lung cancer and silicosis declined with increasing exposure to dust.	Hessel et al., 1986
	Case-control study. N = 231 lung cancer deaths, 318 controls that died between 1975 and 1986.	Same as Hessel et al., 1986.	231	Reported no difference in cumulative exposure, intensity of exposure, number of shifts worked, or number of shifts in high-dust jobs between case control and cancer deaths	Odds ratio was adjusted for smoking. Authors found no association between exposure to silica, silicosis and lung cancer.	Hessel et al., 1990

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
	Cohort and case-referent study. N = 3,971 white miners employed at start of 1970. Followed for 9 years.	Cumulative dust exposures	530	SMR 161 (CI 115-220) overall. From case-referent study, RR of 1.14 (CI 0.63-2.05) per 10 years employment underground and 1.77 (CI 0.94-5.31) per 10 particle-years underground exposure.	RR estimates from case-referent study adjusted for smoking.	Wyndham et al., 1986
	Cohort and nested case-control study. N = 4,925 white male miners employed at start of 1970. Followed through 1989. Two controls per case.	Particle count data converted to respirable dust mass (Beadle and Bradley, 1970, and Page-Shipp and Harris, 1972). Average cumulative exposure of subjects in case-control study was 3.7 mg/m^3-yrs respirable dust.	143 deaths observed in cohort. 159 cases selected for case-control study.	SMR 139.8 (CI 117.8-164.6) overall. Case-control study showed no relationship between lung cancer and dust exposure.	Smoking history included in model. Authors concluded that risk factors such as unhealthy life-style contributed to excess risk as well as silica exposure.	Reid and Sluis-Cremer, 1996
	Cohort study. N = 2,209 white male miners employed between 1936 and 1943. Followed from 1968-1986.	Particle count data from Beadle (1971).	77	RR 1.023 (CI 1.005-1.042) per 1,000 particle-years of exposure based on Cox proportional hazards model.	Model adjusted for smoking and year of birth. Lung cancer was associated with silicosis of the hilar glands not silicosis of lung or pleura. Possible confounding by radon exposure among miners with 20 or more years experience.	Hnizdo and Sluis-Cremer, 1991

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
	Nested case-control study from population study by Hnizdo and Sluis-Cremer,1991. N = 78 cases, 386 controls.	Particle count data converted to respirable dust mass (Beadle and Bradley, 1970, and Page-Shipp and Harris, 1972).	78	RR 2.45 (CI 1.2-5.2) when silicosis was included in model.	Lung cancer mortality associated with smoking, cumulative dust exposure, and duration of underground work. Latter two factors were most significantly associated with lung cancer with exposure lagged 20 years.	Hnizdo et al., 1997
Western Australia gold miners -	Cohort study. N = 1,974 miners that participated in medical surveys in 1960 and 1961. Follow up through 1975.	No exposure assessment conducted.	59	O/E ratio 1.4 ($p < 0.01$) overall. RR 1.41 (CI 0.069-2.96): comparing below-ground workers to above-ground workers	Arsenic and radon exposures were well-below levels associated with cancer risk. Observed interaction between smoking and duration of underground exposure.	Armstrong et al., 1979
	Cohort and nested case-control study. N = 2,297, follow up of Armstrong et al. (1979). Follow up through 1993.	Expert ranking of dustiness by job.	Nested case control of 138 lung cancer deaths	SMR 126 (CI 107-159) lower bound; SMR 149 (CI 126-176) upper bound. From case-control, RR 1.31 (CI 1.10-1.7) per unit exposure score.	Association between exposure and lung cancer mortality not stat. sig. after adjusting for smoking, bronchitis, and silicosis. Authors concluded lung cancer restricted to miners who received compensation for silicosis.	de Klerk and Musk, 1998

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
U.S. gold miners	Cohort study. N = 440 miners employed at least 5 years. Follow up from 1960 to 1973.	Exposures assessed by particle count and quartz analysis of airborne and settled dust. Exposures deemed to be below the OSHA standard.		SMR 370 ($p < 0.01$) for pulmonary malignancies	Arsenic, chromium and nickel were present in trace amounts. Authors believed cancer excess related to exposure to asbestos-like fibers.	Gillam et al., 1976
	Cohort study, extension of GIllam et al. (1976). N = 3,328 workers followed through 1977.	Same as above	43	No excess lung cancer mortality reported.		Brown et al., 1986
	Cohort and nested case-control study, same population as Brown et al. (1986); workers with at least 1 year underground work between 1940 and 1965. Follow up through 1990.	Particle count data, conversion to mass concentration based on Vt. Granite study, construction of JEM. Median quartz exposures were 0.15, 0.07, and 0.02 mg/m^3 prior to 1930, from 1930-1950, and after 1950 respectively.	115	SMR 113 (CI 94-136) overall. SMRs increased for workers with 30 or more years of latency, and when local cancer rates used as referents. Case-control study showed no relationship of risk to cumulative exposure to dust.	Smoking data available for part of cohort, habits comparable to general US population; attributable smoking-related cancer risk estimated to be 1.07.	Steenland and Brown, 1995a, 1995b

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
Other Mining						
Chinese Tin, Tungsten, and Copper miners	Cohort study. N = 54,522 workers employed 1 yr. or more between 1972 and 1974. Follow up through 1989.	Measurements for total dust, quartz content, and particle size taken from 1950's-1980's. Exposures categorized as high, medium, low, or non-exposed.		SMRs 198 for tin workers (no CI reported but stat. sig.). No stat. sig. increased SMR for tungsten or copper miners.	Non-statistically significantly increased risk ratio for lung cancer among silicotics. No increased gradient in risk observed with exposure.	Chen et al., 1992
	Nested case-control study. Same population as Chen et al., 1992.	JEM based on total dust sample data and quartz content of settled dust (Dosemeci et al., 1993).	87 among tin miners, 93, among tungsten miners	OR 1.5, 1.9, 3.1 for low, medium, and high-exposure groups, respectively (p for trend = 0.004)	Correction for smoking did not influence observed trend with silica exposure.	McLaughlin et al., 1992
	Same as above, examination of interactions with other carcinogens and silicosis.	Same as above.		OR for lung cancer increased with severity of silicosis, OR of 1.4 (CI 1.1-2.0) overall. Cancer risk not increased with increasing exposure.	Cancer risk among silica-exposed more evident absent exposure to nickel, radon, and PAH's. No influence observed from arsenic or cadmium.	Cocco et al., 2001

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
	Nested case-control study. N = 7,855 tin miners included in McLaughlin et al., 1992. Followed through 1994.	Total dust measurements and quartz content of settled dust. Conversion to respirable crystalline silica measures based on side-by-side sampling (Zhuang et al., 2001)	130 lung cancer cases (627 controls)	Strong positive exposure-response trend with total dust and arsenic exposure.	No excess of lung cancer among workers in mine where arsenic concentrations were lowest, despite high prevalence of silicosis. Authors concluded arsenic and smoking were most important factors for lung cancer risk.	Chen and Chen, 2002
	Cohort study. Same tin miner population as in Chen et al., 1992. Follow up through 1994	Total dust measurements and quartz content of settled dust. Conversion to respirable crystalline silica measures based on side-by-side sampling (Zhuang et al., 2001)	138	SMR 249 (CI 209-294) overall. RR 3.55 ($p < 0.01$) for exposed miners compared to unexposed.	Lung cancer mortality increased with increasing cumulative total dust exposure and cumulative respirable silica exposure. Role of arsenic could not be ascertained.	Chen et al., 2006
British Coal workers	Cohort study. N = 17,820 miners from 10 colliaries.	Quartz exposure assessed from personal respirable dust samples.	973	Significant relationship between cumulative silica exposure (lagged 15 years) and lung cancer mortality VIA Cox regression.	Adjusted for smoking.	Miller et al, 2007; Miller and MacCalman, 2009

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
Industrial sand industry						
North American industrial sand workers	Cohort and nested case-control study. N = 4,626 workers. Follow up from 1960-1996.	Exposure assessment based on 4,269 compliance dust samples taken from 1974-1996 and analyzed for respirable quartz. Exposures prior to 1974 based on particle count data and quartz analysis of settled dust and dust collected by high-volume air samplers, and use of a conversion factor (1 mppcf = 0.1 mg/m^3).	109 deaths overall.	SMR 160 (CI 131-193) overall. Positive trends seen with cumulative silica exposure (p = 0.04 for unlagged, p = 0.08 for lagged).	Smoking data from 358 workers suggested that smoking could not explain the observed increase in lung cancer mortality rates.	Steenland and Sanderson, 2001
	Cohort study. N = 2,670 workers employed for 3 years or more prior to 1980 (overlaps with Steenland and Sanderson (2001) cohort). Followed through 1994.	Exposure assessment not utilized.	83	SMR 150 (p = 0.001) for deaths occurring 20 years or more from hire, based on U.S. rates. SMR 139 (p = 0.001) based on regional rates.	Observed excess due to 4 plants in two states, no excess lung cancer seen in plants in three other states or in Quebec.	McDonald et al., 2001

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
	Case-control study from McDonald et al. (2001) cohort.	Assessment based on 14,249 respirable dust and silica samples taken from 1974 to 1998. Exposures prior to this based on particle count data. Adjustments made for respirator use (Rando et al., 2001).	95 cases, two controls per case.	OR 1.00, 0.84, 2.02 and 2.07 for increasing quartiles of exposure p for trend = 0.04).	Adjusted for smoking. Positive association between silica exposure and lung cancer. Median exposure for cases and controls were 0.148 and 0.110 mg/m^3 respirable silica, respectively.	Hughes et al., 2001
	Cohort and nested case-control study. Follow up of McDonald et al., 2001 cohort (minus Canadian workers) through 2000.		102 deaths overall in cohort.	SMR 147 (p = 0.001) overall for workers who died 20 or more years after hire. From case-control, ORs of 1.00, 0.94, 2.24, and 2.66 for increasing quartiles of (lagged) exposure (p for trend = 0.006)	Exposure-response analysis adjusted for smoking. Lung cancer was related to average silica concentration but not duration of employment.	McDonald et al., 2005
United Kingdom industrial sand workers	Cohort study. N = 2,703 workers employed at least one year between 1950 and 1986. Follow up through 2001.	Assessment based on 2,429 personal and 583 area samples analyzed for respirable dust and silica. Earlier exposures estimated by linear extrapolation. GM of exposures was 0.09 mg/m^3 respirable silica.		No association between cumulative silica exposure and lung cancer.	No smoking data available. Mean cumulative exposure of cohort was 0.31 mg/m^3-yrs. Over half of cohort deaths had less than 10 years service.	Brown and Rushton, 2005a, 2005b

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
Pottery industry						
United Kingdom pottery workers	Cohort study. N = 3,669 workers under age 60 and employed in 1970-1971. Follow up through 1985.	Mean exposures to respirable quartz were 0.01mg/m^3 – 0.2mg/m^3.	60	SMR 140 (CI 107-180) nationally adjusted rate; and SMR 132 (CI 100-169) locally adjusted rate	Found increasing SMR with increasing quartile of cumulative exposure and with duration of employment. Smoking information available.	Winter et al., 1990
	Proportionate mortality study. N = 7,020 workers born between 1916 and 1945. Follow up to June 30, 1992.			PMR 124 (CI 106-144); PMR 122 (CI 104-143) after exclusion of asbestos exposure	Asbestos as confounding factor, but adjusted for in analysis. 70 percent of deaths came from one town with high background rate of lung cancer.	McDonald et al., 1995
	Cohort and nested case-control study. N = 5,115 workers first employed between 1929-1982.	Assessment based on >1,000 personal air samples for respirable dust taken from late 1960's to 1992. Also used particle count data from 1950 to the 1960's. JEM included 569 jobs in 11 job processes; used to estimate maximum, cumulative, and average lifetime exposures to respirable crystalline silica.	52 lung cancer cases were included (excluded 36 cases)	SMR 191 (CI 148-242) based on national rates, SMR 128 (CI 99-162) based on local rates.	Smoking-adjusted ORs were elevated (stat. sig.) for mean concentration of silica, but not for cumulative exposure nor duration of employment.	Cherry et al., 1998

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
Chinese pottery workers	Cohort study. N = 13,719 workers employed in 1972-1974. Follow up through 1989.	Measurements of job-specific total dust and quartz content of settled dust used to classify workers into one of four total dust exposure groups.		SMR 58 ($p < 0.05$) overall. RR 1.63 (CI 0.8-3.4) among silicotics compared to non-silicotics.	No reported increase in lung cancer with increasing exposure.	Chen et al., 1992,
	Nested case-control study. N = 62 cases from Chen et al. (1992) cohort.	Assessment based on total dust area measurements taken from 1950 to 1987, and estimates of percent respirable dust and quartz content (Dosemeci et al. 1993).		OR 1.0, 1.8, 1.5, and 2.1 with increasing cumulative exposure (not stat. sig.).	ORs adjusted for smoking. Authors found positive but inconsistent trends of lung cancer risk with exposure.	McLaughlin et al., 1992
Dutch ceramic workers	N = 1,794 workers employed in 1972-1986 and who worked more than two years. Follow up to 1991.	No quantitative exposure data: used qualitative categories of exposure based on job description.	30	SMR = 88	161 deaths total in cohort (9 percent of cohort). Stat. sig. excess of lung cancer among those with simple pneumoconiosis.	Meijers et al., 1996
German stone, quarry and ceramic workers case-control study	Population-based case-control study. Cases diagnosed between 1980 and 1994. N = 133 cases vs. 231 controls (stone quarry); 114 cases vs 564 controls (ceramic)	Exposures classified as either above or below the then-German MAK (0.15 mg/m^3 respirable silica) based on available exposure measurements and professional judgment. Cristobalite exposure in ceramics industry not assessed.		No exposure-related trends with lung cancer observed.	All controls selected from silica-exposed populations; cases and controls with silicosis were eliminated.	Ulm et al., 1999

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
Diatomaceous earth industry						
U.S. Diatomaceous earth workers	Cohort study. N = 2,570 workers employed at least 1 year between 1942 and 1987.	Exposures were to cristobalite. Semi-quantitative assessment based on exposure measurement records, review of process history, interview of employees. Adjusted to account for increased respirator use after 1950.	59	SMR 143 (CI 109-184); RR = 2.88 (CI 1.13-7.33) for workers with 20 or more years experience compared to low-exposed referent group.	RR increased for increasing exposure groups. Incomplete smoking data available but analysis of potential effect of smoking could not explain observed excess lung cancer mortality. Asbestos a potential confounding factor.	Checkoway et al., 1993
	Cohort study, re-analysis of previous study. N = 2,266 workers from 1 plant for whom quantitative exposure estimates could be derived.	Included quantitative assessment of silica and asbestos exposures.	52	SMR 141 (CI 105-185). RR for increasing categories of silica exposure were 1.00, 1.37, 1.80, and 1.79 (15-year lag).	ORs adjusted for cumulative asbestos exposure.	Checkoway et al., 1996

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
	Cohort study. Same as Checkoway et al., 1993, excluding 317 workers whose exposures could not be characterized, and including 89 workers with asbestos exposure who were previously excluded from the 1993 study. Follow up through 1994.	Assessment based on almost 6,400 samples taken from 1948-1988; about 57 percent of samples represented particle counts, 17 percent were personal respirable dust samples. JEM included 135 jobs over 4 time periods (Seixas et al., 1997)	77	SMR 129 (CI 101-161) based on national rates, and SMR 144 (CI 114-180) based on local rates. Risk ratios by exposure quintile were 1.00, 0.96, 0.77, 1.26, and 2.15, with the latter being stat. sig. RR = 2.15 and 1.67	Smoking history available for half cohort. Under worst-case assumptions, the risk ratio for the high-exposure group would be reduced to 1.67 after accounting for smoking.	Checkoway et al., 1997
	Cohort study. N = 1,809 workers selected from the 1993 study for whom chest x-ray films were available.	Same as above.		SMR 157 (CI 43-403) for silicotics compared to non-silicotics. Non-silicotics had increasing cancer mortality with increasing cumulative silica exposure (p for trend = 0.02).		Checkoway et al., 1999

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
Foundry industry						
Danish foundry workers	Cohort study. N = 6,144 workers participating in silicosis surveillance program in 1967-1969 and 1972-1974. Follow up through 1985.	No quantitative exposure data; used years employment as proxy for exposure.	166 cases diagnosed.	SIR 1.30 (CI 1.12-1.51). Upward trend in SIR with increasing employment duration.	Other confounders not addressed in study.	Sherson et al., 1991
U.S. (Michigan) foundry workers	Cohort and case-control studies. N = 5,337 white males; 2,810 non-white males; 627 females. Workers employed at least 6 months from 1950 to 1979. Follow up through 1984 and 1989.	Silica exposure index created from available exposure data.	220 deaths in case-control study; 2,220 controls.	SMR 1.23 (CI 0.96-1.54) for whites; SMR 1.32 (CI 1.02-1.67) for non-whites (1984 follow up). ORs decreased with increasing exposure quartile.	Other confounders were disclosed but not adjusted for in study.	Andjelkovich et al., 1990, 1992, 1994

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
Chinese iron and steel workers	Case control study. All lung cancer deaths occurring between 1980 and 1989 among workers in industry.	Cumulative exposure to total silica dust.	610 deaths, 610 controls	OR 1.8 (CI 1.1-2.8) among foundry workers. Modest increasing trend in OR with cumulative silica exposure among steel workers (p for trend = 0.007).	Lung cancer among foundry workers increased with benzo(a)pyrene exposure.	Xu et al., 1996b (case-control)
Swedish aluminum foundry workers	Nested case-control study. N = 5,016 workers. Study used 31 cases and 233 controls.	Used cross-sectional exposure data; used "correction" factors to estimate respirable crystalline silica levels.	46 deaths in cohort.	No statistically significant trend with exposure.	No smoking data provided.	Westberg and Bellander, 2003
Silicon carbide industry						
Norwegian silica carbide workers -	Cohort study. N = 2,620 workers with at least 6 months in one of three plants. Follow up started from the latter of 1953 or after 6 months of employment, through 1966.	Combination of particle count, total dust, and respirable silica measurements. Constructed JEM for all plants.	74 lung cancer cases total.	SIR 1.9 (CI 1.5-2.3)	Exposures were to silica, cristobalite, silica fibers, PAHs; possibly asbestos. Exposures to various dusts highly correlated. Poisson analysis indicated that SiC fiber exposure was a stronger predictor of lung cancer incidence.	Romundstad et al., 2001

Table I-11. Summary of Cancer Studies

Industry Sector/Population	Type of Study and Description of Population	Exposure Characterization	No. of Lung Cancer Deaths/ Cases	Risk Ratios (95% CI)	Additional Information	Source
Canadian silica carbide workers -	Cohort study. N = 585 workers employed at any time from 1950-1980. Follow up through 1989.	Limited to total dust measurements.	24	SMR 169 (CI 109-252)	Co-exposures to other carcinogens.	Infante-Rivard et al., 1994
Construction and building materials						
Finnish road paving and asphalt workers	Cohort study. N = 5,676 workers employed at least 6 months before 1985. Follow up from 1964-1994.	Used IARC protocol to estimate exposures and construct JEM; respirable quartz data available.		SMR 145 (CI 103-198) for asphalt workers and SMR 139 (CI 103-184) among building/ground construction workers.	Exposure to silica showed non-stat. sig. trend for lung cancer.	Kauppinen et al., 2003
Canadian Bricklayers	Cohort study. N = 10,953 union members followed from 1950 through 1993.	No exposure data available; used proxy data (length of employment or union membership).	100	SMR 162 for workers with 20-29 years experience; SMR 150 for workers with 30+ years experience.	Possible exposures to hexavalent chromium and asbestos.	Finkelstein and Verma, 2005

I.C.2. Evaluation of Cohort Studies.

I.C.2.a. Danish stone industry workers.

This was a cohort study of 2,175 Danish stone workers who met the following criteria: 1) they were alive on or after January 1, 1943; and 2) they were less than 65 years old at the time they were first identified from one of the six data sources used. Ninety-five percent of the initial cohort was successfully traced, resulting in a total of 2,071 stone workers included in the study (Guénel et al., 1989b). The cohort was comprised of two separate populations, including 1,081 skilled stonecutters (carving tombstones and ornamental building materials) dispersed throughout Denmark in smaller shops, and 990 unskilled workers (581 in the road materials industry from one company and 409 in the stone cutting industry). The skilled stonecutters typically remained in their trade for many years and tended to have lower exposures to crystalline silica, as opposed to the unskilled workers who predominated in the road and building materials industry. The analysis of cancer incidence in the study was carried out separately for the skilled and unskilled workers because of the differences in work tasks and length of employment (Guénel et al., 1989b).

Exposures to silica dust among workers in the stonecutting and stone road building industries were assessed from data collected between 1948 and 1980, which was available in the archives of the Danish National Institute of Occupational Health. Details of exposure data summarizing current and historical measurements appeared in a separate paper (Guénel et al., 1989a). There were a total of 197 measurements, of which 108 were mass measurements (mg/m^3) and 87 were by particle count (particles/cm^3). Most measurements (163) were taken from three operations in the road material and building industry (crushing, sieving, and drilling), while only 34 measurements were taken from two operations in the stonecutting industry (hand cutting and surface finishing). The median respirable silica exposure in the road material industry was 0.16 mg/$m^{3,}$ with 70 percent exceeding 0.10 mg/m^3. Respirable silica exposure in the stonecutting industry was more moderate, with a median exposure of 0.05 mg /m^3 and 45 percent exceeding 0.10 mg/m^3. Crushing was associated with the highest median respirable silica exposure (0.26 mg/m^3), while the lowest median exposure level was found for cutting operations (0.05 mg/m^3). Median exposures for workers engaged in sieving and drilling were 0.1 and 0.09 mg/m^3, respectively (Guénel et al., 1989a).

Smoking data were not available for the cohort. The expected numbers of lung cancer cases were based on the Danish national incidence rates for men, after adjustment for region. A total of 44 lung cancer cases were observed for the cohort of skilled workers and 24 lung cancer cases for the cohort of unskilled workers. The standardized incidence ratio (SIR) for lung cancer was 2.00 (95% Confidence Interval (CI) 1.49-2.69) for all skilled stone workers, and 1.81 (95% CI 1.16-2.70) for all unskilled stone workers. The highest SIRs were observed for the subgroups of skilled sandstone cutters (SIR = 8.08; 95% CI 3.23-16.16) and skilled granite stone cutters (SIR = 4.04; 95% CI 2.02-23.0) from Copenhagen (Guénel et al., 1989b). The authors noted that the excess risk of lung cancer among the Copenhagen stone cutters was higher for those workers hired

before 1940, prior to improvements in ventilation, but there was no detailed information provided on the relationship between incidence and magnitude or duration of exposure. Based on observing a lower-than-expected incidence of bladder cancer among the workers, the investigators concluded that smoking alone was unlikely to explain the excess risk of lung cancer. They also commented that stone workers in this study had not been exposed to other known lung carcinogens in the workplace and therefore believed that the results of the study suggested a relationship between exposure to crystalline silica and increased lung cancer mortality (Guénel et al., 1989b).

I.C.2.b. U.S. granite shed and quarry workers.

Vermont granite shed and quarry workers have been studied extensively since recognition in the 1930's of high silicosis and TB rates among them. The silica content in respirable dust was approximately 9 percent (Theriault et al., 1974a), and granite rock contained approximately 30 percent crystalline silica or quartz. Davis et al. (1983) were among the first researchers to investigate the possible association between silica exposure and lung cancer mortality.

Measurement of airborne concentrations took place from 1924 to 1977, including six surveys. Those measurements taken from 1970 to 1976 were of respirable dust and silica, analyzed by gravimetric analysis and XRD and/or infrared spectrometry (IR), respectively. The previous four surveys, conducted from 1924 to 1966, were particle count measurements collected by using either standard or midget impingers, with quartz analysis by petrographic, colorimetric or XRD techniques (Davis et al., 1983; Theriault et al., 1974a). Exposure measurements made in 1965-1966 and again in 1972 comparing particle count measurements to respirable mass sampling, with analysis for silica by XRD and IR, provided an empirical basis for converting particle count to respirable dust mass and respirable quartz percentage of the dust (Ayer et al., 1973). In Davis et al. (1983), respirable mass measures were converted to particle counts by comparing matched pairs of particle count and respirable mass measurements taken concurrently. Results of these two experiments, combined with measurements of the percent crystalline silica in the samples, yielded the following relationship: 10 mppcf = 0.075 mg/m^3 respirable silica.

The Davis et al. (1983) study was a proportional mortality study of 969 deceased white male granite workers employed in granite quarries and sheds, who worked 1 year or more from 1952 through July, 1978. Davis et al. (1983) observed 28 deaths due to silicosis (vs. none expected), 65 deaths due to tuberculosis (vs. 6.5 expected), 22 deaths from emphysema (vs. 16.9 expected), and 62 deaths of lung cancer (vs. 52.6 expected). The proportionate mortality ratios (PMRs) for all of these causes of death were statistically significantly elevated, except for lung cancer (PMR = 120, 95% CI 90-105). When subjects were grouped into quartiles by cumulative exposure to respirable silica (identified as low, medium, high, and very high), PMRs for silicosis and tuberculosis increased with increasing exposure, but PMRs for other causes of death, including lung cancer, did not. All but one of the deaths from silicosis and all deaths from tuberculosis occurred among workers who had started work before dust controls began to be implemented in the late 1930's, after which exposure was significantly reduced. In

summary, this study did not find a consistent association between respirable silica exposure and lung cancer.

Costello and Graham (1988) conducted a cohort mortality study of 5,414 Vermont granite workers (1,527 death certificates traced) employed between 1950 and 1982 to evaluate the relationship between silica exposure and lung cancer mortality. This was an improvement over the Davis et al. (1983) study of this population since death rates were evaluated longitudinally, and because the number of deaths in the cohort had increased by 558 since the Davis et al. study. There was limited discussion of exposure measurements, but exposure data were not used in the analysis. Cohort mortality was compared with white male U.S. population rates. The standardized mortality ratios (SMR) for all workers for silicosis and tuberculosis were significantly elevated (SMR = 636 and 586, respectively) and the SMR for shed workers was approximately twice that for quarry workers, reflecting the generally higher exposures to respirable quartz experienced by shed workers. There was a limited amount of smoking data.

Dust controls were developed and introduced into the industry between 1938 and 1940, with continuing improvement in dust control such that exposures to silica were reduced approximately ten-fold in the mid-1950's (Theriault et al., 1974a). These quasi-experimental conditions allowed separation of workers into groups having higher or lower exposures. As expected, the standardized mortality for silicosis and tuberculosis was significantly elevated for workers hired before 1930; the SMR for tuberculosis was 893.9 (116 deaths) and the SMR for silicosis was 999.0 (36 deaths). For workers hired after 1940, the SMRs for tuberculosis and silicosis were 60 and 94, respectively, suggesting the efficacy of controls (as well as population-wide measures to reduce mortality from tuberculosis).

The SMR for lung cancer among workers hired before 1930 was also elevated with an SMR of 129 (53 deaths) but was not statistically significant. For workers hired after 1940, the SMR for lung cancer was 95 (43 deaths). Additional analysis of SMR for lung cancer for workers classified by latency and tenure revealed a statistically significant excess number of deaths for shed workers with more than 30 years tenure and more than 40 years latency (SMR = 181; 47 deaths) and for shed workers with 10-29 years tenure and 25-39 years latency (SMR = 164; 21 deaths). These workers had been hired before 1930 (thus experiencing high exposure to silica), and all 84 workers (of 118) whose smoking habits could be determined, had been smokers. The authors concluded that these findings suggest "that granite dust exposure does not act as a carcinogen by itself" (Costello and Graham, 1988).

Graham et al. updated this study in 2004 based on 2,436 deaths among cohort members (vs. 1,527 in the 1988 report). The study design was similar to that of the earlier one. Death rates were evaluated among workers hired both before and after 1940, which corresponded to periods before and after dust controls began to be implemented. Available exposure data was not analyzed quantitatively. SMRs for tuberculosis and silicosis were elevated for the group as a whole, but nearly all such deaths occurred among the granite workers hired before 1940. The SMR for cancer of the trachea,

bronchus, and lung for the entire group was statistically significantly elevated (SMR = 118; 211 deaths). For all granite workers hired before 1940, the SMR for lung cancer was statistically significantly elevated (SMR = 126; 91 deaths); for workers hired after 1940, the SMR was elevated but was not statistically significant (SMR = 113; 120 deaths). The SMR for lung cancer was elevated overall for shed workers (SMR = 131, 193 deaths) and was statistically significantly elevated for both shed workers hired before 1940 (SMR = 148, 95% CI 119-182, 90 deaths) and after 1940 (SMR = 124, 95% CI 102-151, 103 deaths). When comparing the lung cancer mortality experience of shed workers segregated by job tenure and latency, Graham et al. (2004) concluded that the mortality experience of shed workers hired before 1940 was similar to those hired after 1940, despite the fact that the earlier group of shed workers had been exposed to higher dust levels. The authors concluded that these "results do not support the hypothesis that granite dust exposure has a causal association with lung cancer."

Attfield and Costello (2004) analyzed the occurrence of lung cancer deaths among the same population studied by Graham et al. (2004) but used quantitative exposure data to evaluate relationships between exposure to respirable crystalline silica and lung cancer mortality. According to the authors, and as noted by IARC (1997), the previous 1998 study by Costello and Graham used proxies for exposure based on date-of -hire and job tenure, with the potential of exposure misclassification and a lessened ability to evaluate quantitative exposure response.

Airborne concentrations were measured in six surveys from 1924 to 1977. Attfield and Costello (2004) adapted the job exposure matrix (JEM) developed by Davis et al. (1983) discussed previously and classified three eras as pre-, intermediate-, and post-dust control periods for the time periods before 1940, from 1940 to 1950, and after 1950, respectively. Most of the 203 unique job and department title combinations were grouped into 13 similarly exposed job groups which represented 75 percent of the work history entries. Each job group or unique job title was assigned an exposure for one of the three time periods and linked to individual workers' employment histories to calculate cumulative exposure measured in mg/m^3-years. Particle counts were converted to respirable mass using the conversion equation reported by Davis et al. (1983), i.e., 10 mppcf = 0.75 mg/m^3.

The authors calculated SMRs and Standardized Risk Ratios (SRRs) for all causes of death using national death rates from 1940 to 1999 as the reference group. Poisson regression was used to fit various models. Details of Attfield and Costello (2004) quantitative exposure-response analysis and accompanying estimates of lung cancer risk associated with exposure to crystalline silica are provided in Section II, Preliminary Quantitative Risk Assessment.

Attfield and Costello (2004) found SMRs of 210 for pneumoconiosis including silicosis, 1288 for respiratory tuberculosis, and 141 for diseases of the respiratory system ($p < 0.01$ for all values, confidence interval or number of deaths not provided). Cumulative exposure was divided into eight exposure groups ranging from <0.25 to >6.0 mg/m^3 -years with an approximately equal number of lung cancer cases in each exposure

category. The mean cumulative exposure was 2.1 mg/m^3–years. The rates of non-malignant respiratory disease increased with increasing cumulative exposure and were statistically significant among all groups exposed to 1.0 mg/m^3–years or more for respiratory tuberculosis and among all groups exposed to 1.5 mg/m^3 –years or more for pneumoconiosis and diseases of the respiratory system.

When all silica dust exposure categories were included in the analysis for lung cancer mortality, the investigators obtained a statistically significant trend when cumulative exposure was log-transformed ($p < 0.01$), but not for untransformed exposure. For untransformed cumulative exposure, with a 15-year exposure lag, SMRs were 77, 98, 126, 125, 133, 147, 170, and 116 for the respective exposure groups of <0.25, 0.25-<0.5, 0.5-<1.0, 1.0-<1.5, 1.5-2.0, 2.0-3.0, 3.0-<6.0 and >6.0 mg/m^3-years. Lung cancer mortality was observed to rise reasonably consistently through the first seven increasing exposure groups, but fell in the highest exposure group. Attfield and Costello (2004) also conducted analyses omitting the highest cumulative exposure group (6.0 mg/m^3-years or more). With the highest exposure group omitted, a strong positive exposure-response trend was found for either untransformed or log-transformed cumulative exposure ($p < 0.005$). Attfield and Costello (2004) concluded that their quantitative analysis provided clear evidence that exposure to crystalline silica in the range of cumulative exposures experienced by the cohort increased the risk of lung cancer. The authors justified their conclusions from results that excluded the highest exposure group based on the following considerations:

- Data for the seven lower exposure groups comprised about 85 percent of the total number of deaths in the cohort and demonstrated a monotonic exposure-response relationship;

- The highest exposure group was believed to have exerted a disproportionate influence over the observed exposure-response relationship, yet the underlying exposure data for this exposure group was more likely to include unreliable exposure estimates given that 83 percent of these workers had 20 or more years of exposure before the introduction of controls, when exposure measurements were most uncertain. (The authors also noted in this highest exposed group the potential of "a highly selected healthy worker" effect and that lung cancer may have been obscured as a cause of death by competing high rates of silicosis and tuberculosis deaths.)

- Exposure levels of interest today (i.e., cumulative exposures in the range of 2 to 4 mg/m^3–years reflecting exposure to current standards and recommended exposure limits) fell within the range of the six remaining exposure groups in the cohort; and

- Estimates of risk derived from the exposure-response relationships excluding the highest exposure group were consistent with risk estimates

reported in other studies (i.e., Rice et al., 2001 for diatomaceous earth workers).

Graham (2004) questioned the appropriateness of eliminating the highest exposure group from the Attfield and Costello (2004) exposure-response analysis. He argued that trends in the SMRs for silicosis and tuberculosis validated the exposure measurements and that the absence of elevated risk for the highest exposure group weakened the claim that silica causes lung cancer. Attfield (2004) responded, explaining further that such anomalies were commonly seen in cohort studies. The authors reiterated that exposure levels of greatest concern were in the range where the exposure-response relationship was monotonic. They also referred to Stayner et al. (2003) who described several other reported instances where epidemiological studies of occupational hazards found non-monotonic exposure-response relationships resulting from an observed reduction in mortality rate among the most highly exposed workers compared to the remaining cohort members. Stayner et al. (2003) explained that this could arise because of a healthy worker effect, depletion of susceptible individuals in the population, a natural limit in the occurrence of disease with a high background rate, exposure misclassification, or other factors.

Finally, Attfield and Costello (2004), in absence of most participants' smoking data, discussed why they believed cigarette smoking was unlikely to explain the observed association of increased silica exposure and lung cancer. They argued that it was unlikely that smoking would be correlated with exposure to crystalline silica (for example, that shed workers, who were highly exposed to silica, would smoke more often than quarry workers). They also stated that there is an extensive literature on the limited capacity of smoking to cause confounding, particularly when using quantitative data and internal references for relative risk estimates as was done in their study, and they further stated that elevations in the incidence of diseases typically associated with smoking were not observed among the more highly exposed workers. Instead, non-malignant disease (bronchitis, emphysema, ischemic heart disease) mortality was higher in the quarry workers (lower exposed group) than they were in shed workers. This is the opposite of what one would expect if excess lung cancer mortality was due to smoking.

OSHA believes that the finding by Attfield and Costello (2004) of a positive exposure-response relationship for lung cancer among granite workers is more convincing than are the results from the Graham et al. (2004) study. In particular, OSHA believes it likely that some of the workers hired after 1940 continued to be exposed to dust levels that, although somewhat lower than before 1940, were still appreciably higher than those that resulted after dust controls had been fully implemented after 1950. For example, Attfield and Costello (2004) summarized respirable quartz levels for several granite shed jobs and reported that for cutter/marker/surfacer jobs, respirable quartz airborne concentrations averaged 0.37 mg/m^3 prior to 1940, 0.22 mg/m^3 between 1940 and 1950, and 0.07 mg/m^3 after 1950. Similarly, crane operators, which included shed derrickmen, were exposed to average quartz levels of 0.14 mg/m^3 before 1940, 0.09 mg/m^3 between 1940 and 1950, and 0.03 mg/m^3 after 1950. OSHA notes that in Graham et al.'s 2004 analysis, about one-fourth of the lung cancer deaths among post-1940 hires

were associated with 40 or more years of latency, indicating that these workers were, for the most part, hired between 1940 and 1950 and, therefore, had intermediate exposures. In essence, the post 1940 sub-cohort was not limited to those having among the lowest exposures; this could have contributed to the observed lack of a statistically significant difference in the mortality outcomes between the pre and post 1940 hires. Given these considerations, OSHA believes that the finding by Attfield and Costello (2004) of a positive exposure-response relationship among granite workers, which was based on a quantitative assessment of the exposure of each cohort member, provides evidence of a causal relationship between exposure to crystalline silica and lung cancer.

I.C.2.c. U.S. crushed stone industry workers.

This study is a cohort mortality study of 3,246 males employed 1 year or longer between 1940 and 1980 at 20 crushed stone operations (including limestone, granite, traprock, sandstone, marble and shale) (Costello et al., 1995). Crushed stone operations were selected from a Mine Safety and Health Administration (MSHA) listing of active establishments in 1978. Crystalline silica in the form of alpha-quartz was found to be a component of respirable dust at all operations, comprising 37 percent, 11 percent, and 15 percent by weight of the personal respirable dust samples collected at granite, limestone, and traprock operations, respectively. Geometric mean airborne concentrations of respirable silica were 0.6 mg/m^3 for granite operations and 0.4 mg/m^3 for both trapwork and limestone operations (Kullman et al., 1995). Personal work histories were obtained from the companies' personnel records. Workers were excluded from the analysis if their company records were missing, date of birth was unavailable, or did not meet the entry requirements for the cohort. Underlying cause of death was coded according to the ICD 8^{th} revision. SMRs were calculated by employing U.S. white male mortality rates for whites and U.S. nonwhite male rates for nonwhites.

The overall lung cancer SMR was not statistically significantly elevated (SMR = 129; 95% CI 96-170). The SMR for lung cancer among traprock workers was not elevated (SMR = 63; 95% CI 13-184). The overall lung cancer SMR for limestone workers was elevated, although this was not statistically significant (SMR 150; 95% CI 95-225). The overall lung cancer SMR for granite workers was elevated and, although based on a small sample size (7 deaths), was statistically significant (SMR 335, 95% CI 134-690). The workers in granite facilities with 20 or more years latency and more than 10 years of tenure had a statistically significantly elevated lung cancer SMR of 354 (95% CI 142-729). In general, the U.S. crushed stone workers were not exposed to other suspected pulmonary carcinogens (with the exception of one operation where asbestos exposure was found). Smoking data were not available for the cohort.

I.C.2.d. Finnish Granite Workers.

In this study, Koskela et al. (1987) examined lung cancer mortality in a cohort of 1,026 granite workers. Follow-up was from 1972 to 1981 with a total of 20,165 person-years of observation. The SMR for lung cancer mortality was elevated for the cohort overall (SMR = 129, 22 deaths), but the report did not state whether this increase was

statistically significant, nor was the confidence interval provided. Mortality from lung cancer was increased for workers with at least 15 years of job tenure (SMR = 221, $p < 0.01$, 21 deaths).

Airborne concentration data was available predominately from 1970 to 1972, from air sampling conducted by the Finnish Institute of Occupational Health. Most of the airborne concentration measurements were from personal sampling using a cyclone pre-selector. Airborne concentration ranges were provided for major work operations such as drilling, pneumatic hammering, rock surfacing and other activities. Airborne concentration monitoring, according to Mannetje et al. (2002a), was of total and respirable dust and respirable silica content as determined by XRD. This is a relatively small cohort with only 9 years of average exposure to relatively high silica airborne concentration levels ranging from 0.3 – 4.9 mg/m^3. The referenced exposure study was in Finnish and has not been reviewed by OSHA.

There was minimal potential confounding in this study by other occupational carcinogens. Smoking histories were obtained from relatives retrospectively and may therefore be subject to recall bias. The authors stated that smoking rates were similar to those of other occupational cohorts of a similar time period (data not provided).

Koskela et al. (1990) extended follow-up from 1981 to 1985 for a total of 13 years of follow-up. The SMR for lung cancer mortality was 156 (31 observed deaths, 95% CI 106-221) and for workers followed for at least 15 years, the SMR was 220 (28 observed deaths, 95% CI 147-319). Geometric mean quartz concentrations were reported by the authors to range from 1.0 to 1.5 mg/m^3 based on the data described by Koskela et al. (1987). Smoking and previous non-quarry occupational exposure histories were analyzed by questionnaire. Confounding due to previous exposure to other occupational carcinogens for more than 5 years was limited to only 33 workers and smoking data were obtained for 75 percent of the cohort and indicated that smoking habits were similar to other Finnish workers (Koskela et al., 1990).

Koskela et al. (1994) extended follow-up from 1981 to 1989 and conducted a case-control study of lung cancer mortality. This study also conducted a detailed assessment of the type and qualities of granite mined including the percentage of quartz content. The SMR for lung cancer mortality was 140 (31 observed deaths, 95% CI 98-193). A nested case-control for lung cancer mortality was conducted for the 31 lung cancer deaths with two referents for each case matched by age, year of entry and quality of available industrial hygiene data. Geometric mean concentration was reported by the authors as being between 1.0 to 1.5 mg/m^3. Historical airborne concentration data were reconstructed by an industrial hygienist, but details on the approach were not provided. Pairwise comparison showed that only nine cases had clearly higher exposures than did individual referents (Koskela et al., 1994). The authors examined mortality patterns by region, type of granite, and relative percentage of silica in the granite. Workers for one region that had low or no silica content in its granite rock experienced no elevated lung cancer mortality rates. For workers in other regions the risk of lung cancer mortality reflected workers' estimated silica exposures. In the Vehma and Kuru regions, where

native rock contains a high percentage of silica, SMRs for lung cancer mortality were 126 (CI 71-208) and 211 (CI 120-342), respectively (Koskela et al., 1994, Table 4).

The studies conducted by Koskela et al. (1987, 1990, and 1994) demonstrated an increased risk of lung cancer in granite workers. However, the quality of the airborne concentration estimates is difficult to evaluate given the limited information provided in the reports. As part of their IARC multi-center exposure-response study, Steenland et al. (2001a) conducted an additional seven years of follow-up and reported finding a slight positive exposure-response trend. However, a re-analysis of that data conducted as part of an OSHA-sponsored uncertainty analysis (Toxichemica, Inc., 2004) found no apparent exposure-response relationship between crystalline silica exposure and lung cancer mortality after correcting a small number of errors in the assignment of cumulative exposure values. It does not appear that lung cancer mortality was associated with cumulative exposure to respirable silica dust in this cohort.

I.C.2.e. Chinese refractory brick workers.

Dong et al. (1995) conducted a retrospective cohort mortality study of 6,266 male workers (silicotics and non-silicotics) employed before 1962 at 11 brick refractory plants in China and followed between 1963 and 1985. Demographic and employment history data were obtained through an interview and an examination of the personal records of each plant (Dong et al., 1995). No airborne concentration monitoring results were reported in the study. All deaths were determined from funeral allowance records at each refractory plant and the underlying cause of death was obtained from medical records or certificates and coded according to the Chinese classification of diseases. The investigators calculated the standardized risk ratios (SRR) by comparing the mortality rates of silica-exposed workers with those of a population of male steel workers. In order to minimize confounding, steel workers ever exposed to known occupational carcinogens or silica dusts were excluded from the referent population (methodological details not provided). The investigators evaluated the smoking status, latency period, radiological status, silicosis, and duration of employment in silica brick or silica clay brick manufacturing. For the total cohort and for silicotics (as determined by chest X-ray, profusion category 1 or higher), there were statistically significant excesses for lung cancer mortality (SRRs of 1.49 ($p < 0.01$) and 2.10 ($p < 0.01$), respectively). Dong et al. (1995) found a statistically significant excess of lung cancer mortality for both smoking and nonsmoking silicotics (SRRs of 2.34 ($p < 0.01$) and 2.13 ($p < 0.05$), respectively). Non-silicotics (48 percent of the population) showed an elevated but not statistically significant SRR for lung cancer (SRR = 1.11).

These results suggested that, in this cohort, the workers with silicosis appeared to be at a higher lung cancer risk. The investigators also found that the lung cancer risk increased with increasing latency for the silicotics, but not for those who did not have silicosis. There was a clear gradient for lung cancer by three Chinese radiological categories (I, II, III) of silicosis (SRRs of 1.97, 2.34, and 2.55, respectively), as well as by latency period (data not presented). To summarize, there was a statistically significant excess risk of lung cancer in Chinese refractory brick workers who had radiographic

silicosis. The authors suggested that the excess lung cancer mortality observed may have underestimated the true risk to the extent that workers with silicosis prematurely died of that disease (Dong et al., 1995). Although the prevalence of silicosis in this cohort is high (52 percent), the study presents no exposure data. Thus, it is not helpful in ascertaining any dose-response relationship.

Xu et al. (1996b) in a case-control study found an increased odds ratio for lung cancer mortality among refractory brick maintenance workers. Incident lung cancer cases were defined as those having worked at the steelworks for 10 years or more and diagnosed between 1987 and 1993. The refractory brick maintenance workers were a subpopulation of 40 cases within a larger case-control study of 610 incident lung cancer cases within a large iron and steelworks facility. Xu et al. (1996b) noted that refractory brick workers with 15 years or more of work had a statistically significantly elevated incidence of lung cancer (OR = 2.9, CI 1.4-5.9). Xu et al. (1996a, 1996b) noted it was not possible to adequately distinguish the carcinogenic effects of silica from other dusts as both silica and asbestos exposures were present in the refractory brick area.

I.C.2.f. Italian refractory brick workers.

A cohort of 231 workers actively employed as of January 1, 1960 was assembled by Puntoni et al. (1988) from one refractory brick (firebrick) plant in Genova, Italy. Follow-up was through the end of 1979 with the vital status being determined for the entire cohort. Job assignment analysis was not conducted because of high employee mobility between departments. No analysis by latency and length of exposure was possible since neither the date of hire nor the age at hire were available. Smoking data was not available and only limited cross-sectional airborne concentration data were presented but not used in data analysis. Mortality for the brick worker cohort was elevated for cancer of the lung, bronchus, trachea and pleura (SMR = 183, CI 91-327, 11 deaths) and for nonmalignant respiratory disease (SMR = 304, CI 177-486, observed deaths 17, 11 of which were silicosis). This cohort was incorporated into a larger cohort assembled by Merlo and discussed below.

Merlo et al. (1991) conducted a retrospective cohort study of 1,022 male refractory brick workers employed for at least 6 months between 1954 and 1977 and followed through 1986. The plant was opened in 1931 with production interrupted between 1952 and 1957 to improve production and environmental controls. The authors stated that worker exposures to crystalline silica prior to the mid-1950s were higher than in later years. There was likely to be little chance of exposure to other carcinogens since asbestos had never been used in the production processes and polyaromatic hydrocarbons (PAH) levels were minimal (Merlo et al., 1991). Smoking information was not available for the whole cohort but indirect adjustment for smoking had virtually no effect on results. A marginally statistically significant excess of lung cancer mortality was observed for brick workers (SMR 151, 95% CI 100-218, 28 deaths) compared to the Italian male population. Analysis by year of employment revealed that the workers first employed before 1957 (year of dust control introduction) had a statistically significantly elevated SMR of 177 (95% CI 103-284, 17 deaths). Those employed after 1957 had a

non-statistically significantly elevated SMR of 123 (95% CI 61-220, 11 deaths). A statistically significant increase in lung cancer SMR was observed in the subgroup of workers with 19 or more years since first exposure (SMR 201, 95% CI 107-344, 13 deaths). Brick workers' mortality from other respiratory diseases, excluding silicosis, was almost double the mortality rate due to lung cancer (respiratory disease SMR = 403, lung cancer SMR = 224; CI not provided), in a highly exposed sub-cohort, that worked prior to 1957 and had more than 19 years of plant experience.

Although cross-sectional industrial hygiene data were presented for respirable and silica dust for areas of the brick plant for 1973 and 1975, they were not available for prior years. There was no exposure analysis by job title, exposure groups or job-exposure matrix presumably because of the job mobility reported by Puntoni et al. (1988). The authors concluded that their findings supported a relationship between exposure to crystalline silica and increased lung cancer mortality. This was particularly true for those who worked prior to 1957, when exposures were higher, and for those who had greater than 19 years of work.

I.C.2.g. South African gold miners.

There are a number of studies of lung cancer among South African gold miners, including two case-control studies by Hessel et al. (1986, 1990) and three studies of two different cohorts. The larger cohort was first investigated by Wyndham et al. (1986) with a follow-up and cohort redefinition and accompanying nested case-control study by Reid and Sluis-Cremer (1996). A smaller cohort study was conducted by Hnizdo and Sluis-Cremer (1991), with a nested case-control study by Hnizdo et al. (1997).

Each of these studies relied on extensive dust concentration measurements and engineering control observations compiled by Beadle and Bradley (1970), and published by Page-Shipp and Harris (1972). These environmental assessments were conducted in 20 mines between 1956 and 1959 using three dust measurement techniques, which included:

- Hand-held Konimeter samples taken at 10-minute intervals throughout the shift (22,000 samples, all of which were ignited, acid treated, and counted);

- Modified thermal precipitator samples (e.g., fitted with elutriators) taken at 10-minute intervals throughout the shift (22,000 samples analyzed before and after acid treatment with a photoelectric sensor to measure surface area of respirable dust); and

- Standard thermal precipitator samples taken continuously throughout the shift (650 area samples) analyzed before and after acid treatment by high-power light microscopy for particle count in at least 15 size ranges.

Measurements were made while following approximately 650 gold miners representing 11 occupational exposure groups throughout their work shifts. The summary by Page-Shipp and Harris (1972) provided mean particle count and particle surface area data as well as estimates of respirable dust mass concentration, which was based on theoretical calculations using the surface area data.

Beadle and Bradley (1970) estimated that the percentage of quartz content of total mine dust was 31 percent with high variability in the mines. The mine mean values measured within 6 mines ranged from 14 percent to 57 percent. More recently, Churchyard et al. (2004) reported that in South African gold mines the silica content of respirable dust ranges ranged from 12 percent (SD = 5.6) to 16 percent (SD = 5.8) based on two separate series of measurements using cyclonic air sampling and analysis by X-ray diffraction.

One of the first investigations into whether exposure to respirable silica dust was a risk factor for lung cancer was a case-control study by Hessel et al. (1986). Cases and controls were selected from all deaths reported to the miners' pension fund between January 1979 and October 1983; this included all white miners with at least 15 years of service, as well as some with less than 15 years of service if they chose to remain in the fund. Two controls for each of the 133 lung cancer cases identified were matched by year of birth and by smoking history. Exposure to silica for each case and control was quantified by multiplying the number of shifts worked in an occupation with a weighting factor assigned to reflect the relative degree of dustiness of that occupation. Occupations were grouped into four levels of dustiness (non-dusty, low, moderate, and high). The presence of silicosis was assessed by both radiographic and autopsy findings.

The authors found no association between lung cancer and a silica exposure index, duration of employment, or number of shifts worked in high dust. The odds ratios for lung cancer and either radiological or parenchymal silicosis at autopsy declined with increasing exposure to dust. The authors also reported finding a non-statistically significant trend toward increasing severity of parenchymal silicosis among lung cancer cases, which they believed indicative of an increased susceptibility to silicosis among lung cancer cases.

Hessel et al. (1990) conducted an expanded case-control study of necropsied miners that included 231 primary lung tumor cases and 318 controls that died from 1975 to 1986 (excluding deaths that occurred in the same time frame as the earlier study). Cases and controls were matched by age at death. Their findings showed no differences between cases and controls in cumulative dust exposure, dust intensity, shifts employed underground and shifts in high dust jobs. The odds ratio (OR) (adjusted for age at death, smoking, and cumulative dust exposure by conditional logistic regression) for silicosis of the parenchyma was 1.10 (95% CI 0.79-1.60); for silicosis of the pleura the OR was 0.80 (95% CI = 0.54-1.20); and for silicosis of the hilar lymph glands the OR was 1.29 (95% CI = 0.83-2.00). No case-control differences were noted for any of the exposure indicators, including cumulative dust exposure, total dusty shifts, and shifts in high dust.

The authors conclude there is no apparent association between either silica dust exposure or silicosis and lung cancer in this study population.

Wyndham et al. (1986) studied a cohort of 3,971 white South African gold miners born between 1916 and 1930 who were alive and actively employed at the start of 1970 (ages 39-54), and who were followed for nine years. SMRs were based on mortality rates of white South African males as the comparison population. There were 530 deaths within the cohort with an SMR for all causes equal to 118. SMRs were statistically significantly elevated for chronic respiratory disease (SMR = 165, 95% CI 108-243), nephritis (SMR = 381, 95% CI 164-751) and heart disease (SMR = 115, 95% CI 100-140). There were elevated risks for lung cancer (SMR = 161; 95% CI 115-220) and gastric cancer (SMR = 157; 95% CI 78-281). The authors used a case-referent approach to examine gold miner risk factors such as cumulative dust exposure and years employed underground to further explore lung cancer, chronic respiratory disease and heart disease. Smoking history was included in the model. For lung cancer mortality, the smoking-adjusted risk ratio (RR) was 1.14 per 10 years employed underground (95% CI 0.63-2.05) and 1.77 per 10 particle-years of underground exposure (95% CI 0.94-3.31). The authors concluded that years employed underground was not a sensitive indicator of risk.

Reid and Sluis-Cremer (1996) published an 11-year follow-up study of the cohort studied by Wyndham et al. (1986). This paper included a cohort and nested case-control study of mortality comprised of 4,925 white-male South African gold miners to determine whether dust exposure contributed to risk of lung cancer, chronic obstructive pulmonary disease (COPD), or ischemic heart disease (IHD).

The cohort definition was less restrictive than that of Wyndham et al. (1986), resulting in a larger study group, 4,925 versus 3,971. The cohort comprised white gold miners, aged 39 to 54 at the start of 1970, who were still working as of January 1, 1970 and who had attended the Medical Bureau for Occupational Diseases for a required physical exam in 1969. As such, the cohort represented virtually all of the miners who were working in the region of interest as of the beginning of 1970. The Reid and Sluis-Cremer (1996) study included workers of contractors and of mines who were not members of the Mining Provident (Insurance) Fund. The vital status of the cohort was followed through the end of 1989 (20 years of follow-up), and mortality was compared to standardized ratios for all white male South Africans.

In the case-control study, cases included those miners who had died from any of the three diseases of interest. For lung cancer and COPD cases, two controls for each case were randomly selected from the cohort who was born the same year as the case and who survived the case; one control was selected for each case of IHD. Under the randomization procedure used by the authors, it was possible for a case for one disease to be a matched control for a case for one of the other diseases of interest, and a miner could have been selected as a control for two different disease cases. For the case-control analysis, the authors presented the results only for miners who had at least 85 percent of their service in gold mines and who worked underground for at least 15 percent of their gold mining service. Eighty-seven percent of the cohort fulfilled these criteria. These

case-control selection criteria were also used by Wyndham et al. (1986) with 93 percent of the cohort having had more than 85 percent of their service in the gold mines. It appears then that the broader cohort definition used by Reid and Sluis-Cremer (1996) somewhat diluted the intensity of exposure of the overall cohort but would not likely have affected the case-control analysis.

Airborne dust concentrations for the case-control analysis were estimated from thermal precipitator particle count (after acid washing) data converted to respirable dust mass, presumably the same data as described by Beadle and Bradley (1970) and Page-Shipp and Harris (1972). Seven occupational groups were defined based on degree of dustiness and cumulative exposure for each case and control was determined by linking occupation-specific mean dust exposure estimated for these seven occupation categories with the miner's occupational history and expressing the miner's exposure as years-mg/m^3. Cumulative exposure was calculated from the start of employment up to 5 years before the death of each case for each case-control set; the average cumulative exposure of subjects included in the case-control study was 3.7 mg/m^3-years respirable dust over an average of 27 years of service. Duration of employment was used as a surrogate for exposure to radon and its progeny. Smoking history was abstracted from the physical exam conducted in 1969. Analysis of the relationships between cumulative exposure, number of shifts in underground mining, smoking history, and mortality was conducted using conditional logistic regression (Reid and Sluis-Cremer, 1996).

The overall SMR for the 2,032 miners who had died was 129.6 (95% CI 124.0–135.4), significantly higher than expected. The principal causes of excess mortality were lung cancer (SMR = 139.8; 95% CI 117.8–164.6), ischemic heart disease (SMR = 124.1; 95% CI 115.0–133.7), COPD (SMR = 198.0, 95% CI 162.1–219.0), cirrhosis of the liver (SMR = 155.3; 95% CI 113.3–207.9), and renal failure (SMR = 163.5, 95% CI 104.7–243.3). The authors also observed additional causes of statistically significant excess mortality involving the pulmonary system. These included: tuberculosis, bronchitis, emphysema, chronic obstructive airways, pneumoconiosis, and corpulmonale. The case-control study indicated the principal risk factor for COPD, IHD, and lung cancer was cigarette smoking. Cumulative exposure to respirable dust had a modest but not a statistically significant effect on lung cancer mortality, with reported odds ratios of 1.08 (95% CI 0.94–1.2) and 1.12 (95% CI 0.97–1.3) excluding and including smoking, respectively. Cumulative exposure was associated with a statistically significant increase in COPD (OR = 1.23, 95% CI 1.0–1.5 without smoking in the model; OR = 1.20, 95% CI 1.0–1.4 with smoking in the model). However, the authors reported that none of the COPD cases were non-smokers, suggesting to them that, in this study, exposure to dust could cause COPD only in conjunction with smoking. Number of shifts of underground service was not shown to increase lung cancer, COPD, or IHD mortality.

Reid and Sluis-Cremer (1996) concluded that little of the 30-percent excess mortality seen in this cohort was likely attributable to dust exposure and that the excess was better explained by a greater prevalence among miners of unhealthy lifestyles compared to South African white males, given that 86 percent of the cohort had smoking histories and that the main causes of mortality (lung cancer, IHD, COPD, liver cirrhosis)

are known to be associated with smoking and excessive alcohol consumption. The authors also suggested that lifestyle factors could have interacted with risk factors in the mine environment to increase the risk of some of these diseases, such as the combination of dust exposure and smoking to produce COPD.

Hnizdo and Sluis-Cremer (1991) studied 2209 South African white male gold miners who began mining between 1936 and 1943 and who were evaluated for respiratory disease between 1968 and 1971. Mortality was followed from 1968 to 1986. The study objectives were:

- To evaluate dose-response relationships between exposure to silica dust and lung cancer risk;
- To examine the combined effect of exposure to silica dust and smoking; and
- To investigate the association between lung cancer and silicosis detected at necropsy.

Miners were selected for the cohort only if they were between the ages of 45 and 54 at the time of the pulmonary disease survey and had a minimum of 10 years of underground gold mining experience. Vital status was ascertained using files of several South African sources, and causes of death were determined from the best available evidence, including the extensive postmortem records maintained for medico-legal purposes (84 percent of deceased subjects had an autopsy). Of the 945 deaths (43 percent of the cohort), there were 77 lung cancer deaths accepted (66 confirmed by necropsy, five by biopsy, and six from the death certificate). To estimate silica exposures for the cohort, the authors relied on mean respirable particle count data for 11 occupational groups, as developed by Beadle (1971) and described above. Cumulative dust measures were calculated by multiplying the number of shifts worked in each occupation by the mean respirable dust count for that occupational group; cumulative exposures were expressed as respirable particle-years. Smoking information was obtained from the 1968-71 pulmonary disease survey and was checked for changes in smoking status from the miners' longitudinal medical files. Overall, the authors showed that, in contrast with the rest of the cohort, the 77 cases of lung cancer had higher cumulative silica exposures, smoked more, and had a greater percentage of miners who had ever smoked (96% vs. 88%), had poorer pulmonary function, and had more respiratory disease than the rest of the cohort.

Using a Cox proportional hazards model, smoking produced a highly significant ($p < 0.001$) correlation with lung cancer risk in models that adjusted for age. In models that adjusted for age and cigarette equivalent pack-years (to account for pipe smoking), the following four cumulative dust variables were statistically significant predictors of lung cancer mortality: particle-years accumulated to 1949 ($p < 0.01$); particle years accumulated to 1959 ($p < 0.05$); particle-years accumulated to start of follow-up in 1968 ($p < 0.01$); and particle-years accumulated to end of follow up in 1986 ($p <0.05$). There

was an increasing trend in the relative risk for lung cancer for both increasing cumulative exposure and smoking. Based on the proportional hazards model, the authors estimated a relative risk for lung cancer of 1.023 (95% CI = 1.005 to 1.042) per 1,000 particle-years of exposure, after adjusting for smoking and year of birth. This means that the most veteran white gold miners (all employed more than 10 years) exposed to 50,000 particle-years of silica dust would have 3.18 times greater risk of dying from lung cancer than those exposed to only 15,000 particle-years. Analysis using a general relative risk model indicated that the combined effect of exposure to silica dust and smoking was greater than the sum of individual effects. The synergy appeared to be greatest for miners with more than 35 pack-years of smoking history and more than 30,000 particle-years of exposure (Hnizdo and Sluis-Cremer, 1991).

Of the 945 deaths in the cohort, autopsy reports were available for 745 that permitted the investigators to examine lung cancer risk and the presence of silicosis. After adjusting for age at death, cumulative exposure, and pack-years, lung cancer was found to be associated with silicosis of the hilar glands (OR = 1.2, 95% CI 10.7-2.0) but not with silicosis of the lung or of the pleura (OR = 0.9, 95% CI 0.5-1.6).

Hnizdo and Sluis-Cremer (1991) concluded that their study showed a statistically significant exposure-response relationship between exposure to silica dust, pack-years of smoking, and lung cancer mortality. The results of this study were consistent with those of another cohort study (Wyndham et al., 1986), but not with the two case-control studies conducted up to that time (Hessel et al., 1986, 1990). Hnizdo et al. (1991) suggested that since exposure to silica is known to increase all-cause mortality, it is possible that controls from the Hessel studies had sufficient exposure to result in overmatching of cases and controls with respect to exposure, making it more likely that a weak association would go undetected.km

Hnizdo and Sluis-Cremer (1991) also raised the possibility that radon exposure may have confounded the associations reported with silica dust. Although they acknowledged that radon exposure was generally considered to be low (an average working level of 0.4 WL ranging from 0.1 to 3.0 WL) miners having more than 20 years of experience at least theoretically could accumulate a level of radon exposure that has been associated with an increased risk of lung cancer.

Hnizdo et al. (1997) conducted a nested case-control study from their earlier cohort study (Hnizdo and Sluis-Cremer, 1991) to investigate relationships between lung cancer mortality and smoking, cumulative silica dust exposure, years of underground mining, silicosis, lung cancer cell type, and history of uranium ore exposure. The authors identified 78 cases of lung cancer (for which necropsy data were available for 69) and 386 controls (5 controls per case). The controls were matched for year of birth and survival of the case. Mean exposures to respirable dust were estimated for nine occupational categories based on the measurements that had been taken in the 1960's and estimates of the average time spent underground in each occupation (Page-Shipp and Harris, 1972). Dust exposure for each study subject was determined by combining

his/her occupational history with the estimated average respirable dust exposure for each of the occupation categories. The measures of exposure were cumulative dust exposure ($CDE = \sum D_i T_i$, with CDE = cumulative dust exposure [mg/m^3-years], D_i = dust for i^{th} job and T_i, = time spent in the i^{th} job) or years spent in dusty jobs. Exposures were lagged 0, 5, 10, and 20 years. Exposure to radon gas and its progeny was estimated indirectly based on mine-specific data on annual uranium production and grade of uranium ore. Smoking habits were obtained from questionnaires administered during each miner's regular medical evaluation. The presence of radiological silicosis was assessed from chest X-ray films; year of onset of silicosis was defined as the earliest film categorized as ILO 1/1 or higher up to three years prior to death.

Lung cancer mortality was found to be associated with cigarette smoking, cumulative dust exposure (with and without a 20-year lag), silicosis, and duration of underground mining (with and without a 20-year lag). The most significant predictors showing a dose-response trend were cumulative dust exposure and duration of underground mining, both lagged by 20 years prior to the death of the case. When silicosis was added to the model, lung cancer mortality was associated with the occurrence of silicosis (RR = 2.45, 95% CI 1.2-5.2) and smoking but was no longer associated with cumulative exposure and years of underground mining. Although Hnizdo et al. (1997) acknowledged that this finding might suggest that silicosis is a more important risk factor for lung cancer than silica exposure, they pointed out that the relationship between cumulative exposures, years in underground mining, and silicosis is complex, and that these variables are highly correlated. Thus, it is not possible to say with certainty that these results indicate silicosis, and not just exposure to silica, increases the risk of lung cancer. In addition, the results of this study showed a multiplicative effect of smoking and silicosis on lung cancer; the cohort study (Hnizdo et al., 1991) showed a similar multiplicative effect of smoking and cumulative silica exposure on lung cancer mortality.

The authors found no significant association of lung cancer with variables representing uranium production and the grade of the uranium ore. As discussed above, the level of radon exposure in this cohort was low (average = 0.4 WL) compared to other cohorts of uranium miners, but high enough to potentially have some confounding effect on a silica-lung cancer association.

According to the authors, the correlations between exposure and silicosis variables in this study make it difficult to draw causal inferences. They suggested their results are consistent with three possible causal relationships: (1) subjects with high dust exposure who develop silicosis are at increased risk of lung cancer; (2) high levels of exposure to silica dust on its own is important in the pathogenesis of lung cancer and silicosis is coincidental; and (3) the increased lung cancer risk reflects time spent working underground in high levels of dust and with potential radon exposure.

Overall, two cohort studies (Reid and Sluis-Cremer, 1996 and Wyndham et al., 1986, with essentially the same cohort, and Hnizdo et al., 1991) demonstrated excess lung cancer mortality among South African miners exposed to respirable silica-

containing dust; however, in each of these studies, potential confounding by smoking and/or exposure to radon cannot be ruled out. Of the four case-control studies (Hessel et al., 1986, 1990; Hnizdo et al., 1997; Reid and Sluis-Cremer, 1996), only that by Hnizdo et al. (1997) found statistically significant increases in lung cancer risk that were associated with increases in dust exposure, time spent underground, or radiographic silicosis. Although Reid and Sluis-Cremer (1996) did not find a statistically significant correlation between lung cancer and dust exposure, their reported elevated odds ratios were nearly so, both with and without including smoking as a co-variable. As such, OSHA believes that their results are not wholly inconsistent with the findings of the case-control study by Hnizdo et al. (1997). The earlier case-control studies by Hessel et al. (1986, 1990) also failed to find statistically significant associations between dust exposure and increased lung cancer risk, but Hnizdo et al. (1991, 1997) have suggested that these studies might have been biased towards the null by overmatching for exposure and including smoking as a matching criteria (in Hessel et al., 1986), or by not matching on date of birth (in Hessel et al., 1990). Furthermore, OSHA notes that the Hnizdo et al. cohort (1991) and case-control (1997) studies used the most detailed approaches for estimating miners' cumulative exposures in terms of defining occupational categories and estimating their respective mean exposure levels, thus reducing the potential for exposure misclassification that would make it more difficult to see a modest association between lung cancer and exposure to silica dust. Although not conclusive in isolation, OSHA believes the body of evidence from the South African studies is suggestive of an exposure-related association with lung cancer.

I.C.2.h. Western Australia gold miners.

Armstrong et al. (1979) conducted a cohort study of 1974 gold miners and 213 coal miners in the Kalgoorlie area of Western Australia. This discussion will be limited to the findings of the gold miner cohort. The cohort was defined as underground and above-ground gold miners that participated in respiratory medical surveys in 1960 and 1961 that included a questionnaire on respiratory, smoking and occupational histories and radiological evidence of pneumoconiosis. Follow-up was to the end of 1975 for 13-14 years of follow-up. The gold miner cohort experienced 500 deaths, slightly less than 25 percent of the cohort for a total of 15,551 man-years of follow-up. Within this cohort, there was statistically significant ($p < 0.01$) excess mortality for lung cancer (ratio of observed to expected cases (O/E ratio = 1.4, 59 deaths) silicosis (O/E ratio = 6.4, 11 deaths) and accidental death (O/E ratio = 2.9, 13 deaths). Underground miners had increased risk of respiratory cancer mortality in comparison to above-ground miners (RR = 1.41, 95% CI 0.69-2.96). There was an observed trend of increased respiratory cancer mortality with increased employment duration underground but the trend was not statistically significant. There was a slight, but not statistically significant, association between radiographic evidence of silicosis and death from respiratory cancer (RR = 1.13, 95% CI 0.64-1.98).

Potential confounding by arsenic and radon was addressed by the authors. Average levels of arsenic from bulk samples of mine rock was 49 parts per million with a maximum concentration of 335 parts per million. Air measurements were not provided.

Maximum air measurements of radon and radon daughters were 11 picocuries (pci) for radon and a working level of 0.045 pci for radon daughters. Armstrong et al. (1979) explained that even the maximal levels measured were substantially below those that have been associated with lung cancer in other studies.

No exposure assessments for respirable dust or silica were conducted or discussed, nor were analyses conducted by job title or mine work area as a surrogate for exposure. Respiratory cancer mortality was strongly associated with cigarette smoking and smoking prevalence was higher among gold miners (66.3%) than for an external south-west Australia reference group (53.2%). The authors provided evidence of an interaction between lifetime smoking and duration of underground exposure (Table 6 of Armstrong et al., 1979) and stated that cigarette smoking probably explained at least part of the respiratory cancer mortality excess.

De Klerk and Musk (1998) conducted a follow-up of a slightly larger cohort of 2,297 gold miners from Kalgoorlie in Western Australia who participated in surveys of respiratory symptoms, and smoking, and employment histories in 1961-1962 and 1974-1975; it was estimated that 95 percent of miners participated in these surveys. The cohort was followed to the end of 1993 for 30 years of follow-up for lung cancer mortality and incidence of compensation for silicosis.

Complete work histories obtained from the clinic conducting the respiratory surveillance were used to develop an exposure matrix. Detailed measurements of dust counts were not available for the period 1925 to 1976. Semi-quantitative estimates of average and cumulative dust exposure were made by a panel of experts who ranked jobs based on dustiness on a scale of 1 to 10 of increasing dustiness, taking into account changes in dust control technology and procedures. Estimates of average and cumulative exposure to silica were made separately for underground and surface mining activity as the sum of the products of each miner's time spent in each job and the dustiness rank for each job.

More than half (1,386) of the cohort had died by the end of the follow-up, and 631 had been compensated for silicosis. Eighty-four percent of the men in the cohort had smoked at some time and 66 percent were current smokers. The median number of months employed in gold mining was 192 (range 0-594) underground and 50 (range 0-586) in surface activities.

SMRs were calculated using Western Australia mortality rates (specific for age, calendar period, and gender) and using two alternative methods for censoring data from subjects lost to follow-up (257) to provide lower- and upper-bound estimates of the true SMR. The lower- and upper-bound estimates of the SMR for lung cancer were statistically significantly increased (lower SMR 126, 95% CI 107-159; upper SMR 149, 95% CI 126-176). A nested case-control analysis of 138 lung cancer deaths showed that lung cancer mortality was associated with log cumulative silica exposure (RR = 1.31 per unit of log (exposure-score year); 95% CI 1.01-1.70) after adjustment for smoking and bronchitis; however, the association between log cumulative silica exposure and lung

cancer mortality was not statistically significant after adjustment for smoking, bronchitis and occurrence of silicosis, although the relative risk was still increased [RR = 1.20 per unit of log (exposure-score year); 95% CI 0.92-1.56]. The effect of the silicosis variable in the logistic regression model became slightly less influential with increasing time since diagnosis, and had its strongest effect 0 to 1 years after diagnosis. Duration of underground employment was not statistically significantly related to lung cancer mortality ($p > 0.15$) after adjustment for smoking and bronchitis. There was no discussion of potential confounding due to other potential occupational exposures, although Armstrong et al. (1979) partially addressed arsenic exposure and thoroughly addressed radon exposures.

The authors concluded that their findings showed significantly increased lung cancer and pneumoconiosis mortality in this cohort and that the increase in lung cancer mortality was restricted to miners who had received compensation for silicosis. Since silicosis had its strongest effect on lung cancer mortality almost immediately following diagnosis and compensation, the authors believed it possible that lung cancer arose in these subjects from localized immune suppression caused by silicosis. However, since compensated silicosis was strongly associated with cumulative dust exposure, the authors noted that the results could not definitively confirm the role of silicosis or dust exposure in lung cancer mortality.

I.C.2.i. U.S. gold miners.

A number of studies were conducted that examined the health risk to workers employed at the Homestake Gold Mine in Lead, South Dakota (Brown et al., 1986; Gillam et al., 1976; Steenland and Brown, 1995a, 1995b). The first by Gillam et al. (1976) was a retrospective cohort study of 440 male miners who were employed for at least 5 years in underground jobs and who had never worked in another underground mine. These men were followed from 1960 to 1973. A SMR of 370 ($p < 0.01$) was reported for pulmonary malignancies. The authors reported that crystalline silica concentrations were not apparently elevated and arsenic, chromium, and nickel were present in trace concentrations; radon daughters were not detected. The authors postulated that the lung cancer excess was related to exposure to asbestos-like cummingtonite-grunerite fibers in combination with cigarette smoking and a possible additive role for crystalline silica was proposed. In contrast, Brown et al. (1986) failed to find an excess of lung cancer mortality among 3,328 miners followed through June 1977, nor was there a trend with estimated cumulative exposure to silica or with latency.

Steenland and Brown (1995a) studied the same cohort as Brown et al. (1986) and extended the follow-up period by 14 years, through 1990. There were a total of 1,551 deaths in the cohort (47%), including 115 from lung cancer (compared to 861 total deaths (26%) and 43 lung cancer deaths reported by Brown et al., 1986). The cohort included workers who worked underground for at least 1 year between 1940 and 1965; most of the cohort was first employed before 1950.

Cumulative exposures were estimated using a job-exposure matrix in which underground jobs were grouped into five major categories based on similarities in job function and exposure to dust. A sixth category included all jobs that were not full time. Average dust exposures were calculated for each job category using company measurements of particle count concentrations taken between 1937 and 1975. The silica content of respirable dust was estimated to be 13 percent, while that of settled dust was estimated to be 39 percent (Zumwalde et al., 1981). Prior to 1950, the silica exposure levels were estimated to range from 10 to 30 mppcf, which was about 1 to 3 times higher than the then-recommended ACGIH TLV, but lower than dust levels reported for other industry sectors. After implementation of dust controls in 1950, dust levels fell below the TLV. Using a conversion factor derived from studies of the Vermont granite sheds, where silica content was similar to that seen in the gold mine, the authors estimated the median of the miners' average exposure levels to be 0.05 mg/m^3 respirable quartz. The medians of the average exposure levels prior to 1930, between 1930 and 1950, and after 1950 were estimated to be 0.15, 0.07, and 0.02 mg/m^3, respectively.

Miners were also exposed to a variety of non-asbestiform minerals, principally cummingtonite-gunnerite and tremolite-actinolite. Exposure to the potential lung carcinogens arsenic and radon were below the existing OSHA and MSHA standards, respectively, when measured in the mid-1970s.

Smoking data were available for 602 men aged 35 to 64; these data indicated only small differences in smoking habits between the gold mine workers and the general U.S. population and lung cancer rates were estimated to reflect these differences. SMRs were calculated using U.S. or local rates for overall mortality. In addition, the authors conducted a nested case-control study selecting five age-matched controls for each case.

The researchers found a slight excess of lung cancer (not statistically significant) for the cohort as a whole (SMR = 113 with 95% CI 94-136 based on the national rate) and no evidence of an exposure-response association, even though a clear exposure-response trend was found for respiratory tuberculosis and pneumoconiosis. The SMRs for lung cancer among workers followed for 30 or more years from the first underground employment and for workers in the highest exposure category were 127 (95% CI 102-155) and 131 (95% CI 87-189), respectively. Trends with duration of exposure were inconsistent. When local county or South Dakota rates were used as the referent rates, SMRs for lung cancer were 125 (95% CI 103-151) for workers followed for 30 or more years and 159 (95% CI 131-192) for the most highly exposed workers. A nested case-control analysis of the 115 lung cancers and a set of matched controls failed to show a relationship between lung cancer and cumulative dust exposure (Steenland and Brown, 1995a). There was also no apparent relationship between lung cancer and the mention of silicosis on death certificates. Based on the available smoking data, Steenland and Brown (1995a) estimated the lung cancer risk ratio attributable to smoking to be 1.07.

The authors reported finding elevated mortality from a variety of other causes, including nonmalignant renal disease, arthritis, systemic lupus, sclerosis, lupus and scleroderma. Renal disease mortality was elevated among the most highly exposed

workers (those hired prior to 1930) and showed a significant exposure-response trend. The authors concluded that there was an excess of lung cancer in the cohort but that the excess was not related to estimated cumulative dust exposure, a finding in contrast to other studies of gold miners (de Klerk and Musk, 1998; Hnizdo and Sluis-Cremer, 1991; Wyndham et al., 1986). Although the reasons for this discrepancy are not known, the authors suggested differences in the biological activity of minerals present in the mines and potential confounding in the positive studies by exposures to radon or arsenic as explanations.

I.C.2.j. Chinese tin and tungsten miners.

A series of mortality and nested case-control studies have been conducted on a cohort of Chinese tin miners. The early studies in the series (Chen et al., 1992; McLaughlin et al., 1992) also included other metal mining and pottery workers. The cohort was comprised of over 68,000 workers from 21 mines and 8 factories, including 10 tungsten mines (n = 28,481), six copper/iron mines, 8 potteries, 1 clay mine, and 4 tin mines (n = 7,875). The results for the pottery workers will be discussed in Section 3.n below.

The first study in the series (Chen et al., 1992) was a mortality study of tin and tungsten mineworkers were employed for at least one year between 1972 and 1974 with follow-up through 1989. Operations in all the workplaces began before 1949, although there were government reorganizations and expansion between 1952 and 1957. The mean age at entry into the cohort in 1972 to 1974 was 34 years. Less than 2 percent of the cohort had begun employment before 1950, 50 percent began during 1950 to 1959, and 47 percent began during 1960 to 1974. Historic data from workplace air sampling for total dust (mg/m^3), percent free silica, and particle size from the 1950s through the 1980s were used to estimate an exposure level for every dust-exposed job in each of several calendar-year periods. Based on job-specific exposure estimates, each cohort member was classified into one of four total dust exposure levels: high (43 percent of cohort), medium (15 percent), low (7 percent), and non-exposed (35 percent). If a worker had more than one job, their exposure estimate was based on the job having the highest dust exposure level provided the worker worked in that job for at least one year. Vital status and cause of death information was obtained mainly from employment registers, accident records, and medical records. Silicosis registries had been required in all workplaces where silica exposure occurred after 1963 and annual chest x-rays were routinely taken.

Lung cancer mortality was statistically significantly increased only for tin miners (not for other miners) for the periods 1972 to 1989 (SMR = 198) and for 1985 to 1989 (SMR = 262). (Confidence intervals not provided.) The authors also reported a rising trend in the risks for lung cancer with increasing dust exposure only for tin miners: the relative risks and 95 percent confidence intervals for medium- and high-exposure groups relative to non/low-exposure groups were 1.15 (0.4-3.3) and 1.72 (1.1-2.7), respectively. For the cohort overall, there was no increased relative risk for lung cancer (SMR = 78) nor an increased gradient of risk for the medium- and high-exposure groups relative to

the low-exposure groups. Also, for the cohort overall there was a non-statistically significant excess risk of lung cancer in silicotics (RR = 1.22, 95% CI 0.9-1.6).

McLaughlin et al. (1992) conducted a nested case-control study of lung cancer in the same cohort of silica-exposed Chinese workers as was studied by Chen et al. (1992). The analysis was based on a job-exposure matrix developed by Dosemeci et al. (1993). Total dust exposure data was available from routine company surveys between 1950 and 1987. All dust exposure data were static area total dust measurements with sample time intervals of 20 to 30 minutes and were analyzed gravimetrically. Approximately 2 million dust measurement records were abstracted for tin, tungsten, copper and iron mines. Assignments of exposure were by plant, job, and calendar year. Approximately 51 percent of the exposure assignments for workers in tin mines, tungsten mines and potteries were based on quantitative data. This ranged from 1 to 2 percent for the early 1950s to approximately 70 percent in the 1980s. For exposures prior to 1950, the 1950 exposure data were applied. Less than 2 percent of the workforce started work prior to 1950 (McLaughlin et al., 1992).

The percentage of silica in the dust was less well characterized as it was based on 134 settled dust samples and was only available for 14 percent of the exposure assignments with the earliest exposures being more poorly characterized than later exposures. Data regarding the silica content of the total dust were available at the facility level only due to lack of specific measurements historically by job title or process type (Dosemeci et al., 1993; Zhuang et al., 2001).

In 1988 to 1989, side-by-side measurements using the Chinese method for total dust sampling and the U.S. method for sampling respirable dust were done in 9 potteries and 20 mines as a special sampling survey conducted by the Tongji Medical College, China, and NIOSH, USA. Three sampling sites were selected at each mine or pottery to be distinct exposure zones representative of high, medium, and low dust levels as determined from historic Chinese sampling data. Respirable dust samples were obtained gravimetrically from 10-mm nylon cyclone samples collected over 8-hour shifts. Sampling lasted typically two days per mine or plant with three respirable samples per day for a total of 120 respirable personal air samples (tin mines - 10, tungsten mines - 56, and potteries - 54). The cyclone samples were analyzed both gravimetrically and by XRD to determine respirable dust and respirable silica dust concentrations, respectively. A conversion factor was developed to convert Chinese settled dust silica estimates into crystalline silica content of respirable dust collected by 10 millimeter cyclone and analyzed by XRD. The Chinese method washes the sample with phosphoric acid, removing most non-crystalline silica and then analyzing the residual by colorimetric analysis. The ratio of the silica content between the two methods is applied to the historical estimates of the percentage of crystalline silica in each mine. In general, bulk samples contain a higher percentage of crystalline silica then a corresponding respirable air sampling, but this can vary by industrial process (Dosemeci et al., 1993; Zhuang et al., 2001).

Job-specific data from workplace air samplings for total dust (mg/m^3) and the percentage of silica by mine as collected in settled dust were multiplied together for each cell in the job exposure matrix for each of several calendar-year periods. Based on these job-specific exposure estimates, each case or control was classified without knowledge of disease status into one of four silica exposure levels: high, medium, low, and non-exposed (McLaughlin et al., 1992).

The authors analyzed the mortality data by cumulative exposure to dust and arsenic, via categorical analyses (3 categories for dust, 4 categories for arsenic). Extensive dust measurements over time allowed the development of an accurate job-exposure matrix for dust. In contrast, historical data on arsenic exposure were very limited given that no arsenic air measurements were taken prior to 1988. Therefore, for exposures prior to 1988, the job-exposure matrix for arsenic was based on the percentage of arsenic in settled dust samples, for which limited historical data were available.

The tin miner nested case-control study consisted of 87 cases and 371 controls and the tungsten miner study consisted of 93 cases and 400 controls. Up to four controls from the cohort were selected for each case and matched based on working in the same mine and by decade of birth (age).

The highest risks for lung cancer mortality were seen in tin miners, followed by pottery workers (discussed separately below). A reverse trend of decreasing risk with increasing exposure was observed in tungsten miners. Odds ratios for tin miners were 1.5 (no-low exposure, 0.1-8.69 µg/m^3-yr), 1.9 (medium exposure, 8.70-26.2 µg/m^3-yr), and 3.1 (high exposure, >26.3 µg/m^3-yr) for cumulative respirable silica exposure and were statistically significant (p for trend = 0.004). Among tin miners, increasing exposure to arsenic was significantly associated with the risk of lung cancer, whereas exposures to polyaromatic hydrocarbons (PAHs) were less consistently linked to increased risk of lung cancer. Arsenic and PAHs were highly correlated with silica exposures (r = 0.80). This prevented the authors from adjusting for these confounders in the analysis. Cigarette smoking was associated with lung cancer in all the cohorts studied, but the correction for smoking did not influence the association between silica and lung cancer (McLaughlin et al., 1992).

An additional examination of the interaction of other carcinogens (cadmium, nickel, radon daughters, arsenic, and polyaromatic hydrocarbons) with silicosis in this cohort was conducted by Cocco et al. (2001) using data from the nested case-control study of McLaughlin et al. (1992). In this study, data from all 29 worksites were pooled. The authors were able to obtain, for each worker, information on silicosis stage at first diagnosis, any subsequent changes in radiological diagnosis and staging, and the dates of diagnosis. A "modest" association was observed between silica exposure and lung cancer risk, with a statistically significantly increased odds ratio of 1.6 (95% CI 1.1-2.4) in the third quartile of cumulative exposure to respirable silica (10.8-26.9 mg/m^3-yr). However, although the odds ratio for exposure in the fourth quartile ($\geq$ 27 mg/m^3-yr) was elevated, it was not statistically significantly increased (1.2, 95% CI 0.8-1.9). These risk estimates associated with silica exposure did not change with limiting the analysis to non-

silicotics or with radiological stage of silicosis. A "modest" association was also observed between silicosis and lung cancer risk (OR 1.4, 95% CI 1.1-2.0). Although odds ratios for lung cancer among silicotics were not increased with cumulative exposure to respirable silica, the odds ratios increased by severity of silicosis. The trend was statistically significant among workers in the first three levels of cumulative silica exposure but not among those in the higher exposure group. This association did not vary by severity of silicosis, disease progression, or level of silica exposure. Among silicotics, lung cancer risk was significantly increased only with co-exposure to cadmium and polyaromatic hydrocarbons. In the cohort overall, lung cancer risk associated with silica exposure stratified by exposure to the other carcinogens noted above showed that lung cancer risk was more evident among workers exposed to silica but unexposed to nickel, radon daughters, or poly aromatic hydrocarbons. Risk associated with silica exposure did not vary among workers by exposure to arsenic and cadmium. Cocco et al. (2001) believed, however, that strong correlations between exposures to the different agents prevented a detailed evaluation of the role of individual agents. Also, no isolated exposure to the other lung carcinogens occurred in the study. The authors called for further research to resolve the issues involving this complex pattern of interactions.

Chen and Chen (2002) analyzed the same cohort for the four Chinese tin mines (n = 7,855) as were analyzed by McLaughlin et al. (1992). Mortality follow-up was extended through 1994 and the cohort had experienced 1034 total deaths (13% of the cohort) by the end of the follow-up period. The investigators used a nested case-control analysis that included 130 lung cancer deaths and 627 controls. Up to five controls were individually matched to cases based on date of birth, gender, and mine. Smoking data were collected from next-of-kin. The previously discussed exposure matrix created by Dosemeci et al. (1993) was modified for use in this study.

Chinese exposure data from 1990 to 1992 were added to the job-exposure matrix that developed by Dosemeci et al. (1993). Zhuang et al. (2001) estimated conversion factors for converting Chinese total dust measurements to current respirable silica dust measurements based on the side-by-side samples and by calculating the ratio of respirable silica measurements to the total dust measurements. The intent was to create an appropriate composite correction factor for each industry. The industry-wide composite conversion factors for converting Chinese total dust to US respirable silica dust was 0.0429 for tin mines. Respirable fraction of total dust was estimated to be 25 percent ± 4 percent and respirable silica concentration was estimated to be 3.6 percent ± 0.8 percent of the total dust concentration (Gao et al., 2000; Zhuang et al., 2001).

Airborne arsenic concentrations were measured only after 1988. For the period before that, arsenic concentration was estimated by multiplying the total dust concentration by the arsenic content of the settled dust. Analyses were by contingency tables and logistic regression. Chen and Chen (2002) analyzed the mortality data by cumulative exposure to dust and arsenic, via categorical analyses (3 categories for dust, 4 categories for arsenic). Extensive dust measurements over time allowed the development of an accurate job-exposure matrix for dust. In contrast, historical data on arsenic

exposure were very limited given that no arsenic air measurements were taken prior to 1988.

Chen and Chen (2002) found strong, statistically significant positive exposure-response trends for both total dust containing silica and arsenic. These values were highly correlated (r = 0.82), making it difficult to separate the effects of arsenic- and silica-containing dust. However, arsenic concentrations appeared to be low when compared to historical studies showing arsenic exposure levels associated with lung cancer. Measured arsenic (14 samples) among workers in "high" exposure jobs taken in 1988 or later showed a mean of 10$\mu g/m^3$, which is the current permissible OSHA standard. However, descriptive data presented in the paper indicated a mean cumulative exposure of about 500 $\mu g/m^3$-years for arsenic with a mean duration of exposure of 14 years, implying an average exposure concentration of 35 $\mu g/m^3$. When a categorical analysis was conducted comparing the effects of total dust and arsenic, the authors found a statistically significant odds ratio of 2.0 (95% CI 1.1-3.7) for lung cancer mortality among workers in the lowest arsenic exposure category compared with those having no arsenic exposure. The authors also noted that the mean estimated level of arsenic exposure in the lowest exposure category was 3.7 $\mu g/m^3$; an exposure level where excess lung cancer would not be expected.

These data were also analyzed using a number of unconditional logistic regression models to assess the importance of various factors, including smoking, confounding exposures, and the presence of silicosis. These models confirmed that smoking, cumulative exposure to dust, duration of exposure to dust, and cumulative exposure to arsenic were associated with the risk of lung cancer. Of the four tin mines studied, a much lower arsenic concentration was found in one mine compared to the others. No excess of lung cancer was found among workers from this mine despite there having been a high prevalence of silicosis (as was also true of workers from the other mines). Dust concentrations and percentages of silica in the dust were similar in the four mines. Chen and Chen (2002) concluded that exposure to arsenic and smoking played a more important role than silica exposure in lung carcinogenesis among these tin miners and that silicosis seemed unrelated to the observed increased risk of lung cancer. The authors believed that their results provided little support for the hypothesis that respirable silica causes lung cancer.

Chen et al. (2006) conducted a five year follow-up through 1994 of the cohort mortality study of Chen et al. (1992). Fourteen percent of the cohort had died by the end of 1994 with the SMR for all causes of death similar to that of the national average. Malignant neoplasm was the leading cause of death with elevated SMRs for cancer of the nasopharynx (SMR = 341, CI 219-508, 24 deaths), liver cancer (SMR = 197, CI 163-235, 119 deaths), lung cancer (SMR = 249, CI 209-294, 138 deaths), and leukemia (SMR = 231, CI 129-382, 15 deaths) being statistically significantly elevated. Mortality from pneumoconiosis was markedly high (SMR = 3389, CI 2691-4212, 81) and was statistically significant.

In contrast to the earlier study (Chen et al., 1992), this study utilized new data to estimate exposure in quantitative units, rather than semi-quantitative units (Chen et al., 2001). In a categorical analysis of four cumulative total dust exposure groups (<0.1mg/m^3-years, 0.1-29.99 mg/m^3-years, 30-69.99 mg/m^3-years, >70 mg/m^3-years) consistent increased mortality trends were noted in overall mortality and mortality due to lung cancer, pneumoconiosis, pulmonary tuberculosis, and cardiovascular disease. In comparison to the mortality in non-exposed miners, exposed miners experienced elevated mortality for lung cancer (RR = 3.55; $p < 0.01$), respiratory disease (RR = 23.45; $p < 0.01$) and pulmonary tuberculosis (RR = 5.98; $p < 0.01$). The study also found that there was a significant increase in lung cancer among silicotics in comparison to non-silicotics. However, lung cancer mortality was also observed to increase with cumulative dust exposure among workers without silicosis.

The authors concluded that their findings indicated "a positive dose-response relation between exposure to cumulative dust and the mortality of lung cancer. High arsenic content in dust particles, together with crystalline silica, may play an important role in causing increased mortality from lung cancer" (Chen et al., 2006). Unlike the previous paper on this cohort (Chen and Chen, 2002), no attempt was made to disentangle the highly correlated exposures between arsenic and silica. However, separate analyses were done for three mines from Dachang where arsenic concentrations were high and one mine in Limu where there was much lower arsenic exposure. There were differences observed in the trends for lung cancer risk between the Dachang and Limu mines. The cumulative risk of lung cancer was significantly elevated in Dachang mines but only slightly elevated in the Limu mine. The authors suggested that this finding may have been due to the higher arsenic levels in the Dachang mine particles since both Limu and Dachang particles had similar silica levels. However, since arsenic exposure was highly correlated with silica dust exposures ($r = 0.82$), further isolating or quantifying the effect of respirable silica in this cohort was not possible.

Three papers concerning principally arsenic and uranium exposures in Chinese tin mines also reviewed silicosis or silica exposure in reference to lung cancer. Qiao et al. (1997) raised the issue of either silicosis or silica exposure as posing a risk for lung cancer in a study of Yunnan province tin miners who had elevated exposures to radon and arsenic; the age adjusted relative risk for lung cancer mortality for radon was 3.91 and for arsenic, it was 4.94 when comparing workers in the highest to the lowest exposure quartile. When the authors conducted a single variable analysis, the relative risk of lung cancer for silicotics was 1.46 (95% CI 1.02-2.09), suggesting to the authors that "silicosis appears to be in age-adjusted analysis to be a lung cancer risk factor…(and) will require more detailed assessment of exposure to silica and adjustment for potential confounders".

Hua et al. (1992, 1994) published a cohort and a nested case-control study, sequentially. In both papers no specific reference is made to silica exposure, but the authors did examine silicosis as a risk factor in the case-control study. The cohort consisted of 1,113 male Daching tin miners in which the authors found an exposure-response relationship between metal ore dust exposure and lung cancer and an interaction

between smoking and metal ore dust exposure. In the 1994 case-control study, Hua et al. found that the presence of silicosis did not independently contribute to predicting risk in the presence of other variables.

I.C.2.k. British coal miners exposed to respirable quartz.

Miller et al. (2007) and Miller and MacCalman (2009) reported on a follow-up of a mortality study of British coal miners originally conducted by Miller et al. (1997). The two follow-up reports on mortality analyzed a cohort of 17,800 miners and extended the analysis through the end of 2005. By that time there were 516,431 person years of observation, an average of 29 years per miner, with 10,698 deaths from all causes. Causes of deaths of interest included pneumoconiosis, other non malignant respiratory diseases (NMRD), lung cancer, stomach cancer, and tuberculosis. The authors noted that no additional exposure measurements were included in the updated analysis, since all the mines had closed by the mid 1980's. However, some of these men might have had additional exposure at other mines or facilities, not reported in this study. (One of these coal mines has already been discussed in Section I.3.a, above, for the relationship of silica exposure and silicosis progression and morbidity among 547 miners exposed to high levels of quartz during the early to mid 1970's.)

For this cohort mortality study there were analyses using both external and internal controls. The external controls used British administrative regional age-time and cause specific mortality rates from which to make standardized mortality rate (SMR) calculations. The internal controls from the mines used Cox's proportional hazards regression methods, which allowed for each individual miner's measurements of age and smoking status, as well as the individual's detailed dust and quartz time-dependent exposure measurements. Cox regression analyses were done in stages, with the initial analyses used to establish what factors were required for baseline adjustment.

For the analysis from external mortality rates, the all-cause mortality SMR from 1959 through 2005 was 100.9 (95% CI, 99.0-102.8), based on all 10,698 deaths. However, these death ratios were not uniform over time. The period from 1990-2005 had an all-cause SMR of 109.6 (106.5-112.8), while the ratios for previous periods were <100. This pattern of recent 1990-2005 increasing SMRs was also seen in the recent cause-specific deaths from chronic bronchitis, SMR = 330.0 (268.1-406.2); tuberculosis, SMR = 193.4 (86.9-430.5); cardiovascular disease, SMR = 106.6 (102.0-111.5); all cancers, SMR = 107.1 (101.3-113.2); and lung cancer, SMR = 115.7 (104.8-127.7). SMR from overall NMRD was 142.1 (132.9-152.0) in this recent period, and remained highly statistically significant. In their previous analysis on mortality from lung cancer, reflecting follow-up through 1995, Miller et al. (1997), had not found any increase in lung cancer mortality risk.

Among the strengths of this study are the availability of detailed time-exposure measurements of both quartz and total mine dust, detailed individual work histories, and individual smoking histories. All these data were used in the internal analyses using Cox regression methods. Using these analyses, Miller and MacCalman (2009) estimated

relative risks (RR) for a cumulative lifetime exposure of 5 gram-hours/m^3 (ghm^{-3}) respirable quartz (equivalent to approximately 0.055 mg/m^3 for 45 years) and/or 100 ghm^{-3} total dust. They presented estimated relative risks for various causes of death - pneumoconiosis, COPD, ischemic heart disease, lung cancer, and stomach cancer - based on models with either single (dust or quartz) exposures or to simultaneous exposures to both, either with or without 15-year lag periods. Generally, the risk estimates are slightly greater using 15 year lag periods. For the models using only quartz exposures with a 15-year lag, only pneumoconiosis, RR = 1.21 (1.12-1.31); COPD, RR = 1.11 (1.05-1.16); and lung cancer, RR = 1.07 (1.01-1.13) showed statistically significant increased risks.

Exposure to coal dust was not a predictor of lung cancer mortality; exposure to crystalline silica remained statistically significantly associated with excess lung cancer risk when both coal dust and silica dust exposure were included in the regression model. According to Miller and MacCalman (2009), other analyses conducted have not shown that exposure to radon or diesel fume is associated with an increased cancer risk among British coal miners.

OSHA believes that this study of a large British coal mining cohort provides convincing evidence of the carcinogenicity of crystalline silica. This large cohort study with almost 30 years of follow-up demonstrated a positive exposure-response after adjusting for smoking histories, and there was no evidence that exposure to the potential confounders radon and diesel were associated with excess lung cancer risk. Because of the strengths of this study, OSHA has included it in its Preliminary Quantitative Risk Assessment (Section II), where the quantitative aspects of the study are presented in greater detail.

I.C.2.l. North American industrial sand workers.

Steenland and Sanderson (2001) analyzed a cohort of 4,626 U.S. industrial sand workers (18 plants, 11 different states) who had worked at least 1 week and had adequate personal and work history data. Mortality follow-up was from 1960 to 1996. The mortality experience of these workers was evaluated based on SMRs, using the general U.S. population as reference, or as standardized risk ratios (SRRs), using the lowest quartile exposure group of the cohort as the referent population.

A follow up nested case-control study was also conducted that was analyzed by conditional logistic regression to evaluate the relationships between lung cancer mortality and cumulative exposure, average exposure, duration, and peak exposure. In the analysis, each lung cancer case (n = 75) was matched with 100 controls on age, gender, race and survival time. The average year of first employment was 1967, with an average length of employment of 8.8 years

The method of determining exposure and developing a job exposure matrix was reported by Sanderson et al. (2000). Exposure data were based on 4,269 compliance dust samples taken from 1974 to 1996 by the Mine Safety and Health Administration (MSHA) and prior to 1977, U.S. Bureau of Mines (Sanderson et al., 2000). A cross-sectional

industrial hygiene survey conducted for the National Industrial Sand Association in 1946 (Hatch et al., 1947) was used to estimate exposure for prior years. In these earlier surveys, counts of particles smaller than 5 μm were made from midget impinger samples, and the percent quartz was determined by XRD from dust collected from high volume air samples as well as from settled dust. A total of 125 area samples were taken by Hatch et al. (1947) at 19 sand plants characterizing 8 broad job classifications. The particle count data were converted to equivalent job-specific measures of respirable mass of quartz using methods described by Ayer et al. (1973), Rice et al. (1984), and Sheehy and McJilton (1987). This method assumes a constant factor to convert particle counts to gravimetric respirable dust mass equivalents (1 mppcf = 0.1 mg/m^3); respirable silica mass was then estimated based on the quartz content as documented in Hatch et al. (1947). The results reported by Hatch et al. (1947) indicate that the silica content of quartz particles of less than 5μm in size ranged from 90 percent or greater in the pulverizing mill and crusher operations to 24 and 32 percent in some screening and drying operations, as analyzed by XRD of settled air sample particulate of less than 5μm.

Steenland and Sanderson (2001) characterized exposure for 10 job categories, 8 of which were the same job categories as were used in Hatch et al. (1947) and an additional 2 categories (administrative and other) drawn from the 1974 to 1988 data analysis to characterize exposure. A job exposure matrix was created containing 120 cells reflecting 3 time periods, 4 plant groupings, and the 10 job titles. The 1947 data from Hatch et al. were characterized similarly by 10 job groups and four plant groups. Exposure estimates between 1946 to 1974 were made by linear extrapolation from the 1974 to 1988 data back to the 1946 data; exposure for years prior to 1946 was assumed to be the same as that in 1946 (Sanderson et al., 2000).

The authors were not able to identify any significant exposure to other occupational lung carcinogens. Limited data on smoking for 358 workers aged 25 to 64 years were used to estimate the impact of smoking differences on lung cancer rates for the cohort versus the U.S. population, but the data were not sufficient to directly adjust risk estimates. Exposure-response trends were analyzed based on a subcohort of workers for which detailed work histories were available (n = 4,027). The authors also reanalyzed the data restricted to those workers with six or more months employment (n = 3,361) in order to eliminate short-term workers who might have had high excess mortality for reasons unrelated to occupational exposures (Steenland and Sanderson 2001).

Compared to the U.S. male general population, there was an increased mortality from all causes combined (SMR 123; 2,819 deaths), all cancers (SMR 128; 416 deaths), and other diseases. In particular, mortality from cancers of the lung/trachea/bronchus were statistically significantly increased (SMR 160; 95% CI 131-193, 109 deaths). Smoking data analysis revealed a higher prevalence of smoking in the cohort compared with the U.S. population. This would have been expected to cause a 10 to 20 percent increase in lung cancer mortality, which is insufficient to explain the observed 60 percent excess. There was also a large excess of deaths from silicosis (SMR 6,630) or unspecified pneumoconiosis (SMR 777).

Elimination of short-term workers (< 6 months of employment) reduced, but did not eliminate, the overall lung cancer mortality excess (SMR 149, 95% CI 117-187). According to the authors, internal SRR analyses for lung cancer showed a positive, but not statistically significant, trend in SRRs, (p for trend = 0.07) for cumulative silica exposure lagged 15 years. Analysis of the lung cancer mortality by duration of employment did not show a consistent trend. Positive exposure-response trends were found for lung cancer mortality with unlagged cumulative silica exposure (p = 0.04) and with cumulative silica exposure lagged 15 years (p = 0.08). A slightly more pronounced positive exposure-response trend (See odds ratios in Table I-12) was observed in quartile analysis of average respirable silica exposure (p = 0.003). Average is defined by Steenland and Sanderson (2001) as "cumulative exposure divided by duration of exposure." There was a twofold excess risk for those in the highest quartile of either average or cumulative exposure. In contrast, duration of exposure with and without a time lag did not show a trend with lung cancer risk. The authors concluded that this study supports the IARC determination that crystalline silica is a lung carcinogen.

Table I-12. Industrial Sand Workers: Odds Ratios from a Nested Case-Control Study of Lung Cancer Mortality by Quartile of Cumulative and Average Exposure to Respirable Quartz for Males Working Six Months or Greater in 18 Industrial Sand Plants

	Exposure Quartiles				p-value for Trend
	Q1	Q2	Q3	Q4	
Cumulative Exposure					
Range of Exposure Quartile in mg/m^3-years	0-0.18	>0.18-0.59	>0.59-1.23	>1.23	
Odds Ratio – unlagged (# of cases)	1.0 (16)	1.28 (20)	0.73 (12)	1.70 (27)	0.04
Odds Ratio –15-year lag (# of cases)	1.0 (20)	1.35 (21)	1.63 (18)	2.00 (16)	0.08
Average Exposure **					
Range of Exposure Quartile in mg/m^3	0-0.023	>0.023-0.046	>0.046-0.065	>0.065	
Odds Ratio (# of cases)	1.0 (15)	0.92 (12)	1.44 (20)	2.26 (28)	0.003

*Adapted from Steenland and Sanderson (2001, Table 6)
** Average exposure is defined as cumulative exposure divided by duration.

McDonald et al. (2001) conducted a cohort study that overlapped with the industrial sand cohort (18 plants, 4,626 workers) studied by Steenland and Sanderson

(2001). The cohort included 2,670 men employed before 1980 for three years or more in one of eight North American (7 U.S. and 1 Canadian) sand-producing plants and 1 large associated office complex. Information on cause of death was obtained for 99 percent of the deceased workers for a total 1,025 deaths representing 38 percent of the cohort. A case-control analysis based on 95 lung cancer deaths from this cohort was also conducted by Hughes et al. (2001). Both of these studies relied on an analysis of exposure information published by Rando et al. (2001).

Six (6) of the nine (9) facilities from which the cohort was defined were also studied by Steenland and Sanderson (2001), and some cross-checking of data indicated that approximately two-thirds of the subjects studied by Hughes et al. (2001) were included in the Steenland and Sanderson (2001) study (personal communication, K. Steenland, 2003).

The cohort study by McDonald et al. (2001) showed a statistically significantly elevated SMR for trachea/lung/bronchus cancer (SMR = 150, p = 0.001, based on U.S. rates) for deaths occurring 20 or more years from hire. The SMR for trachea/lung/bronchus cancer declined slightly when regional cancer mortality rates were used (SMR = 139, p = 0.001, 83 deaths). SMRs for trachea/lung/bronchus cancer, using U.S. rates, increased with increasing time since hire (87, 127 and 162 for <20, 20-30 and ≥ 30 years, respectively), but not with duration of employment. There was no consistent correlation between duration of employment and lung cancer risk in this cohort. SMRs for NMRD and tuberculosis were statistically elevated for deaths occurring 20 years or more from hire (SMR = 178 (97 deaths) and 393 (8 deaths), respectively; $p < 0.01$). McDonald et al. (2001) also noted a statistically significant elevation in chronic renal disease (SMR = 212; 16 deaths; $p < 0.002$).

The exposure assessment conducted by Rando et al. (2001) was a comprehensive historical reconstruction and was based on substantial exposure data. There were 14,249 respirable dust and silica samples from 9 plants taken from 1974 to 1998. Rando et al. (2001) relied on similar historic data used by Sanderson et al. (2000) in developing a job exposure matrix. Historic samples were taken with the Greenburg-Smith impinger and particles with diameter less than 5.0 µm were counted microscopically. Job-specific samples (346) were taken from the National Industrial Sand Association during 1946 at 19 plants in the U.S. with another survey conducted in 1954 and 1955 (Hatch, 1954; Hatch et al., 1947; Hatch and Schreibis, 1955; Hatch and Wellington, 1955). Exposure estimates prior to 1946 were made based on plant walkthroughs and written documentation, site-specific exposure data for one-half of the cohort, and interviews with plant managers and employees to develop the job-exposure matrix. Overall, Rando et al.'s (2001) assessment was based on exposure measurements that were available for 31 site-specific processes in three large plants representing one-half of the cohort. Industry wide process-specific mean exposure values were used to estimate historical exposure for the workers at the six remaining plants. Finally, adjustments in exposure were made for the use of respirators between 1974 and 1996, considering both the protection factor of respirators and an estimate of the frequency of respirator use.

In reference to the older exposure data, conversion from particle counts to respirable mass was not possible from empirical data because side-by-side samples were not available. Consequently, the authors developed a computational algorithm that considered particle size distribution and collection efficiencies of the impinger-microscope method of counting particles and the cyclone-filter method of measuring respirable mass. A conversion factor of 274 $\mu g/m^3$ per million particles per cubic foot (mppcf) was used to convert historic dust measurements to mass respirable dust equivalents which, according to Rando et al., "[m]ay be positively biased to some (unknown) extent…" Rando et al. (2001) acknowledged that other investigators show smaller industry-specific conversion factors: 110 $\mu g/m^3$ per mppcf for Vermont granite sheds (Ayer et al., 1973) and 90-180 $\mu g/m^3$ per mppcf for U.S. diatomaceous earth (Seixas et al., 1997). The effect of using a relatively high conversion factor in estimating exposure to respirable quartz from particle-count data will be to overstate the historic exposure estimate.

The percentage of silica in the historic sampling conducted by Hatch et al. (1947), Hatch and Schreibis (1955) and Hatch and Wellington (1955) was partially determined from settled dust. Rando et al. (2001) elected to create a profile of percent silica (type of profile not specified by author) based on more current respirable air samples and X-ray diffraction analysis. According to Rando et al. the settled dust samples "… [a]ppear extraordinarily high and are possibly unreliable. On the other hand, silica assays in the modern database are likely to be negatively biased, since high loadings derive primarily from particles released from the sand as it is being processed." This would tend to underestimate historic exposures. OSHA notes that these two potential biases of the exposure estimate might, to some extent, be offsetting.

Hughes et al. (2001) conducted a nested case-control study of 95 lung cancer deaths of the cohort studied by McDonald et al. (2001). Two controls were selected per case, matched on plant and date of birth, and outliving the case. There was no indication in the paper that the exposure history of controls was appropriately truncated when it extended beyond the age when the index case failed. Both categorical analyses and conditional logistic regression were used to examine relationships with cumulative exposure, log of cumulative exposure, and average exposure, although results from the categorical analysis were emphasized in the report. Smoking data were collected from medical records supplemented by information from next of kin or living subjects for 91 percent of cases and controls. Exposure levels over time were estimated via a job-exposure matrix developed for this study. The 50^{th} percentile (median) exposure level of cases and controls for lung cancer were 0.149 and 0.110 mg/m^3 respirable silica respectively, slightly above the current OSHA standard. Silicosis mortality showed a positive exposure-response trend for lung cancer with cumulative exposure and average exposure concentration, tending to validate the exposure estimates. Statistically significant positive exposure-response trends for lung cancer were found for both cumulative exposure (lagged 15 years) and average exposure concentration, but not for duration of employment, after controlling for smoking. With exposure lagged 15 years and after adjusting for smoking, increasing quartiles of cumulative silica exposure were associated with lung cancer mortality odds ratios of 1.00, 0.84, 2.02 and 2.07 (p for trend

= 0.04). This monotonic increase was seen for both lagged and unlagged cumulative exposure, when the four upper exposure categories were collapsed into two. There was no indication of an interaction effect of smoking and cumulative silica exposure (Hughes et al., 2001).

McDonald et al. (2005) conducted a follow-up study extending the observation period by six years, from 1995 to 2000. The primary aim of the follow-up study was to determine if death from chronic renal disease was related to silica exposure and to determine whether the previous findings of lung cancer and silicosis in McDonald et al. (2001) and Hughes et al. (2001) were confirmed. This discussion is limited to the follow-up on lung cancer and silicosis mortality (See Section I.E for a discussion on silica-related renal disease). In the original study, there were 990 deaths among a cohort of industrial sand workers employed in nine plants. The follow-up study was limited to workers in eight U.S. plants, eliminating the Canadian plant, and identified an additional 231 deaths for a total of 1205 deaths (49 percent of the cohort). Vital status and cause of death was obtained and determined for 99 percent of the cohort. Exposure estimation and case-control selection and analysis were similar to the original study. Difference in smoking was analyzed by conditional multiple regression and exposure categories were the same as in the original study (McDonald et al., 2005).

The findings of the follow-up study confirmed the findings of the original studies. SMRs for all causes of death, based on U.S. male death rates, for workers who died 20 or more years after hire were elevated in the follow-up (SMR = 142; $p < 001$) as compared to the initial study (SMR = 118; $p < 0.001$). Elevated SMRs were also identified for lung cancer (SMR = 147, p = 0.001, 102 deaths) and NMRD (SMR = 164; p = 0.001, 116 deaths of which 26 were silicosis deaths) for workers who died 20 or more years after hire. These values were not significantly different than the initial study.

A nested case control analysis found that, with exposure lagged 15 years, increasing quartiles of cumulative silica exposure were associated with increases silicosis mortality, with odds ratios of 1.00 (N = 7), 2.54 (N = 7), 4.55 (N = 8), and 5.16 (N = 8) (p for trend = 0.017). Regarding the association between cumulative silica exposure and silicosis mortality, the authors stated "Taking into account the very small numbers (of cases), the original and updated (odds) ratios agree reasonably well, especially in those lagged 15 years, which demonstrated a clear and statistical trend. Further analysis of more recent data showed that the risk of death from silicosis was independently related to both duration and intensity of exposure and was strongly related to smoking…" (McDonald et al., 2005). In the initial and follow-up studies for both lagged and unlagged exposure, the association between lung cancer and cumulative silica exposure were very similar. For the updated study, with exposure lagged 15 years and after adjusting for smoking, increasing quartiles of cumulative silica exposure were associated with lung cancer odds ratios of 1.00 (14), 0.94 (15), 2.24 (31), and 2.66 (30) (p for trend = 0.006). The slope of the exposure-response was slightly greater than was described in the earlier Hughes et al. (2001) study.

As was observed in the original studies, the follow-up study found that the risk of lung cancer was related to average silica concentration but not to the length of employment. Smoking was independently and strongly related to silicosis and lung cancer. The odds ratio for silicosis among smokers versus nonsmokers was 5.09 (95% CI 1.29-20.07). The respective odds ratio for lung cancer among smokers versus nonsmokers was 5.37 (95% CI 2.33-12.35).

The results of the Hughes et al. (2001) study support the thesis that silica exposure is positively associated with increased lung cancer mortality risk. Furthermore, the two sets of industrial sand studies (four papers by McDonald, Hughes, and Rando, and two papers by Steenland and Sanderson), despite the differences in the cohorts, mutually reinforce each other in terms of their positive findings. Given the quality of the underlying exposure and job history data available for the Hughes et al. (2001) study, and the ability of the study to adjust for smoking history, OSHA considers this study particularly suitable for inclusion in its Preliminary Quantitative Risk Assessment. The McDonald et al. (2005) study is equally convincing and yielded results similar to those of Hughes et al.; however, as explained in the risk assessment section, only the Hughes et al. study contained sufficient information upon which to construct a quantitative exposure-response model.

I.C.2.m. United Kingdom industrial sand workers.

This is a retrospective cohort mortality study of 2,703 United Kingdom (UK) industrial sand workers in seven plants who were employed for at least one year from 1950 to 1986 (Brown and Rushton, 2005b). The cohort was followed until 2001 by which time there were 764 deaths representing 28 percent of the cohort. The overall mortality rate for the cohort was lower than expected in the general population, likely the result of a healthy worker effect. Mortality rates for all cancers, including lung cancer, circulatory diseases, and non-malignant respiratory disease were not elevated. Only two deaths were attributable to pneumoconiosis, one of which was confirmed silicosis. Mortality from lung cancer did not show a correlation with cumulative exposure to respirable silica. Smoking data were not available.

In a separate paper, Brown and Rushton (2005a) developed the job-exposure matrix (JEM) from personal records and a total of 2,429 personal and 583 static area respirable silica measurements that were collected from the seven plants between 1978 and 2000. All exposure measurements were made using current methods for collecting and analyzing respirable silica samples. The JEM profile had five quarry types and three time periods and 12 grouped job titles. Each worker was assigned to job categories based on their work histories and cumulative respirable silica exposures were estimated from the JEM profile. No exposure data were available for between 1950 and 1977; for this period, exposure was estimated by linear extrapolation with the highest exposure assumed to have occurred in 1950 and with exposure decreasing linearly through 1977. The high exposure areas, greater than 0.3 mg/m^3, were predominately located in the dry and silica flour areas. Fifteen (15 percent) of the samples taken within the "dry areas (baggers, dryers, other) and silica flour" areas of the plant exceeded 0.3 mg/m^3 and 90

percent of the samples that exceeded 0.3 mg/m^3 plant wide were in these areas. The authors noted in their discussion that the geometric mean exposure of 0.09 mg/m^3 was higher than the geometric mean exposures reported in the two U.S. sand cohorts (0.026 mg/m^3 from Sanderson et al., 2000 and 0.042 mg/m^3 from Rando et al., 2001) during similar time periods (Brown and Rushton, 2005b).

This study did not find an association between cumulative silica exposure and lung cancer, a result that is inconsistent with the U.S. industrial sand studies (Hughes et al., 2001; McDonald et al., 2005; Steenland and Sanderson, 2001). In a letter review, Steenland (2005a) identified two issues that may explain this discrepancy. First, as indicated by IARC (1997), positive findings for lung cancer have not been consistently reported across studies, possibly reflecting differences in specific mineral properties and toxicities of silica in different workplaces. More importantly, Steenland (2005a) noted that the cumulative exposures of the workers studied by Brown and Rushton (2005b) was significantly lower compared to those experienced by the 10 cohorts used by Steenland et al. (2001a) in the pooled analysis. The Brown and Rushton study (2005a) reported a mean cumulative exposure of 0.31 mg/m^3-years and the maximum exposure quartile consisted of workers exposed to more than 1.0 mg/m^3-years. (The exact distribution of the highest exposure group is not provided by Brown and Rushton, 2005a.) By comparison, the mid-quintile of cumulative silica exposure reported by Steenland et al. (2001a) was 2.0-5.4 mg/m^3-years which is the lowest quintile showing increased relative risk. (Steenland et al., 2001a, pooled analysis had RRs of 1.0, 1.0, 1.3, 1.5, and 1.6 for <0.4, 0.4-2.0, 2.0-5.4, 5.4-12.8 and >12.8 mg/m^3-years.) Steenland (2005a) suggested that the low silicosis mortality reported by Brown and Rushton (2005b) reflects the overall low cumulative exposure in this cohort.

A third consideration, as was noted by Brown and Rushton (2005b), is that a large portion of the cohort had relatively short service times in the industry, with over one-half the cohort deaths and almost three-fourths of the lung cancer mortalities having had less than 10 years service. Considering the apparent high turnover in this industry and the absence of prior occupational histories, exposures from work experience other than in the industrial sand industry could be a significant confounder. This is reinforced by data in Table 1 of Brown and Ruston (2005b), which indicates that 34 of the 81 lung cancer deaths (41%) occurred among workers less than five years after the start of employment, representing less than 10 percent of the person-years at risk. Similarly, only 8 (<10%) of the lung cancer deaths occurred among workers more than 20 years after the start of employment, where an effect might most be expected. Steenland (2005a) also commented on the eight lung cancer deaths occurring in workers with greater than 20 years of employment, noting that the overall deficit in lung cancer could be attributed to workers in one plant, where there was a deficit in all causes of mortality, possibly due to workers from this plant having less follow-up time and exhibiting a greater healthy worker effect. Brown and Rushton (2005b) also noted that the absence of smoking data is another potential confounding factor, but this was minimized by internal comparison between quartiles as previously discussed. Lastly, the authors indicated that this is a relatively young cohort and the use of case-control study design would allow for more detailed exposure reconstruction, prior work history, and process control history.

OSHA believes that the industrial sand study conducted by McDonald et al. (2001), Hughes et al. (2001) and Rando et al. (2001) with a recent follow-up study by McDonald et al. (2005) are the most thorough and complete of the industrial sand studies. Reasons include the availability of exposure data based on modern methods of collection and analysis; exposures were ascertained for individual cohort members; smoking histories were available; the cohort had long-term work experience averaging 19 years (compared to the Steenland and Sanderson, 2001 average of 9 years and Brown and Rushton, 2005a, 2005b, average employment time not provided); and use of a nested case-control design. Furthermore, OSHA believes that the findings of the Brown and Rushton study should be discounted due to the low cumulative exposure profile; the unusual distribution of lung cancer deaths among relatively short-tenured workers; the relative youth of the cohort having inadequate accumulation of exposure years; and possible confounding or misclassification caused by the absence of smoking data, prior work exposures in an apparently highly transitory cohort, and the absence of a more discerning nested case-control study.

I.C.2.n. United Kingdom pottery workers.

Winter et al. (1990) published preliminary findings from a cohort of workers employed as of 1970/1971 and assembled from a sample of 40 plants based on a national cross-sectional survey of the British pottery industry. The cohort was followed until 1985. Because of the difficulties in tracing older cohort members, the analysis was restricted to 3,669 men under 60 years of age at the time of the survey. This limitation was of concern to the authors because of the potential for selection bias given the long latency of lung cancer, and was noted in IARC's 1997 review. A total of 60 lung cancer deaths were observed with associated SMRs of 140 (95% CI 107-180) and 132 (95% CI 100-169) based on national and locally adjusted rates, respectively. Smoking information and exposure measurements were also obtained from the 1970/1971 cross-sectional survey (Winter et al., 1990). Radiographic findings and analysis were not presented. The exposure data varied by industry subtype and job groupings and mean respirable quartz exposures ranged from 0.01-0.20 mg/m^3. The authors used a simplified cumulative exposure model based on job title exposures derived from cross-sectional environmental sampling multiplied by the total number of years worked at the plant by each employee per 1970/1971 job title. Cumulative exposure was grouped into four quartiles for analysis.

There were no excesses of lung cancer mortality by product or job group. However there was an indication of increased lung cancer mortality with increased cumulative exposure (SMR = 108, 99, 162, and 151 for each of the exposure quartiles). There was also a trend of increased lung cancer with increased duration of employment (neither confidence limits or p values were provided).

McDonald et al. (1995) conducted a preliminary analysis of proportionate mortality in a cohort of 7,020 male pottery workers born between 1916 and 1945 with mortality follow-up to June 30, 1992. Dates and causes of death were confirmed and

copies of death certificates were obtained for 92.5 percent of the cohort. The investigators calculated the proportional mortality ratios (PMR) for lung cancer based on deaths from lung cancer in England and Wales, 1961-1992, standardized for the quinquennium of date of birth and age at death. In these analyses, the authors use 90 percent confidence intervals and probabilities based on a one-tailed distribution of the chi-square. The overall PMR for lung cancer was 124 (90% CI 106-144). After exclusion of known asbestos exposure, the PMR for lung cancer was reduced to 122 (90% CI 104-143) but was still statistically significantly increased. Excluding those with pneumoconiosis on the death certificate resulted in a PMR of 123 (90% CI 105-144), which was also statistically significantly increased. For those with pneumoconiosis also on the death certificate, the PMR increased to 175 (90% CI 70-360), but this increase was not statistically significant. The authors noted, however, that 70 percent of the deaths in the cohort came from one town that had a high background mortality rate for lung cancer. When they computed the lung cancer PMR of their cohort relative to that of this town in 1979-1983, the PMR was estimated to be 104 (confidence interval not reported).

McDonald et al. (1995) also conducted a nested case-referent study in order to assess the effect on lung cancer mortality of smoking, duration of exposure, asbestos work, and ILO X-ray score for small opacities. Since there was a substantial difference in smoking habits between cases and referents, the authors decided to compare just the 47 cases and 47 referents that were smokers and for which x-ray readings were available. The results showed a statistically significant effect for silica exposure duration (≥10 years), for pottery work (OR = 2.8, 90% CI 1.1-7.5), and for past asbestos work (OR = 3.8, 90% CI 1.1-12.8), but not for small opacities (OR = 0.8, 90% CI 0.2-3.6), suggesting that the risk of lung cancer was not associated with radiologically-defined silicosis.

Cherry et al. (1995) also conducted a person-years analysis restricted to 470 deaths occurring between January 1985 and June 1992. This analysis resulted in a lung cancer SMR of 128 (90% CI 104-157) compared to local rates.

Cherry et al. (1998) published a full description of results that had been reported in a preliminary manner by McDonald et al. (1995) and Cherry et al. (1995) previously. The investigators excluded men who had been living outside the pottery areas at the time of the first medical examination, worked previously with asbestos or in foundries, or who had been employed for more than one year in coal mining or exposed to other dusts, limiting the analysis to 5,115 male workers. The date of first employment ranged from 1929 to 1982, with 80 percent employed before 1970. Only 52 of 88 identified lung cancer cases met the criteria for inclusion in the nested case-control study due to destroyed work records, evidence of job histories in other industries with expected silica exposure, and in one case, only 10 years of employment since first exposure. Three or four controls were matched to each case on date of birth and date of first exposure making a total of 247 controls.

A job-exposure matrix (JEM) consisting of 569 job titles in 11 major process groups expressed over six decades 1930-1990's was used to calculate individual maximum, cumulative, and average lifetime exposure to crystalline silica. This was

based on employment records, a detailed knowledge of process control and modifications over time and available exposure data (Burgess, 1998). Extensive exposure records were available for the period from the late 1960s to 1992. Over 1,000 personal samples had been taken with a cyclone pre-selector. Infrared analysis was first conducted between 1960 and 1975, followed by x-ray diffraction from 1975 to1980. From the 1950s to the 1960's, approximately 350 particle count samples were taken with a static area sampler. Air sampling was collected using a thermal precipitator and particle counting conducted post incineration. Exposures post-1960 generally ranged from 50 to 200 $\mu g/m^3$ of respirable silica (Burgess et al., 1997; Cherry et al., 1998). Burgess et al. (1997) elected to use the conversion factor developed by Rice et al. (1984). Two data transformations were necessary to express particle counts from a thermal precipitator as cyclonic gravimetric data: (1) the conversion from thermal precipitator to impinger (thermal precipitator expressed in particles per cubic centimeter (ppcc) being equivalent to an impinger measurement = 0.02832 million particles per cubic foot (mppcf); based on Jahr (1969) and (2) the conversion of impinger particle count measurements to gravimetric data using the conversion factor developed by Rice et al. (1984) for the North Carolina dusty trades (1 mppcf = 0.09 mg/m^3 of respirable dust). The conversion factor formula as provided by Burgess (1998) was 50 ppcc x 0.09 x 0.02832 = 0.127 mg/m^3 (Burgess, 1998).

The authors also estimated the percentage of quartz to be 12 percent (+/-2%), for typical respiratory dust in potteries (Bloor et al., 1971) and a post-firing estimate of the percentage of cristobalite of 6 percent (HSE, 1990).

Documentation of historic process modifications, ventilation controls, and rates of production were used to extrapolate exposures for the 1930s and 1940s where exposure data were not available. Burgess et al. (1997) conducted a pilot study on a sub-sample of the larger cohort to determine the sensitivity of the JEM to discern a dose-response for ILO radiological scoring for silicosis prior to conducting the full study. This study indicated prominent increases in silicosis mortality risk with increasing exposure and the p-value for trend was statistically significant for the reported exposure gradients (Burgess et al., 1997).

For the overall cohort, the lung cancer SMRs based on background rates for England/Wales and for local rates were 191 (95% CI 148-242) and 128 (95% CI 99-162), respectively (Cherry et al., 1998). Although the SMR based on local rates barely missed being statistically significant, the authors noted that the observed number of cases differed significantly from expectation ($\chi^2 = 3.91$; $p < 0.05$). The nested case-control analysis calculated separate odds ratios for cumulative exposure, duration of exposure, and mean concentration. This resulted in smoking-adjusted ORs of 1.67 (95% CI 1.13-2.47), 1.66 (95% CI 1.14-2.41) and 1.60 (95% CI 1.11-2.31) for mean concentration lagged 0, 10, and 20 years, respectively. Only mean concentration of exposure was positively related to lung cancer ($p < 0.008$ for all three lag periods). Neither cumulative exposure nor duration of employment was positively related to lung cancer. Mean exposure concentrations of silica were 21 percent higher for cases than for controls and were consistently higher for those with employment durations less than 20 years. The

findings also revealed no evidence of an association between radiological pulmonary opacities and lung cancer. The authors concluded that their findings indicated that the exposure to crystalline silica in the pottery industry carries an increased risk of lung cancer mortality.

I.C.2.o. Chinese pottery workers.

Chen et al. (1992) conducted a mortality study of 13,719 pottery workers employed from 1972 to 1974 at eight pottery factories in south central China with follow-up through 1989. The original study included workers from tungsten, tin, clay, copper and iron mines, but only the study involving the pottery worker subcohort was considered by IARC (1997) to be among the least confounded studies because pottery factories had higher dust levels compared to the mines and more importantly, the exposure to potential confounding pulmonary carcinogens was minimal.

In the cohort study, historic data from workplace air sampling for total dust and quartz analysis of settled dust were used to estimate job-specific exposures in each of several calendar-year periods (Wu et al. 1992; Zhuang et al. 2001). Based on job-specific exposure estimates, each cohort member was classified into one of four total dust exposure levels: high, medium, low, and non-exposed.

A low lung cancer mortality rate (SMR = 58, $p < 0.05$) among pottery workers was found using national mortality rates for comparison; however, an unknown percentage of these workers were considered non-exposed (estimated to be 50 percent by Steenland et al., 2001a). The cohort analysis did not show an increased risk for lung cancer with increasing dust exposure (data not provided). The relative risk for lung cancer mortality among silicotics relative to nonsilicotics was 1.63 (95% CI 0.8-3.4) in pottery workers.

McLaughlin et al. (1992) conducted a more quantitative nested case-control study from the same cohort of 62 male pottery workers who died from lung cancer before 1990. Cases were matched with 238 controls on age (decade of birth) and factory. Exposure to silica dust (expressed as a cumulative exposure measure) was assigned for each study subject based on historical industrial hygiene records and a job-exposure matrix developed by Dosemeci et al. (1993). Exposure data were available from routine company surveys between 1950 and 1987. All exposure data were total-dust area measurements using a gravimetric method with sample times of 20 to 30 minutes. Records were available for approximately 1,000 area samples collected with high flow pumps operating at approximately 25 liters/minute. Assignments of exposure were by plant, job and calendar year. In the case-control study, approximately 51 percent of the assignments were based on quantitative total dust data. This ranged from 1 to 2 percent during the 1950s to approximately 70 percent in the 1980s. For exposures prior to 1950, the 1950 exposure data were applied (McLaughlin et al., 1992). Percentages of respirable dust and silica content of the total dust estimated at the facility level only, due to lack of specific measurements for job titles or process areas were used to estimate silica exposure (Dosemeci et al., 1993; Zhuang et al., 2001).

Vital status and cause of death were determined for each worker. Smoking data were obtained by interviews of the subjects or their next of kin (McLaughlin et al., 1992). The authors found a positive, but not consistent, relationship between cumulative respirable silica dust exposure and lung cancer among pottery workers. When data were adjusted for age and smoking, there was a suggestive trend with increasing quartiles of respiratory crystalline silica exposure (OR equal to 1, 1.8, 1.5 and 2.1 for cumulative exposures of none, low, medium, and high, respectively). The exposure-response gradient did not reach statistical significance and confidence limits were not provided. The IARC panel (1997) provided an independent calculation of confidence limits which is presented in Table I-13.

Table I-13. Odds ratios reported by McLaughlin et al. (1992) for Chinese pottery workers, with confidence intervals provided by IARC

Cumulative Respirable Silica (μg/m3 - years)	OR	No.	95% CI*
None ---	1.0	11	
Low (0.1-8.69)	1.8	17	1.04-2.87
Medium (8.70-26.2)	1.5	27	0.99-2.18
High (> 26.3)	2.1	7	0.80-4.12

*CI = confidence interval

McLaughlin et al. (1992) found the relationship between cumulative silica exposure and lung cancer mortality of interest because only polyaromatic hydrocarbons (PAHs) were present as a potential confounder and adjustment for PAHs did not reduce the association between lung cancer mortality and exposure to silica. Despite the high prevalence of silicosis, there was no evidence of an increased risk of lung cancer among silicotics compared to non-silicotics; silicosis was present in 13 percent and 12 percent of cases and controls, respectively.

McLaughlin et al. (1992) concluded that the findings of their study provide some evidence of an association between silica and lung cancer but that the dose-response relationship did not show a strong trend.

I.C.2.p. Dutch ceramic workers.

Meijers et al. (1996) conducted a retrospective cohort mortality study in male Dutch ceramic workers. The cohort was selected from subjects identified in a nationwide cross-sectional silicosis survey. Most of the workers were drawn from two large mechanized companies, with the remainder coming from 76 small ceramic workshops. In this survey, subjects received a thorough medical examination which included a chest radiograph and questionnaires on job history, respiratory symptoms and smoking habits. If the initial chest radiograph was suggestive of silicosis, a second larger radiograph was

taken and graded according to the ILO scale. In total, 1,794 male workers were selected for the cohort who had worked in the ceramics industry between 1972 and 1982 for more than two years. The cohort was followed up to the end of 1991. SMRs were calculated using the Dutch male population as the referent group.

No quantitative information on exposure to respirable crystalline silica was available. However, the level of exposure was judged to be highly correlated to the stage of production of ceramic ware. This allowed the authors to assign each subject to a qualitative category of average exposure (none, low, moderate or high) based on job description. However, this categorization was based on each subject's job at the time of the medical survey and took no account of possible movement between different jobs during their employment, which could potentially impact significantly cumulative exposure estimates over the period of the study. In fact, subjects identified with simple pneumoconiosis were medically removed from jobs where respirable silica exposure occurred, so a worker might have been classified as having high exposure but could have spent much of his/her later employment time in a job with no or minimal exposure. This is a weakness in the study design and renders the exposure assessments very unreliable. There was no information on the extent to which these subjects may have been exposed to cristobalite as distinct from quartz. The authors did not identify any problems with confounding exposures. There was limited use of talc dust in the molds, but exposure to talc was not considered to be significant.

The mean length of follow-up was 14 years, and mean age at the start of the follow-up period was 40 years. Follow-up was complete for virtually all (99.8 percent) subjects. Around half of the workers had worked for more than 10 years in the industry. There were 124 subjects (around 7 percent of the cohort) with radiographically apparent opacities (simple pneumoconiosis), but in all cases the ILO grading was higher than 1/1. Smoking data suggested that around 80 percent of the cohort smoked, but the absence of a clear excess of lung cancer (SMR = 88 based on 30 lung cancer deaths in the entire cohort) suggests that they may not have been heavy smokers. The prevalence of workers with opacities in the different exposure categories was not stated.

There were 161 total deaths (around 9 percent of the cohort), which was significantly less than expected (SMR = 70) suggesting the presence of a healthy worker effect. There were no statistically significant correlations between mortality from all causes or lung cancer and duration of employment, smoking status or exposure category. There was a statistically significant excess of lung cancer in subjects with simple pneumoconiosis (SMR =220, 10 observed deaths) compared to a deficit in those without pneumoconiosis (SMR = 68). There were more deaths from lung cancer among smokers than non-smokers, but the number of deaths were similar to or less than expected (SMR = 97 for smokers (27 deaths) and 49 for non-smokers (3 deaths)). This study is limited by lack of quantitative exposure data, low overall mortality, and the relatively short period of follow-up of only 14 years. However, the results did reveal a statistically significant excess of lung cancer in those with simple pneumoconiosis. It did not appear that this excess could be attributed to smoking.

I.C.2.q. German stone and ceramic workers.

Ulm et al. (1999) conducted a population-based case-control study of workers in the stone, quarry and ceramic industries diagnosed with lung cancer in the Bavarian district of Germany between 1980 and 1994. There were 133 cases and 231 controls from the stone and quarry industry and 114 cases and 564 controls from the ceramic industry. Cases were identified from insurance and hospital records. Controls were selected differently for the quarry and ceramic cohorts. In the ceramic industry, controls were selected from a silicosis surveillance program affecting almost all employees at multiple plant locations, while in the quarries controls were selected from records of accidents that happened either at work or traveling to or from work. For each industry, cases were matched to controls on gender, age, area of residence, industry type, and smoking habits. Smoking status was determined from medical files and personal interviews. According to the authors "[a]ll controls had been occupationally exposed to silica dust" (Ulm et al., 1999). The study by design eliminated cases and controls that had silicosis, as defined by the requirement for compensation (ILO radiological category $\geq$ 1/1 and reduced lung function). Ulm et al.'s (1999) intent was to eliminate those with underlying silicosis to determine "whether silica dust itself can induce lung cancer or only via silicosis."

In Ulm et al. (1999), details of the exposure assessment were only briefly presented. Analysis by job title as a proxy for exposure is not conducted in the analysis. Exposures were estimated by industrial hygienists using complete occupational histories, available exposure measurements, and differences in exposure caused by changes in plant, type of occupation, or technical equipment. If no exposure measurements were available, the level of exposure was estimated by hygienists familiar with the workplace. It is not possible to evaluate the quality of exposure estimation since information on the number of plants in the study, process descriptions, job or exposure distributions, and sampling and analytical methods used to determine respirable crystalline silica levels were not provided. Cristobalite exposures were also not evaluated in the ceramics industry. Exposures were classified as either high-exposed or low-exposed with the German MAK value of 0.15 mg/m^3 being used as the cut-off point. In a further analysis, exposure indices were classified into four semi-quantitative categories to allow the exploration of exposure response relationships.

Approximately 30 percent of cases and controls were considered exposed to a potentially confounding occupational carcinogen, but there was no clear distinction between cases and controls with the exception that 13 percent of cases were exposed to diesel exhaust compared to 9.2 percent for controls. Even though smoking had been used as a matching criterion, cases as compared to controls had a higher smoking rate (82.4 percent to 66.1 percent) for smoking more than 10 cigarettes per day and controls stopped smoking 10 years earlier than cases.

Three exposure indices were used: median TWA exposure, cumulative exposure, and peak exposure. Odds ratios for lung cancer were calculated for the different measures of exposure, adjusted for age at onset of exposure, year of first exposure,

duration of exposure, latency, and exposure to other occupational carcinogens. No odds ratios were statistically significantly increased. To assess the possible exposure response relationship, ORs for both industries were calculated for four categories of cumulative and average TWA exposure. No trend with either cumulative, average, or peak exposure was observed. The authors concluded that their study showed no association between exposure to crystalline silica and lung cancer.

This paper reflected the mortality experience of populations having relatively low exposures to crystalline silica because (1) the exclusion of subjects with radiographic opacities would tend to over-select those workers with the lowest exposures, and (2) the limited exposure information presented suggests that exposure in these industries in the later decades were less than OSHA's current PEL of approximately 0.1 mg/m^3 respirable crystalline silica. In fact, the mean exposure estimate in the ceramic industry prior to 1940 is estimated to be 0.07 mg/m^3 (Ulm et al., 1999). The authors acknowledged that the low exposures of the cohorts may have reduced the power of the study to detect a small risk. Potential exposure misclassification, as noted above, could further reduce the power of the study. OSHA believes the results of this study should be discounted due to low exposures experienced by the cohort, the limited size of the cohort, and the imprecise methods of exposure classification.

I.C.2.r. U.S. diatomaceous earth industry workers.

Checkoway et al. (1993) conducted a cohort study of 2,570 white male workers at two diatomaceous earth (DE) plants in California who were employed at least one year and who worked at least one day between 1942 and 1987. Vital status was ascertained for 91 percent of the cohort and death certificate information was retrieved for 94 percent of identified deaths. The major exposure of concern in these plants was cristobalite, a polymorph of crystalline silica. Workers who had experienced previous occupational exposure to asbestos from earlier employment were excluded from the main study cohort. The health outcomes of interest in this study were lung cancer and non-malignant respiratory diseases (NMRD). Smoking data were incomplete so investigators decided to examine whether smoking was a confounding factor in two ways: (1) inspection of mortality risks for other smoking related diseases and (2) by hypothetical estimation of the extent of confounding required to produce spurious observed excesses. The most important finding was an excess of lung cancer mortality (SMR = 143, 95% CI 109-184, 59 deaths) for diatomaceous earth workers compared to U.S. population rates. The SMR for lung cancer was also elevated when using lung cancer rates from local counties (SMR = 159). The largest SMRs were found for workers hired before 1930 (SMR = 263, 95% CI 112-515, 8 deaths). The cohort's NMRD mortality, defined by the authors as excluding infectious disease and pneumonia, was also increased (SMR = 259, 95% CI 196-336, 56 deaths).

According to the authors, the crystalline silica exposure index was "semi-quantitative," combining information on duration, differences of exposure between jobs and calendar periods, the crystalline silica content of various plant processes and product mixes, and the use of respirators. Exposure intensity was determined from a review of

process history, industrial hygiene records, and implementation of engineering controls by review of plant records and discussion with knowledgeable employees. Exposures were categorized as none, low, moderate, or high over five time periods with exposure reducing over time. Exposure estimates were also adjusted to account for the increased use of respirators beginning in 1950. The percentage of crystalline silica in respirable dust was estimated to be 1 percent in the diatomaceous earth pre-treatment area and 10 to 25 percent in calcined and flux-calcined processes. An index of cumulative exposure was computed as the sum of the product of the time spent in different jobs adjusted for differences in exposure intensity by job, by time period, by respirator use, and the percentage of crystalline silica in respirable dust.

The investigators found the strongest exposure-response gradients for lung cancer mortality, assuming a 15-year latency, for the workers exposed 20 or more years compared with a reference group of workers with less than 5 years of exposure (RR of 2.88 with 95% CI 1.13-7.33, 6 deaths). The study also found positive exposure-response trends for lung cancer and NMRD with duration of employment in dust-exposed jobs, and with cumulative crystalline silica exposure index. The relative risks for lung cancer with silica exposure lagged 15 years were 1.00, 1.19, 1.37, and 2.74 for the none, low, moderate and high exposure groups, respectively. The authors concluded that the excess of lung cancer could not be attributed solely to smoking.

Checkoway et al. (1996) re-analyzed these data to assess more thoroughly potential confounding by exposure to chrysotile asbestos, which had been used in limited quantities in some operations of the two plants. The reanalysis was limited to 2,266 white male workers from the larger plant who had been employed after 1930 and for whom quantitative exposure estimates could be derived. The exposure characterization of asbestos and the development of a job exposure matrix were conducted independently without industrial hygiene personnel knowing the mortality outcome of individual workers or their previous silica exposure classification. There were 52 cases of lung cancer mortality in this subcohort. Lung cancer was stratified according to cumulative respirable silica and asbestos fiber exposure, and mortality rates were compared to those of the U.S. male population. The SMR for lung cancer mortality of the cohort was 141 (95% CI 105-185). With exposure lagged 15 years, the SMRs for the four categories of increasing silica exposure among workers not exposed to asbestos were 113, 87, 214, and 200, respectively. After adjustment for age, calendar year, duration of follow-up, ethnicity, and cumulative asbestos exposure, risk ratios for the increasing categories of silica exposure were 1.00, 1.37, 1.80, and 1.79, respectively, with a 15-year lag. The authors concluded that asbestos exposure was not an important confounder of the observed association between exposure to respirable silica and lung cancer mortality in this cohort.

A detailed, quantitative job-exposure matrix (JEM) was developed by Seixas et al. (1997) and used by Checkoway et al. (1997) in a 7-year extended cohort analysis to evaluate quantitative exposure-response relationships. Five thousand seven hundred and nine (5,709) computerized samples collected from 1962 to 1988 and 686 sample results taken from 41 written documents from 1948 to 1962 were used to characterize exposure

primarily at one plant. The samples were collected by plant industrial hygienists over a 40-year timeframe from 1948 to 1988. Specific estimates of exposure were made for each individual in the cohort from 135 job titles covering four time intervals (Seixas et al., 1997). The exposure of concern was to cristobalite. Historical plant exposure was determined from particle count data and gravimetric measurements of total and respirable dust. Only 1,069 of the 6,395 samples (17%) were personal respirable mass measurements and approximately 15 percent were either personal or area total (non-respirable) dust samples. Approximately 57 percent of all samples represented particle counts. The investigators could not determine whether approximately 5 percent of the samples were area or personal samples and these were classified as unknown. Most of these unknown samples were from the 41 written reports and reflected particle count data.

Sampling data were available representing 140 workstations that allowed the investigators to compare particle count results with gravimetric results for total and respirable dust (160 matched mean values) and develop mathematical models to transform the various exposure measures to a respirable mass equivalent. Plant documents, industrial hygiene data, and employee interviews identified four time periods, three for which exposure could be characterized quantitatively. There were no exposure data for the fourth period between 1902 and 1947. A subjective scaling factor of 2.5 (log scale) developed by industrial hygienists and others familiar with the plant was used to estimate exposures for time periods prior to 1944 when bagging operations changed from using paper to using less dusty burlap bags (Seixas et al., 1997). The percentage of the cohort's cumulative exposure prior to 1944 is not known. The JEM consisted of respirable dust exposure estimates covering 135 jobs over 4 time periods. The percentage of silica in respirable dust was estimated based on knowledge of plant process and product mix as was previously described by Checkoway et al. (1993).

The 1993 cohort study was updated (Checkoway et al., 1997) to investigate the quantitative dose-response associations of exposure to respirable cristobalite with lung cancer mortality. The investigators in this study: (1) extended mortality follow-up for seven years through 1994; (2) extended job history data for seven additional years for those still working; and (3) used the JEM described above to estimate cumulative exposures of individuals in the cohort. The cohort definition was similar to that from Checkoway et al. (1993) with two exceptions: (1) three-hundred and seventeen (317) workers who were employed in the smaller plant were excluded from the later study because their exposures could not be adequately quantified, and (2) eighty-nine (89) workers who were also exposed to asbestos and thus previously excluded from the cohort were included in the analysis because quantification and adjustment for their asbestos exposure was possible. Cumulative exposure for respirable dust and respirable crystalline silica was divided into quintiles with the lowest quintile serving as the comparison group. Respirable silica exposure categories were: <0.5, 0.5-<1.1, 1.1-<2.1, 2.1-<5.0 and 5.0 or greater mg/m^3-years.

The overall findings were similar to the results from the 1993 paper; based on 77 deaths from cancer of the trachea, lung, and bronchus, the SMR was 129 (95% CI 101-

161) and 144 (95% CI 114-180) based on rates for U.S. and local county males, respectively. The authors noted that nonmalignant respiratory disease (NMRD) had relatively higher mortality (SMR = 201, 95% CI 156-255, 67 deaths) than lung cancer. The largest NMRD mortality excess occurred among workers hired between 1920 and 1939. The NMRD among workers hired since 1960 suggested a persistent risk, according to the authors, even as exposures decreased over time. This finding was in contrast to that for lung cancer where the excess mortality was apparently limited to workers hired before 1960 (Checkoway et al., 1997).

The authors found a positive, but not monotonic, exposure-response trend for lung cancer. The risk ratios for lung cancer with increasing quintiles of respirable crystalline silica exposure were 1.00, 0.96, 0.77, 1.26 and 2.15 with a 15-year exposure lag. Lung cancer mortality was only statistically significantly elevated for the highest exposure category (RR = 2.15; 95% CI 1.08-4.28). The authors also found a strong, statistically significantly increasing trend for NMRD, noting that the dose-response trends for lung cancer were considerably weaker than those detected for NMRD. Checkoway et al. (1997) also found no evidence that asbestos exposure in the diatomaceous earth industry confounded the observed associations with lung cancer. The positive dose-response relationship between cumulative respirable silica exposure and lung cancer was not diminished when adjusted for cumulative asbestos exposure.

Smoking history was available for about one-half of the cohort. The available data suggested that the prevalence of smoking was higher in higher exposure categories when compared to the lowest exposure category (prevalence by increasing exposure category was 0.64, 0.81, 0.84, 0.84, 0.84). Using the method described by Axelson (1978), the authors made a worst case estimate (assuming 20 times greater lung cancer risk in smokers compared to non-smokers) and indirectly adjusted the relative risk (RR) estimates for lung cancer for differences in smoking rates. With exposures lagged 15 years, the worst case effect would be to reduce the RR for lung cancer in the highest exposure group from 2.15 to 1.67. Checkoway et al. (1997) concluded that the association between respirable silica exposure and lung cancer was unlikely to be confounded by smoking or asbestos exposure.

A recent study by Checkoway et al. (1999) was designed to investigate the relationship between radiological silicosis and lung cancer. A subset of 1,809 men from the 1993 cohort were selected based on the availability of chest x-rays of adequate quality. This study demonstrated a trend of increasing lung cancer risk with increasing cumulative silica exposure even in the absence of radiological silicosis. Specifically, 81 members of the cohort (4.5%) had radiological silicosis. The overall mortality from lung cancer was higher in silicotics, (SMR = 157; 95 % CI 43-403) compared to non-silicotics (SMR = 119; 95% CI 87-157), although neither increase was statistically significant. In non-silicotics, there was a statistically significant increase (p for trend = 0.02) in lung cancer mortality with increasing cumulative silica exposure (based on national rates). The authors concluded: “The dose-response relation observed between cumulative exposure to respirable crystalline silica and lung cancer mortality among workers without radiological silicosis suggests that silicosis is not a necessary co-condition for silica

related lung carcinogenesis. However, the relatively small number of silicosis cases in the cohort and absence of radiographic data after employment limit interpretations" (Checkoway et al., 1999). Although smoking history data were limited, the authors indicated that the available smoking data suggested that confounding due to smoking was not likely to explain the findings.

Rice et al. (2001) conducted a re-analysis and a quantitative risk assessment of the diatomaceous earth cohort and found exposure to respirable crystalline silica was a significant variable in several relative risk models examined. OSHA discusses this analysis in detail in Section II, Preliminary Quantitative Risk Assessment.

OSHA notes that the Checkoway et al. (1993) study had been previously reviewed by IARC (1997) and found to be one of the least confounded of the studies evaluated. The investigators had access to 40 years of exposure data for dust, silica and asbestos, which enabled them to quantify exposure in detail, develop a job exposure matrix, and control for potential asbestos confounding in the analysis. Furthermore, the investigators were able to use smoking history data for part of the cohort to rule out smoking as a serious confounder. Thus, OSHA believes that the studies of diatomaceous earth workers, and in particular the quantitative exposure-response analysis by Rice et al. (2001), are appropriate for inclusion in the preliminary risk assessment.

I.C.2.s. Danish foundry workers.

Sherson et al. (1991) studied 6,144 Danish foundry workers who were invited to participate in a silicosis surveillance program from 1967 to 1969 and from 1972 to 1974, with follow-up through 1985. This survey was actually a census as it included virtually all Danish foundries. There were 647 total tumors diagnosed within the cohort and age- and gender-adjusted Danish incident rates were used to calculate SIRs (standard incident ratio). No exposure measurements were reported as part of the study, as no data was provided. A significantly increased standardized incident ratio (SIR) was observed for all cancers (SIR = 1.09, 95% CI 1.01-1.18, 647 cases) and for lung cancer (SIR = 1.30, 95% CI 1.12-1.51, 166 cases). A systematic trend in SIRs was seen with duration of work for lung cancer. The SIR was 0.99, 1.19, 1.28 and 1.85 for durations of employment of <10 years, 10-19 years, 20-29 years, and >30 years, respectively. According to the authors, this study suggests that occupational exposure, as represented by duration of employment, in Danish foundry workers is associated with an increased lung cancer incidence. It is not possible to isolate the effect of silica from other potential confounding workplace carcinogens since these were not addressed in the study design and analysis.

I.C.2.t. U.S. (Michigan) foundry workers.

Andjelkovich et al. (1990, 1992, and 1994) conducted a mortality study of 5,337 white men, 2,810 non-white men, and 627 women who had been employed in a grey iron foundry in Michigan for at least six months from 1950 to 1979. Mortality was followed through 1984 and vital statistics and death certificates were determined for more than 97

percent of the cohort. Age, gender, and race adjusted mortality rates for the U.S. and local counties were used to calculate SMRs. A description of other carcinogenic exposures typically found in the plant was provided but was not used to adjust risk estimates. Non-white employees experienced higher mortality rates for all cancers, including lung cancer. All cancer SMRs for white workers was 0.98 and for non-white workers was 1.16 (not statistically significantly elevated). Lung cancer SMRs were elevated for white males and non-white males (SMR-w = 1.23, CI 0.96-1.54 and SMR-nw = 1.32, CI 1.02-1.67), but only the SMR for nonwhites was statistically significantly elevated.

A follow-up study, extended five additional years to 1989, and a nested case-control study was conducted (Andjelkovich et al., 1994). The study consisted of 220 lung cancer cases and 2,220 controls. Smoking history was obtained by medical records or by questionnaire of the employee or surviving relative. A silica exposure index was created and the odds ratio for lung cancer mortality determined for increasing exposure quartiles with the initial quartile serving as the reference. The odds ratios for lung cancer decreased with increasing exposure quartile (OR = 1.0, 1.27, 1.14, and 0.90; all values not statistically significantly elevated) and do not reflect an association between silica exposure and lung cancer.

I.C.2.u. Chinese iron and steel workers.

Xu et al. (1996b) identified all deaths during the decade 1980 to 89 for workers employed in the iron and steel industry in Anshan, China. There were 610 lung cancer cases diagnosed from 1987 to 1993 and 292 incident cases of stomach cancer (1989-1993). There was one control for each case. Controls were matched by age and gender. Cases and controls had to have worked in the steel complex for at least 10 years. Lifetime occupational histories and smoking data were available. Cumulative dust and cumulative silica exposure, as well as benzo(a)pyrene exposure, a marker for polycyclic aromatic hydrocarbon (PAH) exposures, was established from historical records and available industrial hygiene sampling data.

The risk of lung cancer was increased among foundry workers (OR = 1.8, CI 1.1-2.8). This study also noted that refractory brick workers working 15 years or more had a statistically significantly elevated incidence of lung cancer (OR = 2.9, CI 1.4-5.9). Cumulative exposure to total silica dust and benzo(a)pyrene showed trends of increased lung cancer with increased exposure. For the entire steel complex, a modest non-monotonic trend was noted with increased cumulative silica exposure; OR = 1.7, 1.5, 1.5 and 1.8 for exposures ranging, respectively, from <3.7 to >27.72 mg/m^3-years of respirable dust with a p for trend = 0.007. The authors stated "[W]e could not adequately distinguish the carcinogenic effects of silica vs. other dusts." For example, in the refractory brick area Xu et al. (1996b) indicated that there was a combination of silica and asbestos exposure. IARC in its 1997 review was uncertain if the gradients for lung cancer were adjusted for potential confounding by PAH exposures

I.C.2.v. Swedish aluminum foundry workers.

Westberg and Bellander (2003) conducted a nested case control study of Swedish aluminum foundry workers. The initial cohort consisted of 5,016 foundry workers of which 46 deaths from lung cancer were identified. There were 31 cases and 233 controls in the final study with one year or greater of employment. Controls were matched to cases by gender and age up to time of disease and analyzed as matched pairs. The authors focused on creating an exposure model where there was good current cross-sectional exposure data and relatively sparse historical data. Historical exposure data was available as total dust samples in comparison to the current method of collecting respirable dust with a cyclone. Therefore, a correction factor was necessary since "the quartz concentrations were usually twice as high [in the total dust samples] as with the present cyclone separation method…" (Westberg and Bellander, 2003). Regression models using the determinants of job title, time period, foundry type, and size of production were used to generate process-year historical total dust and crystalline quartz exposure estimates.

These estimates were used to calculate individual cumulative exposures. Testing of model variables was done by multiple linear regression analysis, which indicated that, while total dust explained much of the variation ($r^2 = 0.58$), only a small portion of the variation ($r^2 = 0.13$) was explained by respirable crystalline quartz exposure estimates. No smoking data were provided in the paper, and even though other potentially confounding occupational carcinogens were discussed, no adjustments were made in the analysis. Odds ratios for total dust and silica showed a non-statistically significant trend for increasing lung cancer mortality with increasing cumulative exposure. The maximum cumulative exposure for respirable quartz in the high exposure group was 2.4 mg/m^3-years.

I.C.2.w. Norwegian silica carbide workers.

Romundstad et al. (2001) studied lung and other cancer incidence among workers in the Norwegian silicon carbide (SiC) industry. The final study cohort consisted of 2,620 men who worked at least six months in one of three plants: plant A the largest, started operation in 1913, plant B started operation in 1963 and plant C started operation in 1965. Follow-up of cancer incidence started after six months of employment or from 1953, which ever was later, and continued to the end of 1966. Death certificates were obtained from multiple sources with 2 percent either dying prior to follow-up or 3 percent not being traceable.

Silicon carbide is a combination of quartz and finely ground coke that is heated in an electrical resistance-type furnace at high temperatures ranging from $2,200^0$C to $2,500^0$C creating exceedingly hard materials. The nature of the production process is very dusty and creates multiple exposures, including total dust and respirable quartz in the preparation and mixing areas; SiC fibers and SiC particles, quartz, cristobalite, and small amounts of PAHs in the furnace firing and post-furnace process areas; and potential asbestos fiber exposure to maintenance personnel.

A JEM was created of all three plants. Plant A was the largest and the longest-operating facility. Therefore, workers in plant A contributed most of the person-years of exposure and experienced most of the lung cancer cases (60 cases in plant A versus 8 and 6 cases plant C).

Since 1950 more than 6,000 dust samples had been taken at the three plants. Until 1974, a Watson thermal precipitator was used, taking time-weighted average area samples (n = 4,200) for particle counts. From 1974 to 1996, gravimetric personal measurements of total dust samples were taken. Fewer samples were available characterizing the dust, with 200 measurements of crystalline silica (quartz and cristobalite) analyzed by infrared spectroscopy prior to 1980 and supplemented by XRD after 1980, and 216 short-term SiC fiber measurements analyzed by an optical phase contrast microscope. Romundstad et al. (2001) reported that quartz and cristobalite were present in roughly equal quantities in the oven and sorting departments. Gravimetric measurements for total dust adjusted for the percentage of silica and a correction factor to estimate respirable dust exposure were used to characterize exposures from 1975 to 1996. During the time period 1950 to 1974, thermal precipitator measurements along with changes in work patterns were used to estimate cumulative exposure to respirable crystalline silica. Prior to 1950 when plant A was the only plant operating, there were no exposure measurements. Estimation of pre-1950 exposures were principally based on knowledge of changes of work patterns and the introduction of technology. Romundstad et al. (2001) did not try to estimate gravimetric exposures from particle count data. Instead, four cumulative exposure quartiles were created with an arbitrary scale of 1, 2, 3, and 4, representing ranked exposures of zero, lowest, medium and highest exposures. Categorical smoking data (never, former, current) was available from medical records kept at the plants. Poisson regression analysis was used to investigate internal dose-response relationships and to evaluate potential confounding by smoking.

The cohort's total cancer incidence was elevated (SIR = 1.2, 95% CI 1.0-1.3). This excess was mainly due to lung cancer (SIR = 1.9, 95% CI 1.5-2.3), but the rate of stomach cancers (SIR = 1.5) and cancers of the upper respiratory tract (SIR = 1.7) were increased, though the increase was not statistically significant. Lung cancer was elevated at all three plants with SIRs of 1.9 (60 cases) in plant A, 1.7 (8 cases) in plant B, and 2.0 (6 cases) in plant C. Cumulative exposures to different types of dust were associated with an increase in lung cancer. However, exposure levels to the various dusts and fibers were highly correlated (r = 0.7-0.9). As stated by Romundstad et al. (2001) "[T]otal dust, SiC fiber, SiC particle and crystalline silica exposure measures all showed essentially the same pattern, [referring to the dose-response relationship] possibly because of a strong correlation between these exposures…" In essence, it was difficult to separate out the effects of respirable silica from SiC fibers and total dust, because these dust exposures were associated with similar processes. In the highest exposure category the SIR for SiC fibers was 3.5 (95% CI 2.1-5.6) with comparable results for respiratory crystalline silica and SiC dust (SIR = 3.6 for both). When Poisson regression analysis in which both crystalline silica and SiC fibers were included in the exposure model, the analysis indicated that SiC fiber exposure was a stronger predictor of lung cancer risk than was exposure to crystalline silica. The authors believed that this analysis should be

interpreted cautiously because of the strong correlation between these exposure measurements. Romundstad et al. (2001), after performing an internal regression analysis, concluded that smoking was not a significant confounder in this cohort.

I.C.2.x. Canadian silica carbide workers.

A Canadian study by Infante-Rivard et al. (1994) found an SMR of 169 (95% CI 109-252) for lung cancer mortality and an SMR of 203 (95% CI 121-322) for non-malignant respiratory disease among silica carbide workers. A slight increase in lung cancer deaths with increasing cumulative exposure to total dust was noted, with the risk ratios being 1.67 and 1.48 for middle and high exposure categories, respectively. This study had less exposure data available than did Romundstad et al. (2001) and was limited to total dust measurements. As was the case with the Romundstad et al. (2001) study, this study is difficult to interpret due to the existence of co-exposures of potential occupational carcinogens, which were probably inherent to the production processes.

I.C.2.y. Finnish road paving and asphalt workers.

Kauppinen et al. (2003) conducted a cohort study of Finnish road paving and asphalt workers. The cohort was defined as all workers who worked at least six months before 1985 for one of six road paving companies. Follow-up was from 1964 through 1994 with an average duration of employment of 17 years. Detailed individual job histories were available from company records for 1969 to 1994. A total of 5,676 male workers, including bitumen workers, building/ground construction workers primarily from one large company, and others met the cohort criteria with 666 deaths occurring by the end of 1994. This study was part of the broader IARC Multicenter Study on Cancer among European Asphalt Workers and Kauppinen et al. (2003) followed the IARC protocol in developing an exposure matrix but developed a more detailed job classification and used only Finnish exposure data.

In addition to respirable quartz exposure, road pavers are exposed to bitumen (asphalt) fume, organic vapor, and benzo(a)pyrene, and building construction workers are exposed to asbestos. Available Finnish exposure data were limited to two studies of road paving, two studies of waterproof /roofing of rubberized roof sheets, and studies of two roof sheet factories. Semi-quantitative exposure estimates for respirable quartz and other chemicals were derived by a team of occupational hygienists from structured interviews and available exposure data, and these results were specific for time period, job class, company history, and chemical agent(s) used. A questionnaire to obtain smoking and lifetime occupational histories was administered to 635 living cases of the cohort, which had a 41 percent response rate.

This cohort experienced a total mortality SMR of 111 (95% CI 103-120), which was mainly driven by accidents and violence, malignant neoplasm, and non-malignant diseases of the respiratory system (SMR 123, CI 84-174, 32 deaths). Cancers of trachea, bronchus, and lung were statistically significantly elevated for asphalt workers (SMR = 145, CI 103-198) and among building/ground construction workers (SMR = 139, CI 103-

184). When categorical exposure data were analyzed, no statistically significant trends were noted, principally due to the small number of deaths, but exposure to silica showed a non-statistically significant trend with the highest exposure category having a RR of 2.26 (95% CI 0.89-5.76). The authors noted that the smoking rate among building/ground construction workers was similar to that of the overall Finnish male population. Multivariate Poisson regression models with a 15-year exposure lag suggested exposure-related trends for coal tar, organic vapors, silica dust, diesel exhaust and bitumen fume. In their discussion, Kauppinen et al. (2003) noted "Exposure to silica dust in construction works and asphalt mixing may partially explain the lung cancer excess. The contribution of diesel engine exhaust cannot be ruled out, because the exposure occurs often simultaneously with exposure to silica dust."

I.C.2.z. Canadian bricklayers and associated crafts.

Finkelstein and Verma (2005) conducted a retrospective cohort analysis of 10,953 male brick and stone masons who were members of the International Union of Bricklayers and Allied Craftworkers in the Province of Ontario, Canada. Subjects entered the cohort on the date of joining the union or 1950, whichever was later, and follow-up continued through the end of 1999. Ontario members of the plumbers' union served as the comparison group. The study did not have access to exposure measurements or smoking data but used number of years and type of union membership as a proxy for type of exposure and duration of exposure.

All cause mortality rates were less than expected prior to 30 years of work ($SMR_{10\text{-}19\ yrs}$ = 75 and $SMR_{20\text{-}29\ yrs}$ = 88) but was statistically significantly elevated after 30 years or more of membership (SMR = 120, 95% CI 104-130). With 20 or more years of union membership, statistically significant elevations of lung cancer ($SMR_{20\text{-}29\ yrs}$ = 162, 50 deaths; SMR_{30+yrs} = 150, 50 deaths), stomach cancer ($SMR_{20\text{-}29\ yrs}$ = 200, 8 deaths; SMR_{30+yrs} = 260, 11 deaths), and colorectal cancer ($SMR_{20\text{-}29\ yrs}$ = 180, 18 deaths SMR_{30+yrs} = 150, 17 deaths). When the data were broken down by members of refractory locals compared to all locals there was no difference in lung cancer mortality rates between members of these locals. Finkelstein and Verma (2005) indicated that besides respirable silica, other occupational carcinogens may have been present in bricklayers' work environments, including asbestos, exposure as a bystander to brick removal operations, and hexavalent chromium present in the cement mixture (although hexavalent chromium was found to be below the detection limit in air monitoring of the mixing of cement by Ontario construction workers (Finkelstein and Verma, 2005)). After adjusting for place of birth, age, and year of death, lung cancer rates were higher among bricklayers than plumbers (OR = 1.14), but the difference was not statistically significant. The authors concluded, "[l]ung cancer mortality reflect smoking habits and occupational exposure [to silica]" and noted that plumbers were perhaps not the best comparison group since they were exposed to asbestos and welding fume, both lung carcinogens, which would deflate the lung cancer mortality risk estimate for silica.

I.C.3. Pooled IARC-Sponsored Multicenter Exposure-Response Analyses for Lung Cancer.

As discussed in the introduction to this section, IARC (1997) noted that there were some inconsistencies in exposure-response findings of studies carried out to investigate the relationship between exposure to crystalline silica and lung cancer risk. This finding led Steenland et al. (2001a) to conduct a comprehensive quantitative exposure-response study of lung cancer mortality risks. This study, which was sponsored by and coordinated through IARC, relied on raw data from previously published epidemiological studies for which there were adequate quantitative data on crystalline silica exposures to perform exposure-response analyses. The goal of this study was to estimate exposures to crystalline silica across all studies using a common metric and conduct a pooled analysis of resulting exposure-response trends to determine if the cohort studies overall provide evidence of an exposure-response relationship between crystalline silica and lung cancer. The results of the Steenland et al. (2001a) quantitative exposure-response analysis and the exposure assessment reported by Mannetje et al. (2002a) are described in detail in Section II, Preliminary Quantitative Risk Assessment, but are summarized here.

The pooled analysis relied on data obtained from studies of 10 occupational cohorts, all of which are described in Section I.C.4 above. These cohorts were:

- U.S. gold miners;
- U.S. diatomaceous earth workers;
- U.S. (Vermont) granite workers;
- Chinese pottery workers;
- South African gold miners;
- Australian gold miners;
- Chinese tungsten miners;
- Chinese tin miners;
- Finnish granite workers; and
- U.S. industrial sand workers.

Studies of three other cohorts were also identified as having adequate quantitative exposure data but were excluded due to unavailability of the data (Dutch ceramic workers in Meijers, 1996 and South African gold miners in Reid and Sluis-Cremer, 1996) or because the data were incompatible with the case-control design of the study (English pottery workers in McDonald et al., 1995).

These ten cohorts (5 mines and 5 industrial plants) included 65,980 workers and 1,072 lung cancer deaths (Steenland et al., 2001a). The follow-up period for five cohorts (U.S. gold miners, Chinese pottery workers, Chinese tungsten miners, Chinese tin miners and Finnish granite workers) was extended by 5 to 9 years beyond the original follow-up period described in the original studies. Quantitative exposure data were either already available or developed specifically by a co-investigator (Mannetje et al., 2002a) to estimate cumulative exposures to respirable crystalline silica using cohort-specific conversion factors based on silica content of the dust or results of side-by-side dust sampling data. Mannetje et al. (2002a, 2002b) reported finding a positive, monotonic

exposure-response trend with silicosis mortality, indicating that the exposure assessment was reasonable and unlikely to have resulted in significant misclassification of exposures.

Steenland et al. (2001a) conducted a nested case-control analysis on each cohort using conditional logistic regression. Each case was matched to 100 controls who had survived to at least the same age as the case. Matching was based on race, gender, and date of birth and by research study. Categorical analyses of lung cancer rates by cumulative and average exposure (defined as cumulative exposure averages of the whole exposure period) were conducted by quintiles of cumulative exposure (<0.4, 0.4-2.0, 2.0-5.4, 5.4-12.8, 12.8+) and analysis of cumulative exposure as a continuous variable was performed using a log-linear relative risk model both with and without log transformation of cumulative exposure and with lags of 0, 5, 10, 15, or 20 years. (Details of the results of the risk modeling are presented in Section II, Preliminary Quantitative Risk Assessment).

Tests for heterogeneity revealed that there was considerable heterogeneity between studies for cumulative exposure and average exposure, and use of log-transformed cumulative exposure significantly reduced heterogeneity between studies. There was no clear explanation for the observed heterogeneity. The authors speculated that potential confounding by radon exposure in the South African gold miner cohort leading to a relatively large exposure-response coefficient and possible physical differences in crystalline silica particles in the various work environments might have caused the differences in toxicity.

Steenland et al. (2001a) found a monotonic increase in lung cancer odds ratios with quintiles of cumulative exposure, cumulative exposure lagged 15 years, and average respirable silica concentration, but not with duration or log duration of exposure. For the pooled categorical analysis with cumulative exposure lagged 15 years, the odds ratios and 95% confidence intervals for ascending quintiles of exposure were 1.0 (CI 0.83-1.3), 1.3 (CI 1.0-1.6), 1.5 (CI 1.2-1.8), and 1.5 (CI 1.2-1.9). Use of the log-linear model with log cumulative exposure (unlagged or lagged 15 years) resulted in no substantial heterogeneity between data sets and both yielded positive pooled exposure coefficients suggesting the presence of a positive association between exposure to respirable silica and lung cancer risk. Exposure-response trends were found to be similar between mining and non-mining cohorts. Use of a spline model, which is essentially unconstrained and does not impose a shape to the exposure-response curve, resulted in both an improved fit and a reasonably monotonic increase in lung cancer risk with log cumulative exposure. Eliminating the South African cohort, which had the strongest exposure-response relationship of the studies, resulted in only slight changes in the results from the categorical and continuous analyses. Analysis performed with and without the three Chinese studies, where there was concern over potentially confounding exposure to other carcinogens, did not cause any appreciable change in the pooled exposure coefficient.

Of the ten studies used by Steenland et al. (2001a), six had no information on smoking histories of cases and controls. Steenland et al. (2001a) elected to leave the data unadjusted for the other four studies, stating that the use of internal comparisons between

high- and lower-exposed workers within the cohort reduces the concern of confounding by smoking since both high- and lower-exposed groups would presumably have had similar smoking histories. The authors further stated, "[I]n those studies where complete or partial smoking data were collected and considered in exposure-response analyses either little confounding of exposure response trends were observed (South African and Australian gold miners, diatomaceous earth workers, Finnish granite workers) or smoking was actually a negative confounder (English pottery workers)." The authors concluded:

> Silica appears to be a weaker carcinogen than other lung carcinogens measured by mass in air. [Compared to the exposure-response curves seen for hexavalent chromium, soluble nickel, arsenic, and cadmium,] silica appears the weakest of the five, with lower relative risks and a lower slope of the exposure-response curve.
>
> Despite this relatively shallow exposure–response trend, overall our results tend to support the recent conclusion by IARC (1997) that inhaled crystalline silica in occupational settings is a human carcinogen, and suggest that existing permissible exposure limits for silica need to be lowered (Steenland et al., 2001a).

Steenland and Bartell (Toxichemica, Inc., 2004) also conducted a quantitative uncertainty analysis at OSHA's request in which data from some of the cohorts were updated and follow-up periods extended. Additional quality control revealed a few errors in the original assignments of exposures to cohort members. After correcting for these errors and repeating the analysis using the same log-linear models as before, Steenland and Bartell found only small changes in the exposure-response coefficients derived from each cohort with the exception of the Finnish granite cohort, which changed from positive to negative. There was no appreciable change in the pooled exposure coefficient after updating the cohort data and correcting errors (0.060 from the model based on log cumulative exposure and a 15-year lag, compared to 0.062 as originally reported by Steenland et al., 2001a). In addition, repetitive implementation of the log-linear model with log cumulative exposure using a Monte Carlo method to reflect random errors in estimating exposures of cohort members to respirable silica resulted in a mean pooled exposure coefficient only slightly below the coefficient originally reported by Steenland et al. (2001a), with a variance around the estimate of the mean comparable to the level of statistical uncertainty associated with the use of the log-linear model in the original analysis. This suggests that uncertainties in the underlying estimates of exposure were not likely to be so great as to call into question the finding from the original pooled analysis of an overall exposure-related increase in lung cancer risk. This Steenland and Bartell analysis (Toxichemica, Inc., 2004) strengthens OSHA's confidence in the available data and provides both a qualitative and quantitative estimate of the data's stability, even when subject to systematic error. The methods used in the uncertainty analysis and results obtained are described in detail in Section II, Preliminary Quantitative Risk Assessment.

I.C.4. Multi-National Pooled Population and National Death Certificate Studies.

I.C.4.a. U.S. national (27 states) case-control study.

Calvert et al. (2003) conducted a case-control study using 4.8 million death certificates from the National Occupational Mortality Surveillance data set. Death certificates were taken from 27 states covering the period from 1982 to 1995. Cases were persons who had died from any of several diseases of interest: silicosis, tuberculosis, lung cancer, chronic obstructive lung disease (COPD), gastrointestinal cancers, autoimmune-related diseases, or renal disease. Five controls who had not died from a disease of interest were selected from the same data set for each case and were matched on gender, race, age, state, and year of death. Industry and occupation listed on each death certificate were used to categorize exposure to crystalline silica as no/low, medium, high, or super-high. This assessment was performed by three senior industrial hygienists who were not informed as to whether subjects were cases or controls. Cases and controls assigned to the high and super-high exposure categories were considered to have had exposures at or above the OSHA PEL for silica (approximately 0.1 mg/m^3). Secondary mortality was also evaluated for persons who died of silicosis, which was considered to be a less ambiguous marker of exposure. The mortality odds ratios were calculated for each of the diseases of interest and are shown in Table I-14 by exposure group. Those subjects thought to have had exposure to silica (medium, high or super-high categories) had a significantly elevated risk of death for silicosis, chronic obstructive pulmonary disease (COPD), tuberculosis, and rheumatoid arthritis ($p < 0.05$). The association with silicosis validated the exposure classification system. There was also a significant trend of increasing risk of mortality from these conditions as well as from lung cancer with increasing exposure.

Table I-14. Mortality Odds Ratios by Silica Exposure Category and Cause of Death from a U.S. Death Certificate Study*

Cause of Death	Exposure Category				p for Trend
	**Ever v Low/no	Med v low/no	High v low/no	Super High v low/no	
Silicosis	4.98	2.91	6.84	30.5	<0.001
Pulmonary Tuberculosis	1.47	1.34	1.60	2.48	<0.001
COPD	1.12	1.02	1.29	1.47	<0.001
Lung Cancer	0.99	0.88	1.13	1.13	<0.001

*Adapted from Calvert et al. (2003)
**Medium, high and super high pooled and compared to low/no group
***Super high exposure

When associations between exposure and risk of disease are not strong – as is the case with lung cancer and exposure to crystalline silica – it becomes more difficult to detect the association because errors in measurement of either exposure or outcome tend to bias results toward the null. Such problems can be overcome either by having high quality data or by studying a very large population. The report by Calvert et al. (2003) adopts the latter strategy by evaluating exposure among 4.8 million deaths, with positive results that are generally consistent with other findings discussed in this section.

The study by Calvert et al. (2003) is consistent with earlier reports showing a strong exposure-related increase in the risk of death from silicosis and tuberculosis and a lesser increase in risks for other lung disease (in this case, COPD) and lung cancer. The authors acknowledged the potential for confounding by higher smoking rates for cases compared to controls, and partially controlled for this by eliminating white-collar workers from the control group in the analysis. Upon reanalysis, the investigators reported slightly lower, but still statistically significantly elevated, lung cancer mortality ORs of 1.07 (95% CI 1.06-1.09) and 1.08 (95% CI 1.01-1.15) for the high- and super-high exposure groups, respectively (Calvert et al., 2003).

I.C.4.b. Finnish nationwide job exposure matrix (FINJEM).

Pukkala et al. (2005) wrote a methods paper that evaluated the FINJEM protocol and evaluated the extent and magnitude of occupational exposure among persons employed in several occupations over one or more time periods. Crystalline silica was chosen as an example of a "known" occupational lung carcinogen and prostate cancer was used as a negative control. Crystalline silica was also chosen for study because of the large number of persons exposed, over 60,000 workers or 3 percent of the workforce. Approximately 90 percent of those exposed were men. The cohort consisted of all Finns born between 1906 and 1945 who participated in a national population census on December 31, 1970. Follow-up of the cohort was through 1995. According to the authors, Finland has excellent public health registries and associated databases.[2] The census files contained updated information on death and migration, allowing for precise calculations of person-years of exposure. In addition, data were available on job tenure, socioeconomic class, and cigarette smoking rates. The Finnish cancer registry has collected incident cancer cases since 1953. Between 1970 and 1995, there were 30,137 cases of incident lung cancer among men and 3,527 among women. The number of incident prostate cancer cases was 18,744.

The basic data elements used for exposure assessment for FINJEM are occupation, chemical agent, and calendar time periods of employment. The version of FINJEM used in this study had data for 43 chemical agents and 311 job categories. To make these job categories more homogenous 30 job categories were further subdivided into 2 to 9 industry subgroups, resulting in a total of 393 job categories defined from the database. Exposure data from 1972 to 2000 was collected by the Finnish Institute of

[2] Reporting by the medical community is mandatory with nearly 100 percent coverage by the registry with a high accuracy rate (Pukkala et al., 2005).

Occupational Health (FIOH) (>5,000 samples of respirable quartz or quartz-containing dust) and when such data were not available, exposures were estimated based on the opinions, experiences, and historical knowledge of technological changes of about 20 experts from FIOH. Default cumulative exposure categories for respirable quartz were defined as follows: <1.0 mg/m^3-years (low), 1.0 – 9.9 mg/m^3-years (medium) and >10 mg/m^3-years (high). Job-specific exposures were estimated for two time periods, 1945 to 1959 and 1960 to 1984.

For men, over 18 percent of the 30,137 lung cancer cases worked in occupations with potential exposure to silica dust. After adjusting for socio-economic class, the SIRs for lung cancer in men assigned to no, low, medium, and high exposure categories were 0.97 (95% CI 0.96-0.99), 1.10 (95% CI 1.06-1.14), 1.17 (95% CI 1.12-1.21), and 1.31 (95% CI 1.10-1.55), respectively. For women, the prevalence of exposure was 4 percent with only 5 cases assigned to the highest exposure group. After merging the high exposure group with the medium exposure group and adjusting for socio-economic class, the SIRs for lung cancer in women were 0.99, 1.03, and 1.48 (95% CI 1.19-1.82) for the no, low, and medium/high exposure groups, respectively, with only the SIR for the medium/high exposure being statistically significantly elevated.

In reviewing independent variables in their model, Pukkala et al. (2005) found that age and period of follow-up were poor predictors of lung cancer incidence, but smoking and socioeconomic class had measurable independent effects, as was expected. These two variables were highly correlated in the various models examined. Increasing the lag time (years of latency) within the model resulted in a more pronounced exposure-response association, with 18 years being the latency yielding the strongest exposure-response relationship. Asbestos exposure was also included in the models preferred by the authors.

In their discussion section, Pukkala et al. (2005) reported that exposure studies of respirable quartz in Finnish working populations indicated that exposures greater than 0.1 mg/m^3 were frequently found in metal and nonmetal mines, granite quarrying and processing, crushed stone, foundry, ceramic, and the construction industries. Statistically significant exposure-related trends for lung cancer risk were reported for all of these industry groups except workers in foundries and workers in glass and ceramic industries. The authors interpreted their findings “as signs of causality” between exposure to respirable silica and lung cancer and viewed the results as consistent with the findings of IARC (1997).

I.C.4.c. European multi-center community-based case-control study.

Cassidy et al. (2007) studied 2,852 newly diagnosed lung cancer cases and 3,104 controls, matched on gender and age from 1998 to 2003 in seven primarily Eastern European countries. By investigating new cases, the authors were able to obtain detailed job histories focusing on multiple exposures in jobs held longer than one year and to obtain lifestyle information (by questionnaire), including smoking, socio-demographic information and medical histories from 84 percent of the cases and 85 percent of the

controls. Furthermore, local experts knowledgeable in industrial hygiene assessed exposures for up to 70 chemical agents, based on a protocol adopted from Siemiatycki et al. (1990), without knowledge of case or control status. Detailed silica exposure data were available for approximately 15 percent of the study population. The assessment of silica exposure was principally done by assigning cases and controls to one of three exposure categories, "low", "medium", and "high" and assigning ranges of exposure levels to each of the categories in order to obtain "standardization in the application of the intensity index". There were 15 centers involved in this study, 2 of which used population controls and 13 that used hospital-based controls, which excluded other cancers and diseases related to smoking and tobacco use.

Statistical analysis was based on unconditional regression modeling of the relationship between silica exposure and lung cancer, adjusted for age, study center, tobacco consumption (ever/never smoked and pack-years), and highest school grade completed (a socioeconomic variable). All other occupational agents assessed (70) were considered as potential confounders and were evaluated by fitting dichotomous variables for these agents consecutively. Various approaches were used to quantify exposure to silica, including duration of exposure (years), weighted duration (hours per year by frequency of exposure), and cumulative exposure, which was estimated from the assigned exposure categories. Besides silica dust, only two other occupational exposures, wood dust and insulation dust (including asbestos), were appreciably associated with lung cancer incidence. These variables were added to the unconditional regression model used in the analysis. All lung cancer risk estimates are expressed as adjusted odds ratios (ORs) with 20-year lag periods.

Occupational exposure to crystalline silica, estimated by semi-quantitative methods, was associated with an increased risk of lung cancer (OR = 1.37, 95% CI 1.14-1.65). The risk was most apparent for the duration of exposure (OR = 1.73, CI 1.26-2.39), the weighted duration of exposure (OR = 1.88, CI 1.35-2.61) and upper third (tertile) of cumulative exposure (OR = 2.08, 95% CI 1.49-2.39), $p < 0.0001$ for trends.

Increased rates of smoking were more common among cases than controls. The proportion of ever smoked was 90 percent for cases and 64 percent for controls. The study design allowed for adjustment of this and other study confounders as well as permitting a detailed analysis of the interaction of smoking and silica exposure as risk factors for lung cancer.

Categorical analysis showed a 41 percent increased lung cancer risk (OR = 1.41, 95% CI 1.07-1.87) when comparing current smokers ever-exposed to silica to current smokers who were unexposed. Similarly, increased lung cancer risks were also observed for silica-exposed ex-smokers (OR = 1.31) and never smokers (OR = 1.41) when compared to those who were unexposed. The authors concluded "Although smoking was by far the largest risk for lung cancer, our results did not suggest an interaction between tobacco smoking and exposure to silica on the risk of lung cancer beyond a multiplicative model" (Cassidy et al., 2007).

Cassidy et al. (2007) observed elevated risks of lung cancer for persons who were ever-exposed to silica in the construction (OR = 1.27, 95% CI 1.01-1.60), manufacturing (OR = 2.03, 95% CI 1.30-3.17) and mining (OR = 1.48, 95% CI 1.02-2.13) industries. In addition, clear linear trends of increasing ORs were observed for construction (p = 0.005), manufacturing (p for trend = 0.003) and mining (p = 0.03). The authors stated, "[o]ur results show that silica is associated with an increased lung cancer risk, independent of the source of silica. An increased risk has been observed in mining, manufacturing, and construction industries, with a clear dose-response relationship in the latter" (Cassidy et al., 2007).

In OSHA's view, this study has a number of strengths. The first is the high power achieved by pooling data in a multi-centered, multinational study to assemble a large number of cases evaluated using a uniform protocol. There were 2,417 lung cancer cases of which 435 had greater than 20 years of silica exposure, comprising a very large study. Only one country out of the seven countries included in the study, Slovakia, contributed a sufficient number of cases to observe a statistically significantly elevated lung cancer risk (OR = 1.72 95% CI 1.05-2.83). Second, the authors of this incidence study were able to obtain valuable personal lifestyle risk and demographic data (smoking and social class) which is typically not available in many retrospective occupational cohort studies of silica mortality. Third was the use of industrial hygiene experts to assess exposures to up to 70 chemical agents semi-quantitatively using detailed job histories and available industrial hygiene data, which enabled the investigators to rank exposure to silica dust and several possible confounders. This study demonstrated that exposure to silica was a risk factor for lung cancer among employees in a broad range of industries.

OSHA believes that the population-based design of this study combined with its statistical power, control of confounding factors and use of exposure algorithm and local industrial hygiene expertise to assess exposures make the findings of exposure-related trends particularly compelling for the purpose of evaluating the causal relationship between exposure to crystalline silica and lung cancer; however, because of the semi-quantitative nature of the exposure assessment, OSHA believes that the data are not suitable for evaluating quantitative exposure-response relationships.

I.C.5. Studies of Lung Cancer Risk Among Silicotics.

In this section, OSHA reviews studies that have investigated the relationship between lung cancer mortality and the presence or absence of radiological silicosis. Findings of an increased lung cancer risk among silicotics adds to the evidence of a causal relationship between exposure to respirable crystalline silica and an increased lung cancer risk since silicosis by definition, can only arise from such exposure. However, the more difficult question is whether such findings suggest that silicosis itself is a necessary precursor to lung cancer, or whether associations between silicosis and an increased lung cancer risk simply reflect an increased risk among workers who have had a history of significant exposure to crystalline silica.

IARC (1997) identified two data sets among the numerous silicotic cohort studies as being the most complete and with the least bias and confounding. These were the North Carolina dusty trades cohort (Amandus et al., 1991, 1992) and silicotics in Finland (Partanen et al., 1994). The range of relative risk estimates were higher in these silicotic cohorts compared to risk measures reported in the previously reviewed cohort studies above. This is perhaps not surprising given that silicotics would have had higher cumulative silica exposures as a group than was experienced by the exposed cohorts, which included both silicotics and non-silicotics. For example, the North Carolina dusty trades study, conducted by Amandus et al. (1992), undertook a reanalysis of 306 technically acceptable radiographs from an initial registry of 760 white male silicotics and reported relative risks (RR) for lung cancer mortality ranging from 2.3 for jobs with expected silica exposure only to a RR of 3.4 for silicotics who had ever smoked. Silicotics with simple pneumoconiosis (small opacities with profusion 1, 2 or 3.) had a RR of 2.5. By comparison, most of the studies of exposed cohorts discussed above reported risk ratio measures generally at or below 1.5.

The Finnish study was much larger and covered 811 silicotics over a 40-year period (1936 to 1977). The lung cancer incident ratio (SIR) for all silicotics was 2.9. Statistically significantly elevated SIRs were found by industry and were 1.8 for casting and foundries, 3.7 for mining and quarrying, and 3.3 for the glass and ceramic industry. Statistically significant SIRs were also noted in the construction trades with the SIR for excavation and foundation work being 5.8 and the SIR for building construction being 10.4 (based on 2 cases). Smoking data were available in 40 percent of the population with the authors reporting no evidence of confounding by cigarette smoking in this sub-sample.

Some of the cohort and case-control studies reviewed earlier in this section looked specifically at the lung cancer mortality rate of silicotics and/or non-silicotics (those who did not have evidence of silicosis). In general, these studies have not consistently found associations between the presence or absence of radiological silicosis and elevated lung cancer risk. A number of these studies reported finding no increases in the expected number of lung cancer cases among non-silicotics (de Klerk and Musk, 1998; Dong et al., 1995; Ulm et al., 1999). Other studies that reported finding an association between exposure to silica and increased lung cancer mortality did not find such associations with radiological silicosis. In the study of British pottery workers (Cherry et al., 1998) no evidence was found of a relationship between pulmonary opacities and lung cancer, the prevalence of opacities being 6 percent and 5 percent, respectively, for cases and controls. Among Chinese pottery workers, despite the high prevalence of silicosis observed (in 13 percent of lung cancer cases and 12 percent of controls) there was no evidence of an increased risk of lung cancer among silicotics versus non-silicotics (McLaughlin et al., 1992).

Studies of South African miners involving three separate populations examined the presence of silicosis and lung cancer at autopsy. In a study by Hessel et al. (1990), there was no clear exposure-response trend in odds ratios for lung cancer among subjects showing signs of silicosis of the parenchyma or pleura, and a negative exposure-response

trend was found among those with signs of silicosis in the hilar glands. In a cohort study by Hnizdo and Sluis-Cremer (1991) and a follow-up nested case-control study by Hnizdo et al. (1997), the authors found no clear relationship between silicosis and the risk of lung cancer as determined by autopsy. Miners with silicosis in the lung parenchyma and pleura did not show an increased risk of lung cancer compared to those without evidence of silicosis at these sites. However, the results did show a statistically significantly higher risk of lung cancer in miners with evidence of silicosis of the hilar glands, a finding that contrasts with that reported by Hessel et al. (1990). Hnizdo et al. (1997) reported that they could not disentangle the relative contributions of silica exposure and silicosis in increasing lung cancer risk because of the strong association between exposure and silicosis. Studies of Chinese miners also reported mixed results, with silicotics (defined by Chinese radiological categories) from tin and copper/iron mines but not tungsten mines, showing higher lung cancer mortality compared to non-silicotics (Chen et al., 1992). Overall, the mining studies do not show a consistent pattern with respect to the lung cancer mortality experience of silicotics.

Since the IARC (1997) review, there have been several individual studies and meta-analyses on silicotics designed to examine the relationship between silicosis and lung cancer. A brief review of this literature follows. A study by Chan et al. (2000), consisting of 1,490 male silicotics from Hong Kong (of whom approximately 90 percent were construction workers) concluded that smoking was the predominant risk factor for lung cancer in this cohort and that silica dust contributed little to the lung cancer risk. Although the authors reported a lung cancer SMR of 194 (95% CI 135-270) for the cohort overall, the proportion of workers who ever smoked was 90.6 percent compared to 49.8 percent for the male Hong Kong population. Using Axelson's model and assuming a 20-fold risk factor for smokers versus non-smokers, the authors estimated that the SMR would equal 175 from smoking alone in this cohort, which was close to the observed SMR of 194 (Chan et al., 2000).

Carta et al. (2001) conducted a study of 724 Sardinian male patients who were current or former mine and quarry workers and who were first diagnosed with silicosis between 1964 and 1970. Chest x-ray films categorized by the ILO classification system were available for all patients, as were smoking histories, tests of lung function (FEV_1/VC(vital capacity)), and detailed work histories. Mortality follow-up was through the end of 1997. Detailed exposure data were available for silica from 1945 and for radon from 1972. Exposures were reconstructed back to the 1920s by a team of industrial hygienists based on an analysis of mining techniques, annual production/figures, and documentation of changes in ventilation and drilling techniques. Individual employee cumulative exposure estimates were classified in one of three exposure groups for respirable dust and one of three exposure groups for respirable crystalline silica (<5 gh/m^3, 5-10 gh/m^3, and >10gh/m^3). Radon exposure data was only available from 1972 forward and the cumulative exposures were grouped as either greater than or less than 120 WLM (working level months). The analysis consisted of categorical analysis with SMR values being derived from regional mortality rates supplemented by regression analysis using multivariate proportional hazards modeling and stepwise regression analysis. Carta et al. (2001) also included a nested case-control of 34 lung cancer deaths

with 4 controls randomly selected from the cohort for each case, matching on age and year of entry into the workforce.

Standard mortality rates from NMRD (non-malignant respiratory disease) and tuberculosis (TB) were 603 (95% CI 544-669, 278 deaths) and 2,200 (95% CI 1,738-2,784, 33 deaths), respectively, which largely contributed to an all-cause mortality of SMR 134 for the cohort. The SMR for lung cancer mortality was elevated but was not statistically significant (SMR = 137, 95% CI 98-191, 34 deaths). Non- statistically significant trends of increased lung cancer mortality were observed with increased cumulative exposure to silica and ILO radiographic profusion category. These trends became more pronounced after incorporating a 20-year latency period into the analysis but were still not statistically significant. The authors reported that a clearer trend (data not provided) existed between exposure to radon and lung cancer mortality than silica exposure and lung cancer mortality. The highest SMR for lung cancer mortality was found among ever smokers with evidence of obstructive impairment measured by spirometry at initial diagnosis (SMR = 329 95% CI 223-483).

According to the authors, the analysis showed that smoking, severity of airflow obstruction, and cumulative exposure to radon daughters were the only significant explanatory variables for lung cancer mortality. The nested case-control analysis confirmed a statistically significant association between exposure to radon daughters and lung cancer (OR = 2.21, 95% CI 1.01-4.85 for exposures greater than 120 WLM). In contrast, ORs for lung cancer were not statistically significantly elevated. For example, for the highest ILO radiological category and the highest cumulative silica exposure category, the OR was 1.30 (95% CI 71-268).

Finkelstein (1998) re-analyzed data from a nested case-control study conducted from a cohort of workers under surveillance for silicosis in Ontario, Canada. There were 42 lung cancer cases with 3 matched controls for each case. Smoking histories and chest x-ray films were available from the surveillance program, and x-ray films were analyzed independently by two readers with a very high concordance of classification. Particular attention was given to potential confounding by smoking, using computer simulations since only 1 out of 42 lung cancer cases had never smoked. The relative risk of lung cancer mortality was 3.27 (95% CI 1.32-8.2) for subjects whose films were classified 1/0 or greater (based on the 1980 ILO system), compared to those whose films were classified 0/1or 0/0. The authors concluded that there was an association between the presence of radiographic silicosis and increased lung cancer mortality and that radiographic silicosis should be considered a marker for increased lung cancer risk among workers exposed to silica.

The study of diatomaceous earth workers by Checkoway et al. (1999) was specifically designed to investigate the relationship between the classification of radiological silicosis and lung cancer mortality. The study demonstrated a trend of increasing lung cancer mortality with increasing cumulative exposure to crystalline silica in the absence of silicosis. In this study, 81 workers (4.5 percent) in the cohort had radiological silicosis. The overall mortality from lung cancer was found to be higher

among these silicotics, (SMR 1.57 95 % CI 0.43-4.03) compared to non-silicotics (SMR 1.19 95% CI 0.87-1.57), although neither increase was statistically significant. Among non-silicotics, there was a statistically significant increase in lung cancer mortality (compared to national rates) with increasing cumulative exposure (p for trend = 0.02). The authors concluded, " [t]he dose-response relation observed between cumulative exposure to respirable crystalline silica and lung cancer mortality among workers without radiological silicosis suggests that silicosis is not a necessary co-condition for silica-related lung carcinogenesis. However, the relatively small number of silicosis cases in the cohort and absence of radiographic data after employment limit interpretations."

Several meta-analyses and pooled cohort studies designed to explore relationships between silicosis and lung cancer mortality have been performed (Kurihara and Wada, 2004; Lacasse et al., 2005; Pelucchi et al., 2006; Smith et al., 1995; Steenland and Stayner, 1997; Tsuda et al., 1997). Smith et al. (1995) and Tsuda et al. (1997) performed meta-analyses on cohort and case-control studies of silicotic workers. Smith et al. (1995) originally abstracted data from 29 epidemiologic studies published between 1966 and 1994. Six of these studies were eliminated due to design flaws or unquantifiable biases, leaving 23 studies. The method developed by Greenland (1987) was used to derive a pooled relative risk (RR) estimate for lung cancer among silicotics. This method weights each study's RR measure in a manner inversely proportional to the variances of each study-specific estimate. The pooled RR estimate for the 23 studies was 2.2 (95% CI 2.1-2.4). The pooled RR estimates by study design were 2.0 (95% CI 1.8-2.3) for cohort studies and 2.5 (95% CI 1.8-3.3) for case-control studies (Smith et al., 1995). There was significant heterogeneity between the studies used in the analysis. The authors concluded that the results of the analysis provided evidence of an increased risk of lung cancer in silicotics who do not smoke, and that these findings could be due to either a modifying effect of silicosis or to a direct effect of crystalline silica exposure.

Tsuda et al. (1997) also conducted a meta-analysis to explore the relationship between silicosis/pneumoconiosis and lung cancer mortality. Lung cancer RR measures were pooled from 32 eligible studies (6 from the Japanese literature) published from 1980 to 1994. The pool of studies was thus broader but had better-defined inclusion criteria than those of Smith et al. (1995). The Greenland (1987) method was used to derive the pooled estimate of relative risk. The overall estimated risk ratio was somewhat higher than those obtained by Smith et al. (1995) (RR = 2.7, 95% CI 2.6-2.9). The RRs for lung cancer mortality by study type were 2.8 (95% CI 2.6-2.9) for cohort studies and 2.7 (95% CI 2.3-3.6) for case-control studies. Tsuda et al. (1997) calculated pooled RRs for lung cancer among workers in four separate industry categories and found similar estimates for each (pooled RR 2.68, 2.65, 2.61, and 2.6 for silicotics in mining, quarrying, foundry, and pottery/ceramic work, respectively). Although the authors did not find an association between lung cancer mortality and increasing silicosis severity (determined by ILO profusion category), they concluded that silicosis was causally related to lung cancer mortality with the lung cancer risk being about three times greater among silicotics than in the general population.

Steenland and Stayner (1997) conducted a meta-analysis of 19 studies of silicotics and 16 studies of silica-exposed populations. The process for selecting studies was not described, and the pooled RR was estimated by weighting each risk measure from each study in inverse proportion to the variance of the risk estimate and using a random effects model. The pooled RR for silicotic populations was 2.3 (95% CI 2.2-2.4). Steenland and Stayner (1997) also reviewed 16 studies of silica-exposed workers, which had a pooled RR of 1.3 (95% CI 1.2-1.4), suggesting a higher risk among silicotics compared to silica-exposed working populations. The authors pointed out that it was unlikely that confounding by smoking was responsible for the observed excess risk because a number of the studies included in their analysis controlled for smoking, either directly or indirectly (Steenland and Stayner, 1997).

Kurihara and Wada (2004) conducted a meta-analysis that compared the estimated relative risks of lung cancer among workers exposed to crystalline silica versus those with silicosis. The investigators evaluated studies published between 1966 and 2001 and excluded those studies in which the confounding exposures to asbestos, radon and other potential carcinogens were apparent or where potential confounding by smoking was not sufficiently addressed. A panel of three independent reviewers performed a quality screen to select studies for analysis with differences resolved by consensus. Thirty studies (17 cohorts and 13 case-controls) in 25 papers were selected to evaluate the relationship between exposure to silica and lung cancer and 16 studies (11 cohort and 5 case-control) were reviewed to evaluate the relationship between lung cancer risk and the presence of radiological silicosis. Risk measures were weighted by the inverse of their variances and combined using a random effects model. There was no indication of publication bias (tendency not to publish negative studies) when observations were made by funnel analysis.

The pooled lung cancer RR for silica-exposed populations was 1.32 (95% CI 1.24-1.41), a finding similar to that of Steenland and Stayner (1997). The pooled RR for cohort and case-control studies were 1.29 (95% CI 1.20-1.40) and 1.42 (95% CI 1.22-1.65), respectively. For studies of silicotic populations, the pooled lung cancer RR was 2.37 (95% CI 1.98-2.84). The pooled lung cancer RR among non-silicotic subjects with silica exposure was not found to be elevated (pooled RR = 0.96, 95% CI 0.81-1.15). The investigators also reported that the pooled risk in smokers with silicosis (pooled RR 4.47, 95% CI 3.17-6.30) was twice as high as the pooled risk among non-smokers with silicosis (pooled RR 2.24, 95% CI 1.46-3.43). The degree of radiographic progression as determined by ILO classification of the chest x-ray films was not associated with an increased relative risk of lung cancer in this study.

The authors suggested that silicosis, rather than exposure to crystalline silica itself, increased the lung cancer risk among silica-exposed workers. The authors further suggested that exposure control to reduce silicosis and implementation of smoking cessation programs among silicotics would greatly reduce lung cancer mortality. The authors acknowledged that the sample number (N=8) in their analysis was small and therefore, could not definitively determine whether “exposure to crystalline silica directly increases lung cancer risk.”

Lacasse et al. (2005) reviewed the international epidemiological literature on silicosis as a potential causative agent or marker of lung cancer mortality published between 1966 and 2004 to identify original cohort and case-control studies. Proportional mortality, autopsy, and case series studies were excluded. Two of the authors independently reviewed each study and reached consensus or involved a third reviewer in determining a paper's inclusion in the meta-analysis. Selected papers underwent a funnel analysis, and the authors determined that publication bias was slight. Three separate meta-analyses were conducted: one for the unadjusted SMR; another for the adjusted SMR, according to the method of analysis proposed by Axelson (1978) to account for smoking-related risk; and a third restricted to studies of non-smokers. The SMR values were weighted by the inverse of their variance and pooled using a random effects model. A dose-response analysis also compared ILO category of radiological diagnosis of chest x-rays with the risk of lung cancer mortality.

Thirty-one studies (27 cohort and 4 case-control studies) met the inclusion criteria. Without any adjustment for smoking, the meta-analysis for the cohort studies estimated a pooled SMR = 245 (95% CI 163-366), with a high degree of heterogeneity in underlying risk factors present ($p < 0.0001$). When four of the cohort mortality results were adjusted for smoking in accordance to Axelson's method, the pooled SMR was reduced to 160 (95% CI 133-193), with no significant heterogeneity ($p = 0.52$). When the data were restricted to four studies of silicotics who had never smoked, the pooled SMR was estimated at 152 (95% CI 102-226), a result comparable to that found in the analysis that adjusted for smoking (Lacasse et al., 2005).

The authors also found that lung cancer risk increased incrementally with increased profusion of opacities on x-ray, with the lung cancer RR increasing incrementally by 1.33 (95% CI 1.16-1.53) for each major ILO profusion category (i.e., ILO 1, 2, or 3). Lung cancer risk also increased incrementally with size of opacities with the incremental RR equal to 1.67 for each ILO size category (i.e., ILO categories a, b, or c).

In their discussion, Lacasse et al. (2005) acknowledged that their meta-analysis probably represents an overestimate of the real risk of lung cancer among silicotics because of the inherent biases of observational studies to meet the inclusion criteria. Nevertheless, separate meta-analyses of non-smoking silicotics and the dose-response observed between lung cancer mortality and silicosis severity suggested a true association between silicosis and lung cancer mortality. The authors also stated that it could not be determined from the available literature whether respiratory fibrosis directly increased the risk of lung cancer or, alternatively, whether an increased lung cancer risk could be attributed to exposure to respirable crystalline silica.

Pelucchi et al. (2006) reviewed approximately 45 studies published from 1996 to 2005, including 28 cohort and 15 case control studies. Approximately half of these case-control studies were nested within occupational or silicotic cohorts. Each study was

categorized by the authors as being either a study of silicotics only, silicosis status undefined, or a study of non-silicotics.

The pooled RRs of lung cancer were 1.69 (95% CI 1.32-2.16) in cohort studies of silicotics only, 1.25 (95% CI 1.18-1.33) in cohorts where silicosis status was undefined, and 1.19 for non-silicotics (1 study, RR not statistically significant). The authors concluded that an association between silicosis and lung cancer mortality was established, in agreement with other primary studies and meta-analyses, but that the issue remained open on whether exposure to respirable silica itself was associated with lung cancer. Pelucchi et al. (2006) also performed a pooled analysis of studies of exposed populations by industrial sector, with the industrial sector characterization being similar to that used by IARC (1997). These are presented in Table I-15.

Table I-15. Pooled Relative Risk (RR) for Lung Cancer Mortality from Pelucchi et al. (2006), by Homogeneous Industry Types

Industry Grouping		Cohort Studies		Case-Control Studies
	No.	RR* (95% CI)**	No.	RR* (95% CI)**
Miners (underground and surface)	3	1.17 (1.03-1.32)	4	1.47 (1.19-1.82)
Industrial sand worker	3	1.29 (1.03-1.61)	0	--
Ceramic, diatomaceous earth, and refractory brick	4	1.40 (1.11-1.75)	3	1.26 (0.99-1.62)
Other Miscellaneous exposures	10	1.17 (1.12-1.22)	9	1.24 (1.02-1.52)
Adapted from Pelucchi et al., 2006, Table 1 * RR = relative risk ** 95% CI = 95 percent confidence intervals				

Pelucchi et al. (2006) reviewed these findings and the quality of some of the underlying studies and found the relative risk estimates to be equivocal as to whether exposure to crystalline silica causes lung cancer, particularly due to the weakness of the case-control studies. OSHA notes that the pooled RR estimates for the four industry groups are modest but nevertheless statistically significantly elevated.

In summary, many studies of silicotic cohorts consistently reported higher mortality rates for lung cancer than were seen among non-silicotic or mixed cohorts.

Some of these studies (Kurihara and Wada, 2004; Steenland and Stayner, 1997) also showed an increase in lung cancer mortality among exposed workers absent evidence of radiographic silicosis, although these risks tended to be smaller than those reported for diagnosed silicotics.

The previously cited diatomaceous earth study by Checkoway et al. (1999) also found a statistically significant exposure-response relationship for lung cancer among non-silicotics, and no difference in lung cancer RRs were noted between silicotics and non-silicotics in the pottery industry studies. Checkoway and Franzblau (2000), in reviewing the international literature, found that all epidemiological studies conducted to that point were insufficient to conclusively determine the role of silicosis in the etiology of lung cancer. The authors proposed that the question of whether silicosis is a necessary precursor for lung cancer "[i]s virtually unanswerable from currently available epidemiological literature, and is unlikely to be addressable in future epidemiological studies." Similarly, OSHA believes that meta-analyses designed to investigate this issue demonstrate that workers with radiological silicosis are at higher risk of lung cancer mortality than non-silicotics but that it is not possible with available data to determine whether the increased lung cancer mortality risk reflects higher exposure among silicotics or whether it indicates that silicosis itself plays an etiologic role in the development of lung cancer.

I.C.6. Preliminary Conclusions from the Lung Cancer Evidence.

OSHA conducted an independent review of the epidemiological literature on exposure to respirable crystalline silica and lung cancer, covering more than 30 occupational groups in over a dozen industrial sectors. In addition, OSHA reviewed a pooled case-control study, a large national death certificate study, two national cancer registry studies, and six meta-analyses. In all, OSHA's review included approximately 60 primary epidemiological studies (See Table I-1).

Based on its review, OSHA preliminarily concludes that the human data summarized in this section provides ample evidence that exposure to respirable crystalline silica increases the risk of lung cancer among workers. The strongest evidence comes from the worldwide cohort and case-control studies reporting excess lung cancer mortality among workers exposed to respirable crystalline silica dust as quartz in various industrial sectors; the 10-cohort pooled case-control analysis by Steenland et al. (2001a) confirms these findings. A more recent clinic-based pooled case-control analysis of seven European countries by Cassidy et al. (2007) as well as two national death certificate registry studies (Pukkala et al., 2005 in Finland and Calvert et al., 2003 in the United States) support the findings from the cohort and case-control analysis.

I.C.6.a. Overall and industry sector-specific findings.

Associations between exposure to respirable crystalline silica and lung cancer have been reported in worker populations from many different industrial sectors. The

IARC panel (1997) identified four industry sectors in which studies were judged to be the least confounded that reported findings consistent with this hypothesis (quarries and granite works, ceramic or pottery industries, refractory brick industries, and the diatomaceous earth industry). Based on these and other findings, IARC (1997) concluded that crystalline silica is a confirmed human carcinogen. NIOSH (2002) also determined that crystalline silica is a human carcinogen after evaluating updated literature.

OSHA believes that the strongest evidence for carcinogenicity comes from studies in five industry sectors. These are:

- Diatomaceous Earth Workers (Checkoway et al., 1993, 1996, 1997, and 1999; Seixas et al., 1997);
- British Pottery Workers (Cherry et al., 1998; McDonald et al., 1995);
- Vermont Granite Workers (Attfield and Costello, 2004; Graham et al., 2004; Costello and Graham, 1988; Davis et al., 1983);
- North American Industrial Sand Workers (Hughes et al., 2001; McDonald et al., 2001, 2005; Rando et al., 2001; Sanderson et al., 2000; Steenland and Sanderson, 2001); and
- British Coal Mining (Miller et al., 2007; Miller and MacCalman, 2009).

OSHA credits these studies because in general, they:

- Are of sufficient size and have adequate years of follow up;
- Have sufficient quantitative exposure data to reliably estimate exposure of cohort members;
- Were either unlikely to be confounded by exposure to other occupational carcinogens, or potential confounding by co-exposures was addressed and found to be unlikely;
- For the most part, were able to obtain smoking history data, which permitted controlling for potential confounding or indirectly estimate an independent effect of smoking; and
- Were absent of any apparent selection bias, including choice of referent.

The studies above were all retrospective cohort or case-control studies that demonstrated positive, statistically significant exposure-response relationships between exposure to crystalline silica and lung cancer mortality. Except for the British pottery studies, where exposure-response trends were noted for average exposure only, lung

cancer risk was found to be related to cumulative exposure. There was limited confounding due to other occupational exposures. Where potential confounding could occur, e.g., asbestos in a subset of diatomaceous earth workers or U.S. crushed stone workers; this potential confounding was addressed in the study design or data analysis. As part of their analyses, the authors of these studies also found positive exposure-response relationships for silicosis, indicating that underlying estimates of worker exposures were not likely to be substantially misclassified.

A series of studies of the diatomaceous earth industry (Checkoway et al., 1993, 1996, 1997, 1999) demonstrated positive exposure-response trends between cristobalite exposures and lung cancer as well as non-malignant respiratory disease mortality (NMRD). Checkoway et al. (1993) developed a "semi-quantitative" cumulative exposure estimate that demonstrated a statistically significant positive exposure-response trend between duration of employment or cumulative exposure and lung cancer mortality. Checkoway et al. (1996) conducted a re-analysis to address criticisms of potential confounding due to asbestos and again demonstrated a positive exposure response risk gradient when controlling for asbestos exposure and other variables. Rice et al. (2001) conducted a re-analysis and quantitative risk assessment of the Checkoway et al. (1997) study, which is used by OSHA as part of its assessment of lung cancer mortality risk (See Section II, Preliminary Quantitative Risk Assessment).

In the British pottery industry, excess lung cancer risk was found study to be associated with crystalline silica exposure among workers in a PMR study (McDonald et al., 1995) and in a cohort and nested case-control study (Cherry et al., 1998). In the PMR study, elevated PMRs for lung cancer were found after adjusting for potential confounding by asbestos exposure. In the study by Cherry et al., odds ratios for lung cancer mortality were statistically significantly elevated after adjusting for smoking. Odds ratios were related to average, but not cumulative, exposure to crystalline silica. The findings of the British pottery studies are supported by other studies within their industrial sector. Winter et al. (1990) reported a statistically significant increase in the SMR for lung cancer among British pottery workers, and a non-monotonic increase in lung cancer mortality with increasing cumulative exposure. (This was a crude estimate of cumulative exposure based on job title during cross-sectional environmental sampling multiplied by the total number of years worked at the plant.) A nested case-control study of 13,719 Chinese potters also showed a modest increase in lung cancer mortality associated with increasing quartile of cumulative exposure to respiratory crystalline silica (McLaughlin et al., 1992).

Costello and Graham (1988) and Graham et al. (2004) in a follow-up study found that Vermont granite workers employed prior to 1930 had an excess risk of lung cancer, but lung cancer mortality among granite workers hired after 1940 (post-implementation of controls) was not elevated in the Costello and Graham (1988) study and was only somewhat elevated (not statistically significant) in the Graham et al. (2004) study. Graham et al. (2004) concluded that their results did not support a causal relationship between granite dust exposure and lung cancer mortality. Attfield and Costello (2004) looking at the same population developed a quantitative estimate of cumulative exposure

(8 exposure categories) adapted from a job exposure matrix developed by Davis et al. (1983). They found a statistically significant trend with log-transformed cumulative exposure. Lung cancer mortality was observed to rise reasonably consistently through the first seven increasing exposure groups, but fell in the highest cumulative exposure group. With the highest exposure group omitted, a strong positive dose-response trend was found. Attfield and Costello (2004) concluded that their quantitative analysis provided clear evidence that exposure to crystalline silica in the range of cumulative exposures typically experienced by contemporarily exposed workers have an increased risk of lung cancer mortality. OSHA believes that the study by Attfield and Costello (2004) is of superior design that allowed for the quantification of exposures by exposure group, along with a detailed explanation of why the lack of smoking data in this cohort had a small probability of affecting the results. The conclusions of the Vermont granite worker study (Attfield and Costello, 2004) are supported by the findings in studies of workers in the U.S. crushed stone industry (Costello et al., 1995) and Danish stone industry (Guénel et al., 1989a, 1989b).

Studies of overlapping cohorts in the industrial sand industry (Hughes et al., 2001; McDonald et al., 2001, 2005; Rando et al., 2001; Sanderson et al., 2000; Steenland and Sanderson, 2001) reported comparable results. They both found a statistically significantly increased risk of lung cancer mortality with increased cumulative exposure in both categorical and continuous analyses. The cohort of McDonald et al. (2001) entered the workforce, on average, a decade earlier than the Steenland and Sanderson (2001) study; it has more years of exposure in the industry (19 versus 8.8 years); and is more concentrated working within eight plants. The Steenland and Sanderson (2001) cohort worked in 16 plants, 7 of which overlapped with the McDonald, et al. (2001) cohort. McDonald et al. (2001), Hughes et al. (2001), and Rando et al. (2001) had good smoking histories for the cohort and access to plant records, processes, and modern and historic exposure measurements to conduct historical reconstructions and develop a job exposure matrix. Steenland and Sanderson (2001) had less access to plant facilities, less detailed historic exposure data, and used MSHA enforcement records for estimates of recent exposure. The findings of these studies (Hughes et al., 2001; McDonald et al., 2005; Steenland and Sanderson, 2001) are mutually reinforcing in that they show very similar exposure response patterns of increased lung cancer mortality with increased exposure gradients.

Excess lung cancer mortality was reported in a large cohort study of British coal miners (Miller et al., 2007; Miller and MacCalman, 2009). These studies examined the mortality experience of 17,800 miners through the end of 2005. By that time there were 516,431 person years of observation, an average of 29 years per miner, with 10,698 deaths from all causes. Overall lung cancer mortality was elevated and a positive exposure-response relationship with crystalline silica exposure was determined from Cox regression after adjusting for smoking history. Three of the strengths of this study are the detailed time-exposure measurements of both quartz and total mine dust, detailed individual work histories, and individual smoking histories. For lung cancer, analyses based on these Cox regression methods provide strong evidence that, for these coal

miners, quartz exposures were associated with increased lung cancer risk, but that simultaneous exposures to coal dust did not cause increased lung cancer risk.

Studies of lung cancer mortality in metal ore mining populations are more mixed. Many of these mining studies were subject to confounding due to exposure to other potential carcinogens such as radon and arsenic. IARC (1997) noted that in only a few ore mining studies was confounding from other occupational carcinogens taken into account. IARC (1997) also noted, where confounding was absent or accounted for in the analysis (gold miners in the U.S., tungsten miners in China, and zinc and lead miners in Sardinia, Italy), an association between silica exposure and lung cancer was absent. OSHA believes that many of the studies conducted since IARC's 1997 review more strongly implicate crystalline silica as a human carcinogen. Pelucchi et al. (2005), in a meta-analysis of studies conducted since IARC's (1997) review, reported statistically significantly elevated relative risks in underground and surface miners in three cohort and four case-control studies (See Table I-15). Cassidy et al. (2007), in a pooled case-control analysis, showed a statistically significant increased risk of lung cancer mortality among miners. Cassidy et al. (2007) also demonstrated a clear linear trend of increasing odds ratios for lung cancer with increasing exposures.

Among workers in Chinese tungsten and iron mines, mortality from lung cancer was not found to be statistically significantly increased (Chen et al., 1992; McLaughlin et al., 1992). In contrast, studies of Chinese tin miners found increased lung cancer mortality rates and positive exposure-response associations with increased silica exposure (Chen et al., 1992). Unfortunately, in many of these Chinese tin mines, there was potential confounding from arsenic exposure, which was highly correlated with exposure to crystalline silica (Chen and Chen, 2002; Chen et al., 2006).

Gold mining has been extensively studied involving four separate cohort and associated nested case-control studies conducted in three different countries and two independent case-control studies conducted in South Africa. Similar to other metal mining, gold mining lung cancer risk is subject to confounding, particularly from radon exposure. The U.S. gold miner study (Steenland and Brown, 1995a) did not find an increased risk of lung cancer, while the western Australian gold miner study (de Klerk and Musk, 1998) showed a statistically significant elevated SMR. Logistic regression analysis of the western Australian case control data showed that lung cancer mortality was statistically significantly associated with log cumulative silica exposure after adjusting for smoking and bronchitis. The authors concluded that their findings showed statistically significantly increased lung cancer mortality in this cohort but that the increase in lung cancer mortality was restricted to silicotic members of the cohort.

Four studies of gold miners were conducted in South Africa. Two case control studies (Hessel et al., 1986, 1990) reported no significant association between silica exposure and lung cancer, but these two studies were subject to underestimating risk, according to Hnizdo and Sluis-Cremer (1991). Two cohort studies (Reid and Sluis-Cremer, 1996 and Hnizdo and Sluis-Cremer, 1991) and their associated nested case-control studies found elevated SMRs and odds ratios, respectively, for lung cancer. Reid

and Sluis-Cremer (1996) attributed the increased mortality due to lung cancer and other non-malignant respiratory diseases to cohort members' lifestyle choices. However, OSHA notes that the study reported finding a positive, though not statistically significant, association between cumulative crystalline silica exposure and lung cancer, as well as statistically significant association with renal failure, COPD, and other respiratory diseases that have been implicated with silica exposure. Thus, OSHA believes that this study is not wholly inconsistent with others that have reported increased lung cancer mortality among silica-exposed workers.

In contrast, Hnizdo and Sluis-Cremer (1991) found a positive exposure-response gradient between cumulative exposure and lung cancer mortality after accounting for smoking. In a nested case-control study from the same cohort, Hnizdo et al. (1997) found a statistically significant increase in lung cancer mortality that was associated with increased cumulative dust exposure and time spent underground. These studies were the strongest South African studies in terms of their rigorous methodology and quantification of exposure. Consequently, OSHA believes that exposure misclassification was less likely to occur in these latter two studies. Although not conclusive in isolation, OSHA considers the mining study results, particularly the gold mining and the newer mining studies, as supporting evidence of a relationship between exposure to silica and lung cancer risk.

Further evidence for a causal relationship between exposure to respirable crystalline silica and lung cancer mortality comes from the pooled analysis of 10 occupational cohorts (5 mines and 5 industrial facilities) conducted by Steenland et al. (2001a), which demonstrated an overall positive exposure-response relationship between the log cumulative exposure to silica and lung cancer mortality.

OSHA also reviewed a center-based case-control study (Cassidy et al., 2007), which pooled cancer incidence data from seven European countries in 15 regional centers. This large study, with 2,852 newly diagnosed cases, was able to obtain good personal data on smoking as well as good exposure estimates of exposure to silica dust and other potentially confounding occupational exposures. The authors concluded: "Our result(s) support the hypothesis that silica is an important risk factor for lung cancer. This risk could not be explained by exposure to other occupational carcinogens or smoking" (Cassidy et al., 2007).

In addition, a recent analysis of 4.8 million death certificates from 27 states within the U.S. for the years 1982 to 1995 showed a statistically significant pattern of increased mortality risk due to lung cancer as well as increased mortality due to silicosis, tuberculosis, and NMRD among persons with occupations in industries with medium and high exposure to respirable crystalline silica as determined by an expert panel of industrial hygienists (Calvert et al., 2003). A national records and death certificate study was also conducted in Finland by Pukkala et al. (2005) who found a statistically significant increase in incidence rates of lung cancer among men and women with estimated medium and heavy exposures.

OSHA believes that these large national death certificate studies and the pooled European community-based case-control study strongly supportive of the previously reviewed epidemiologic data and supports the conclusion that occupational exposure to crystalline silica is a risk factor for lung cancer mortality.

I.C.6.b. Smoking, silica exposure, and lung cancer.

Smoking is known to be a major risk factor for lung cancer. However, OSHA believes it unlikely that the observed exposure-response trends reported in most of these studies are explained by smoking. This is particularly true in retrospective cohort or nested case-control studies that demonstrate a gradient of increased disease risk with increasing exposure, as is the case with studies of diatomaceous earth, British pottery, Vermont granite, British coal, South African gold, and industrial sand workers. Also, the fact that these positive associations are found in multiple studies in multiple sectors is supportive of crystalline silica being an independent risk factor from smoking, since it becomes increasingly unlikely that smoking alone could explain the observed exposure-response trends across a large group of studies.

Studies by Hnizdo et al. (1997), McLaughlin et al. (1992), Hughes et al. (2001), McDonald et al. (2001, 2005), Miller and MacCalman (2009), and Cassidy et al. (2007) had detailed smoking histories with sufficiently large populations and sufficient time from first exposure for lung cancer to become manifest to quantify the interaction between crystalline silica exposure and cigarette smoking. In a cohort of white South African gold miners (Hnizdo and Sluis-Cremer, 1991) and in the follow-up nested case-control study (Hnizdo et al., 1997) found that the combined effect of exposure to respirable crystalline silica and smoking was greater than additive, suggesting a multiplicative effect. This synergy appeared to be greatest for miners with greater than 35 pack-years of smoking and higher cumulative exposure to silica. In the Chinese nested case-control studies reported by McLaughlin et al. (1992), cigarette smoking was associated with lung cancer, but correction for smoking did not influence the association between silica and lung cancer in the mining and pottery cohorts studied. The studies of industrial sand workers by Hughes et al. (2001) and British coal workers by Miller and MacCalman (2009) found positive exposure-response trends after adjusting for smoking histories. Cassidy et al. (2007) found that current smokers ever exposed to silica had approximately a 40 percent increased incidence of lung cancer (OR = 1.41, 95% CI 1.07-1.87) than unexposed current smokers. Similar estimates of increased risk were observed among exposed ex-smokers and non-smokers, but these results were not statistically significant for these populations. Cassidy et al. (2007) "[d]id not observe any interaction beyond a multiplicative model between tobacco smoking and silica exposure."

In reference to control of potential confounding by cigarette smoking in crystalline silica studies, Stayner (2007), in an invited journal commentary, stated:

> "Of particular concern in occupational cohort studies is the difficulty in adequately controlling for confounding by cigarette smoking. Several of the cohort studies that adjusted for smoking have demonstrated an excess

of lung cancer, although the control for smoking in many of these studies was less than optimal. The results of the article by Cassidy et al. presented in this journal appear to have been well controlled for smoking and other workplace exposures. It is quite implausible that residual confounding by smoking or other risk factors for lung cancer in this or other studies could explain the observed excess of lung cancer in the wide variety of populations and study designs that have been used. Also, it is generally considered very unlikely that confounding by smoking could explain the positive exposure-response relationships observed in these studies, which largely rely on comparisons between workers with similar socioeconomic backgrounds."

Given the findings of investigators who have accounted for the impact of smoking, the weight of the evidence reviewed here implicates respirable crystalline silica as an independent risk factor for lung cancer mortality. This finding is further supported by animal studies demonstrating that exposure to silica alone can cause lung cancer (e.g., Muhle et al., 1995).

I.C.6.c. Silicosis and lung cancer risk.

In general, studies of workers with silicosis, as well as meta-analyses that include these studies, have shown that workers with radiologic evidence of silicosis have higher lung cancer risk than those without radiologic abnormalities or mixed cohorts. Three meta-analyses attempted to look at the association of increasing ILO radiographic categories of silicosis with increasing lung cancer mortality. Two of these analyses (Kurihara and Wada, 2004; Tsuda et al., 1997) showed no association with increasing lung cancer mortality, while Lacasse et al. (2005) demonstrated a positive dose-response for lung cancer with increasing ILO radiographic category. A number of other studies, discussed above, also found increased lung cancer risk among exposed workers absent radiological evidence of silicosis (Cassidy et al., 2007; Checkoway et al., 1999; Cherry et al., 1998; Hnizdo et al., 1997; McLaughlin et al., 1992). For example, the diatomaceous earth study by Checkoway et al. (1999) showed a statistically significant exposure-response for lung cancer among non-silicotics. Checkoway and Franzblau (2000), reviewing the international literature, found all epidemiological studies conducted to that date were insufficient to conclusively determine the role of silicosis in the etiology of lung cancer. OSHA preliminarily concludes that the more recent pooled and meta-analyses do not provide compelling evidence that silicosis is a necessary precursor to lung cancer and might simply reflect that more highly exposed individuals are at a higher risk for lung cancer.

Animal and *in vitro* studies have demonstrated that the early steps in the proposed mechanistic pathways that lead to silicosis and lung cancer seem to share some common features. This has led some of these researchers to also suggest that silicosis is a prerequisite to lung cancer. Some have suggested that any increased lung cancer risk associated with silica may be a consequence of the inflammation (and concomitant oxidative stress) and increased epithelial cell proliferation associated with the

development of silicosis. However, other researchers have noted that other key factors and proposed mechanisms, such as direct damage to DNA by silica, inhibition of p53, loss of cell cycle regulation, stimulation of growth factors, and production of oncogenes, may also be involved in carcinogenesis induced by silica (see Section II.F. for more information on these studies). Thus, OSHA preliminarily concludes that available animal and *in vitro* studies do not support the hypothesis that development of silicosis is necessary for silica exposure to cause lung cancer.

I.C.6.d. Relationship between silica polymorphs and lung cancer risk.

The current OSHA standard reflects a once-held belief that cristobalite is more toxic than quartz (i.e., the PEL for cristobalite is one-half the PEL for quartz). Available evidence indicates that this does not appear to be the case with respect to the carcinogenicity of crystalline silica. A comparison between cohorts having principally been exposed to cristobalite (the diatomaceous earth study and the Italian refractory brick study) with other well conducted studies of quartz-exposed cohorts suggests no difference in the toxicity of cristobalite versus quartz. The data indicates that the SMRs for lung cancer mortality among workers in the diatomaceous earth (SMR = 141) and refractory brick (SMR = 151) cohort studies are within the range of the SMR point estimates of other cohort studies with principally quartz exposures (quartz exposure of Vermont granite workers yielding an SMR of 117; quartz and possible post-firing cristobalite exposure of British pottery workers yielding an SMR of 129; quartz exposure among industrial sand workers yielding SMRs of 129, (McDonald et al., 2001) and 160 (Steenland and Sanderson, 2001)).

OSHA believes that the current epidemiological literature provides little, if any, support for treating cristobalite as presenting a greater lung cancer risk than comparable exposure to respirable quartz. Furthermore, available toxicological literature no longer supports the hypothesis that cristobalite has a higher toxicity than quartz, and quantitative estimates of lung cancer risk do not suggest that cristobalite is more carcinogenic than quartz. (See Section I-F, Physical Factors that May Influence Toxicity of Crystalline Silica, for a fuller discussion of this issue.) OSHA preliminary concludes that respirable cristobalite and quartz dust have similar potencies for increasing lung cancer risk; this position is consistent with previous positions taken by IARC (1997) and NIOSH (2002).

I.C.7. Cancer of Other Sites.

Respirable crystalline silica exposure has also been investigated as a potential risk factor for cancer at other sites such as the larynx, nasopharynx and the digestive system including the esophagus and stomach. Although many of these studies suggest an association between exposure to crystalline silica and an excess risk of cancer mortality, most are too limited in terms of size, study design, or potential for confounding to be conclusive. Other than for lung cancer, cancer mortality studies demonstrating a dose-response relationship are quite limited. Also, most of the better quality studies reviewed above (Vermont granite, British pottery, industrial sand, and diatomaceous earth) did not find statistically significant excess cancer mortality rates for sites other than the

respiratory system. In their silica hazard review, NIOSH (2002) concluded that, exclusive of the lung, an association has not been established between silica exposure and excess mortality from cancer at other sites. A brief review of the relevant literature is presented below.

I.C.7.a. Cancer of the larynx and nasopharynx.

There are several studies that have hinted at an increased incidence of laryngeal cancer among workers exposed to crystalline silica. In part due to the small size of the occupational cohorts studied, none of these studies found statistically significant results. In addition, many of these studies did not control for smoking, an important potential confounder for laryngeal cancer. One of the earliest cancer studies among Vermont granite workers looked at the proportion of deaths due to cancers at various sites (Davis et al., 1983). The authors reported an overall increase in respiratory cancer mortality as well as mortality from cancer of the larynx. The proportionate mortality ratio (PMR) values were 130 (95% CI 100-160) for respiratory cancer mortality, 190 (95% CI 80-440, 5 cases observed) for laryngeal cancer mortality and 120 (95% CI 90-150) for lung cancer mortality. However, later studies of this population with extensive follow-up failed to find excess mortality from laryngeal cancer (Costello and Graham, 1988; Graham et al., 2004).

Another early study by Selikoff (1978) of New York City tunnel workers reported finding an SMR for laryngeal cancer mortality of 3.80 (3 observed). No industrial hygiene monitoring was provided, but the author indicated that asbestos exposure, if any, was small and that these workers experienced high silica quartz exposures. A population based study by Neuberger and Kundi (1990) in Vienna, Austria, of the dusty trades (foundries, metal working, and glass, brick and stone work, etc.) found increased mortality from lung cancer (SMR = 148, 175 observed), laryngeal cancer (SMR = 143, 4 observed), and stomach cancer (SMR = 166, 77 observed).

Puntoni et al. (1988) reported finding an SMR of 405 (95% CI 83-1182, 3 observed) for laryngeal cancer among refractory brick plant employees. Puntoni et al. (1988) noted that laryngeal cancer was limited only to the silicotic population, whereas lung cancer was more evenly distributed among the study population. Sorahan and Cooke (1989) in a cohort of 10,491 United Kingdom foundry workers reported increases, though not statistically significant, in nose and naval cavity cancers and cancer of the larynx. The SMRs were 251 (4 observed/1.6 expected) for the nose and nasal cavity and 116 (8 observed 6.9 expected) for the larynx. Cherry et al. (1998) and Chen et al. (1992) did not observe an increased rate of esophageal cancer among British or Chinese pottery workers, respectively. Chen et al. (1992) found statistically significantly increased mortality from nasopharyngeal cancer among Chinese tungsten and tin miners, but not among Chinese pottery workers. Two well-done studies of U.S. cohorts (diatomaceous earth and industrial sand workers) reported increases, though not statistically significant, in laryngeal cancer mortality (Checkoway et al., 1997; McDonald et al., 2001).

In summary, many of these initial studies, including three of the better-quality lung cancer studies (Checkoway et al., 1997; Davis et al., 1983; McDonald et al., 2001) suggest an association between exposure to crystalline silica and increased mortality from laryngeal cancer. However, the evidence for an association is not strong due to the small number of cases reported and lack of statistical significance of most of the findings.

I.C.7.b. Gastric (stomach) cancer.

In their 2002 hazard review of respirable crystalline silica, NIOSH identified numerous epidemiological studies and reported statistically significant increases in death rates due to gastric or stomach cancer. The following cancer studies were reviewed and cited in NIOSH (2002). The studies are listed below by industry author and date (see NIOSH, 2002 for full bibliographic references):

- Iron ore miners (Lawler et al., 1985; Mur et al., 1987; St. Clair Renard, 1984);
- Canadian gold miners (Kusiak et al., 1993; Miller et al., 1983; Muller et al., 1983; Shannon et al., 1987);
- Lead and zinc miners (Belli et al., 1989);
- Brick workers (Katnelson and Mokronosova, 1979);
- Foundry workers (Newberger and Kundi, 1990);
- Jewelry workers (Dubrow and Gute, 1987; Hays et al., 1993; Sparks and Wegman, 1980); and
- Farmers/farmworkers (Blair and Zahm, 1991, 1993).

Moshammer and Neuberger (2004) reported on a prospective community based study examining the long term disease effects of occupational non-fibrous dust(s) exposure (including crystalline silica) on life expectancy and specific causes of death. Subjects were 3,260 male Viennese workers, selected at a mean age of 54 during preventive check-ups between 1950 and 1960 and who were followed prospectively until death (50 years of follow-up during which essentially the entire cohort had died). Half of the subjects (1,630) were exposed at work to non-fibrous, mineral particulates and were matched for year of job entry, age, and smoking status, with non-exposed workers. Average life expectancy of those exposed to dusty occupations was 1.6 years less than that of non-exposed workers ($p < 0.001$). Only a small part of this decrease in life expectancy was related to "acknowledged occupational diseases such as silicosis and silicotuberculosis" and other pneumoconiosis (SMR = 6,712). Chronic obstructive pulmonary disease (COPD) (SMR = 182 95% CI 130-256), bronchial cancer mortality (SMR = 142 95% CI 114-176), and stomach cancer mortality (SMR = 177 95% CI 125-251) were found more frequently among those exposed to dust. The authors postulated

that the finding of an increased incidence of stomach cancer might be related to particles swallowed after clearance from the airways. By design, this study could not distinguish the differences between exposure to crystalline silica and other mineral dusts.

PMRs and proportionate cancer mortality ratios (PCMRs) were evaluated for 12,873 members of the Operative Plasterers' and Cement Masons' International Association who died between 1972 and 1996, using United States age-, race-, and calendar-specific death rates (Stern et al., 2001). Among cement masons, statistically significant elevated mortality was observed for cancer of the stomach (PCMR = 133 $p < 0.01$) and benign neoplasm (PMR = 132 $p < 0.01$). This was an initial study and was suggestive of elevated stomach cancer mortality among cement masons who would presumably have been exposed to crystalline silica (Stern et al., 2001).

Finkelstein and Verma (2005) conducted a preliminary retrospective cohort study of 10,953 male members of International Union of Bricklayers and Allied Craftworkers from Ontario, Canada, who were exposed to silica and other inorganic dusts. The comparison group was comprised of Ontario members of the plumbers' union. The study did not have access to exposure measurements or smoking data but used type of union local and years of union membership as proxies for type of exposure and duration of exposure.

Elevation of lung cancer, pneumoconiosis, and stomach cancer mortality was noted among union members. For workers with 20 or more years of union membership, the SMR for lung cancer was 158 (95% CI 130-190, 100 observed) and for stomach cancer was 235 (95% CI 140-370, 19 observed). Stomach cancer mortality rates also increased with increasing decade of union membership, but the increase was statistically significant only for those with more than 30 years of membership (11 observed deaths). The studies by Stern et al. (2001) and Finkelstein and Verma (2005) suggest that exposure to dust from construction materials such as brick and concrete are a risk factor for stomach cancer.

Parent et al. (1998) conducted detailed population-based case-control analyses of incident gastric cancer cases identified between 1979 and 1985. The analysis included 250 male cases, aged 35 to 70 years, residing in Montreal, Canada, who were diagnosed with gastric cancer with histological confirmation. This was part of a larger study of cancer cases at 19 anatomical sites, from which 533 age-stratified controls were selected, but excluded cancer of the lung and esophagus. A two-part interview was conducted with each case or control: a structured questionnaire on socio-demographic variables and personal habits and a second semi-structured questionnaire obtaining a detailed job history. In total, 16 occupation and industry categories and 32 substances that were identified either in exploratory analyses or in previous studies as potential risk factors for gastric cancer were evaluated. A panel of chemists and industrial hygienists, blinded to the case or control status of the subject, ranked the likelihood, frequency, and intensity of the expected exposure based upon the detailed job histories. Unconditional logistic regression was used in the analysis with smoking status, years at school (measure of socioeconomic status), and birthplace or country of origin treated as covariates.

Among cases who had worked at least 10 years as excavators or pavers or as electric or electronic workers, the authors found an increasing risk of gastric cancer with increasing years of work. Crystalline silica was one of three exposures that was statistically significantly associated with increased stomach cancer mortality (OR = 1.7 95% CI 1.1-1.7, N = 25); the other substances were grain dust (OR = 1.9 CI 1.2-3.1, N = 23) and leaded gasoline (OR = 2.0 CI 1.2-3.3, N = 22). For crystalline silica, the risk of gastric cancer increased with the frequency and concentration of exposure, but there was no evidence of an exposure-response pattern based on the duration of exposure (Parent et al., 1998).

Tsuda et al. (2001) conducted a population-based case-control study to examine the effect of silica exposure on gastric and esophageal cancer mortality. Both cases and controls were selected from cancer death certificates, controls being colon and other types of cancer exclusive of lung cancer. The study was restricted to male subjects from the Tobi area of Japan. For gastric cancer, the age and smoking-adjusted OR was 1.22 (95% CI 0.74-2.01) and for esophageal cancer, the OR was 1.53 (95% CI 0.87-6.23). Although results did not reach a statistically significant level, the authors concluded that the results suggest that an increased mortality associated with gastric and esophageal cancers was related to silica exposure.

In a study by Koskela et al. (1987) of 1,026 Finnish granite workers exposed to silica from 1940 to 1985, mortality from gastrointestinal cancer was significantly increased (SMR of 200 95% CI 110-380, 15 deaths observed). No other Finnish cohorts had statistically significant increased rates of gastrointestinal cancer.

González et al. (1991) conducted a population-based study consisting of 354 cases of gastric carcinoma diagnosed among the residents of four regions of Spain. The cases were matched by age, sex, and geographical area. The subjects were interviewed to obtain information on bio-demographic characteristics, work history, and occupational exposures to inorganic and organic dusts (no exposure measurements). The risk of stomach cancer was statistically significantly increased for employment in coal mining, construction, and the leather industries as well as occupations with expected silica or other mineral exposure after adjusting for potential confounding by socioeconomic status and consumption of vegetables and fruits.

Xu et al. (1996b) conducted a nested case-control of stomach (292 incident cases) and lung cancer among iron and steel workers in Anshan, China. For lung and stomach cancer a statistically significant dose-response was observed for total dust and benzo(a)pyrene exposure, but not for the silica fraction of total dust. (In China, routine sampling for silica is conducted as a total dust area measurement, supplemented by silica content of settled dust.) For stomach cancer, after adjusting for consumption of pickled vegetables, prior gastric diseases, family history of stomach cancer, low intake of fruits and vegetables and education level, the risk of stomach cancer was statistically significantly elevated for those employed 15 or more years in the fire resistant brick factory (OR = 2.5, 95% CI = 1.1-5.8), in general (dusty) loading (OR = 3.2, CI = 1.2-8.9),

as boiler workers and cooks (OR = 2.6, CI = 1.2-5.6), and as coke oven workers (OR = 5.4, CI = 1.8-16.0). This confirmed an earlier PMR study by Xu et al. (1996a) that showed an increase in stomach and esophageal cancer mortality among refractory brick workers. In contrast, Chen et al. (1992), found no excess stomach cancer mortality in tin, iron and copper mining, and the ceramic industry. Chen et al. (1992) also found a statistically reduced mortality in tungsten mining (SMR = 48) in a cohort of 68,000 Chinese workers of primarily metal mining and the ceramics industry. Dong et al. (1995) in a retrospective cohort of silica and clay brick workers in 11 refractory plants found a slight non-statistically significant increase in mortality due to stomach cancer (SMR = 130) among 6,266 male workers.

In summary, OSHA preliminarily concurs with observations made previously by Cocco et al. (1996) and the NIOSH (2002) crystalline silica hazard review that the vast majority of epidemiology studies of silica and stomach cancer have not sufficiently adjusted for the effects of confounding factors or have not been sufficiently designed to assess a dose-response relationship (e.g., Finkelstein and Verma, 2005; Moshammer and Neuberger, 2004; Selikoff, 1978, Stern et al., 2001). Other studies did not demonstrate a statistically significant dose–response relationship (e.g., Calvert et al., 2003; Tsuda et al., 2001). Therefore, OSHA believes the evidence is insufficient to conclude that silica is a gastric carcinogen.

I.C.7.c. Esophageal cancer.

Wernli et al. (2006) evaluated the associations between occupational exposures in the textile industry and the risks of esophageal cancer and stomach cancer. The authors conducted a case-cohort study nested in a cohort of predominately female textile workers in Shanghai, China. One hundred two (102) incident esophageal cancer and 646 incident stomach cancers diagnosed between 1989 and 1998 were compared with an age-stratified reference subcohort (n = 3,188). Work histories were obtained for all study subjects from factory personnel records or interviews. Exposures were reconstructed for chemicals and dusts by linking work history data with a job exposure matrix. Twenty-three (23) chemical or dust groupings and 12 specific hazardous agents, including silica dusts, were evaluated. Cox proportional hazards modeling was used to estimate RRs. Information about personal risk factors, including smoking history, (ever/never) alcohol consumption, and reproductive history was obtained in a baseline questionnaire administered from 1989 to 1991.

Risk of esophageal cancer was associated with long-term exposure to silica dust ($\geq$10 years) in a metal foundry setting that was part of the textile complex (hazard ratio = 15.8, 95% CI 3.5-70.6) as well as exposure to metals (hazard ratio = 3.7, 95% CI 1.9-7.1). There was also a modest increase of esophageal cancer risk associated with exposure to acids, bases, and caustics. Increased risks of stomach cancer were modest, with either no or erratic trends with increased duration of these exposures. The authors acknowledged that the increase in risks may be attributed to exposure to PAHs (polycyclic aromatic hydrocarbons) that were not assessed in this study.

Yu et al. (2005) conducted a mortality study of esophageal cancer in a cohort of 2,789 male silicotic workers in Hong Kong during 1981 to 1999. The registry of silicotics primarily consisted of construction workers who either worked within caissons and tunnels or those who worked in surface construction occupations. The SMR for esophageal cancer for the entire cohort was 222 (95% CI 136-343, based on 20 deaths). For a subgroup of caisson workers who had a higher exposure to silica dust, the SMR was 421 (95% CI 181-830, based on 8 deaths). The RR of esophageal cancer for caisson workers with silicosis was reduced to 234 (95% CI 101-462) after adjustment, using the indirect method proposed by Axelson, for the effects of smoking and alcohol drinking. For non-caisson silicotic workers, no excess risk of esophageal cancer was observed after indirect adjustment for the effects of smoking and alcohol drinking.

The authors believed that the excess risk of esophageal cancer mortality among caisson workers with silicosis could best be explained by the very heavy exposure to respirable crystalline silica dust in their working environment, reported by the authors to be greater than hundred times the TLV. Exposure data for respirable silica and other possible exposures (welding fumes, combustion products) for caisson or surface construction workers was available, but not used, in the analysis. The authors stated, "no measurements were taken during pneumatic rock drilling because extremely high dust concentrations led to absorption of alpha particles and rendered counting inaccurate." The authors also referenced Lam et al. (1988) who reported a wide range of radon and radon daughters concentrations in caissons. OSHA believes that if radon particles are absorbed by the dust and dust is inhaled and partially cleared or has a longer residence time in the lung and esophagus due to overloading, excess alpha radiation would be expected to be delivered to these organ areas leading to lung or esophageal cancer.

Using duration (years) of exposure and severity of silicosis as surrogates of exposure, Yu et al. (2005) noted a non-statistically significant dose response trend for the eight caisson workers who died of esophageal cancer for both the duration of exposure and severity of silicosis. The authors have accounted for other known confounders such as smoking and alcohol by indirect adjustment and still maintain a statistically significant result among caisson workers. They noted that the differences of esophageal cancer mortality rates between caisson work and surface construction work is unlikely to be caused by socioeconomic confounding as these construction workers are generally of the same socioeconomic class.

In this study we have presumably a moderate to heavily exposed population represented by the non-caisson workers and a very heavily exposed workforce represented by the caisson workers. Yu et al. (2005) attribute the excess lung cancer to the very heavy silica exposure of caisson workers. However, OSHA believes that results of this study may not be applicable to the broader population of silica exposed workers as the presence and absorption of radon onto dust particles from pneumatic drilling may result in confounding.

Pan et al. (1999) conducted a nested case-control design within a cohort of industrial workers who were exposed to refractory brick dust in a large iron-steel

complex in China. Esophageal cancer cases (125 cases) and 250 controls were identified from the death registry file of the company and matched on age. Past exposure information was obtained through the development of a job-exposure matrix via the reconstruction of work histories from work files. Dust exposures were categorized into eight broad categories of dust exposure, dust/chemical exposure, or non-exposed. This included relatively "pure" silica dust exposures defined in this study as exposure to refractory grade quartz and possibly cristobalite during the making, laying and repairing of blast furnaces. However, OSHA notes that refractory repair of blast furnaces may also be associated with exposure to metals such as chromium, vanadium, arsenic and other residues on old refractory brick ILO (1983). Smoking, drinking, and eating habits were determined from interviews with next of kin (>95% for cases and controls). In the initial bivariate analysis ORs were unadjusted but were later adjusted for confounding factors in the multivariate analysis using unconditional logistic regression.

After adjusting for confounders, occupational exposure to refractory grade silica dust was the most important risk factor among all the variables investigated (OR = 2.8, 95% CI 1.4-5.7) and there was a clear dose-response by duration of exposure. For those exposed to refractory silica dust for 25 years or greater, the excess risk was statistically significant (OR = 8.7, 95% CI of 1.7-47.1). Drinking of alcohol (OR of 1.8) and cooking with coal (OR of 2.0) were also risk factors for esophageal cancer. High consumption of a fruit diet (OR of 0.5) and a meat diet (OR of 0.6) were protective factors. Thus, the relationship between occupational exposure to silica dust and the risk of esophageal cancer found in an earlier SPMR study (Xu et al., 1966a) was also seen here. The authors suggested that ingestion of silica particles after lung clearance may increase the risk of esophageal cancer among workers exposed to silica.

Cucino and Sonnenberg (2002) analyzed data files from the National Center for Health Statistics of the U.S. to study the causes of death by occupation and industry. The number of deaths from esophageal cancer was retrieved from computerized U.S. vital statistics. Mortality by occupation or industry was expressed as standardized proportional mortality ratio (PMR), adjusted for age, gender, and ethnicity. Between 1991 and 1996, 63,717 subjects died from esophageal squamous cell carcinoma. Mortality was particularly high among non whites and men. Mortality from esophageal squamous cell carcinoma occurred more frequently among subjects exposed to silica dust, such as brick masons and stonemasons (PMR = 137, 95% CI 111-163), concrete and terrazzo finishers (PMR = 164, 95% CI 117-211), roofers (PMR = 142, 95% CI 101-183), and construction laborers (PMR = 112, 95% CI 100-115). It was also high in such industries as unspecified machinery or manufacturing (PMR = 116, CI 105-126) and such occupations as unspecified material handlers, janitors, or cleaners (PMR = 111, CI 101-121). The authors concluded that mortality from esophageal squamous cell carcinoma appeared to be low in occupations associated with less consumption of alcohol and tobacco and was high among occupations potentially associated with exposure to silica dust and chemical solvents or detergents.

In a similar PMR study, Fillmore et al. (1999) analyzed death certificate data on occupation and industry from 24 states in the U.S. between 1984 and 1993 (NOMS

database). The authors' primary purpose was to compare PMRs for men and women exposed to silica. Industry and primary job titles as they appear in death certificates, a crude estimate of exposure, were used to define "possible" and "probable" silica exposure. Approximately 20,000 women and 500,000 men were estimated to be exposed using these criteria. Both men and women had higher than expected PMRs for respiratory diseases, lung cancer, and esophageal cancer. The PMR for esophageal cancer with possible silica exposure in women did not reach statistical significance (PMR =121, 95% CI 92-157, 59 deaths) while the PMR in men was lower, but statistically significant (PMR = 105, 95% CI 102-109, 3,488 deaths). With probable silica exposure (both industry and job title with expected exposure) the PMR for esophageal cancer was more robust for women, but still not statistically significant (PMR = 266, 95% CI 97-579, 6 observed deaths) while the PMR for esophageal cancer for men was essentially similar as those possibly exposed (PMR = 108, 95% CI 102-115, 1,028 observed deaths). This study and the previously reviewed study by Cucino and Sonnenberg (2002) are considered by OSHA to be preliminary due to the crude estimates of exposure. Also, confounding by non-occupational factors (smoking and alcohol use) was not adjusted for in either study.

Calvert et al. (2003) conducted a large case control study using a similar, but somewhat expanded database (NOMS 27 states, 1982 to 1995) as Fillmore et al. (1999). The study evaluated the mortality risk for a number of cancers and respiratory and other diseases previously associated in the literature with crystalline silica exposure. The methodology of this study was reviewed in depth in the previous section on lung cancer. The odds ratios (OR) for esophageal and stomach cancer were 0.94 and 0.98, respectively, with a slight, but not statistically significant, dose response (increasing disease with increasing ranked exposure estimates) for esophageal cancer.

Weiderpass et al. (2003) conducted a census-based study of incident cases for gastrointestinal and esophageal cancer, including 389 esophageal cancer cases of 413,817 predominately industrial and service Finnish female workers identified between 1971 and 1995. The relative rates for new cases of esophageal and other cancers were determined from a job exposure matrix for 183 job titles over four time periods for 25 chemical agents ranked into three exposure categories (zero or reference, low, and medium/high). Liver and esophageal cancer rates were adjusted for alcohol use. The authors found no statistically significant association between any of the agents analyzed and esophageal and liver cancer (389 cases each). The RR for esophageal cancer was slightly elevated at 1.57 (95% CI 0.85-2.91, p = 0.51). The results of this study are similar to those of Calvert et al. (2003) with neither study supporting an association between silica exposure and esophageal cancer.

In summary, three well-conducted nested case-control studies of Chinese workers indicated an increased risk of esophageal cancer mortality attributed by the study's authors to respirable crystalline silica in refractory brick production, boiler repair, and foundry workers (Pan et al., 1999; Wernli et al., 2006) and caisson construction work (Yu et al., 2005). Each study demonstrated a dose-response association with some surrogate measure of exposure, but confounding due to other occupational exposures is possible in

all three work settings (heavy metal exposure in the repair of boilers in steel plants, PAH exposure in foundry workers, radon and radon daughter exposure in Hong Kong caisson workers). Other less well-constructed studies also indicated elevated rates of esophageal cancer mortality with silica exposure (Tsuda et al., 2001; Xu et al., 1996a).

In contrast two large national mortality studies in Finland and the United States, using qualitatively ranked exposure estimates did not show a positive association between silica exposure and esophageal cancer mortality (Calvert et al., 2003; Weiderpass et al., 2003). OSHA preliminarily concludes that the epidemiological literature is not sufficiently robust to attribute increased esophageal cancer mortality to exposure to respirable crystalline silica.

I.C.7.d. Other miscellaneous cancers.

In 2002, NIOSH conducted a thorough literature review of the health effects potentially associated with crystalline silica exposure including a review of lung cancer and other carcinogens. NIOSH noted for workers who may have been exposed to crystalline silica, there have been infrequent reports of statistically significant excesses of deaths for other cancers. A summary of these cancer studies as cited in NIOSH (2002) have been reported in the following organ systems (see NIOSH, 2002 for full bibliographic references):

Table I-16, Miscellaneous Cancers

Cancer Type	Lead Author, Year Published
Salivary gland	Zheng et al. 1996
Liver	Chen et al. 1992 Hua et al. 1992
Bone	Steenland and Beaumont 1986 Forastiere et al. 1989
Pancreatic	Kauppinen et al. 1995
Skin	Partenan et al. 1994 Rafnsson and Gunnarsdottir 1977
Lymphopoetic or hematopoietic	Redmond et al. 1981 Silverstein et al. 1986 Steenland and Brown 1995
Brain	Rafnsson and Gunnarsdottir 1977
Bladder	Bravo et al. 1987

According to NIOSH (2002), an association has not been established between these cancers and exposure to respirable crystalline silica. OSHA believes that these isolated reports of excess cancer mortality at these sites are not sufficient to draw any inferences about the role of silica exposure. The findings have not been consistently seen among epidemiological studies and there is no evidence of an exposure response relationship.

I.D. ***Other Nonmalignant Respiratory Disease.***

In addition to causing silicosis, exposure to crystalline silica has been associated with increased risks of other nonmalignant respiratory diseases (NMRD), primarily chronic obstructive pulmonary disease (COPD). COPD is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases. In patients with COPD, either chronic bronchitis or emphysema may be present or both conditions may be present together. Chronic bronchitis is defined clinically (and typically ascertained by questionnaire reporting of symptoms) as chronic productive cough for three months in each of two successive years in a patient in whom other causes of productive chronic cough have been excluded. Emphysema is defined pathologically (generally examined either at autopsy or radiographically) as the presence of permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis. The relative contribution of chronic bronchitis and emphysema to the COPD process is often difficult to discern (ATS, 2004). The following presents OSHA's discussion of the literature describing the relationships between silica exposure and nonmalignant respiratory disease.

I.D.1. Emphysema.

Longitudinal studies of South African gold miners have been conducted by Hnizdo and coworkers (1991, 1994). In a retrospective cohort study, Hnizdo et al. (1991) conducted a post-mortem examination of the lungs of 1,553 South African gold miners in order to make quantitative estimates of increased risk of emphysema in relation to cumulative respirable dust exposure. For each miner, information was available on the number of shifts worked in each occupation and mine. The average respirable dust level of each occupation had been previously evaluated (Beadle, 1971). Hnizdo et al. (1991) grouped occupations into five categories that were assigned dust factors proportional to these previously evaluated respirable dust measurements. The respirable dust exposure for each miner was calculated by number of dusty shifts, years spent in high-dust occupations, and cumulated dust index calculated as the sum of the product of the number of shifts in an occupation and the occupational dust factor, divided by 1,000. These three dust measurements were then cumulated up to 35, 45, and 55 years of age and to death. Dust was measured by standard thermal precipitator and then treated with heat and acid. The authors noted in a later report that the respirable dust after this treatment contained about 30 percent silica (Hnizdo and Sluis-Cremer, 1993).

In the current study, the authors estimated that, based on a 30-percent silica content, exposures of the cohort ranged from 0.05 to 0.8 mg/m^3 respirable crystalline silica. For miners working in high dust occupations, such as "shaft sinkers" and "developers," the average cumulative respirable dust exposure over an 8-hour shift was about 3.12 mgh/m^3. Hnizdo et al. (1991) found that both panacinar and centriacinar emphysema were positively related to respirable dust exposure. Centriacinar emphysema was also related to the presence of silicosis. Of the exposure variables, cumulative respirable dust exposure to 45 years of age was found to be the strongest predictor of

emphysema. A logistic regression model showed a statistically significant association between emphysema and years of employment in high-dust occupations. The authors estimated that a gold miner with 20 years of exposure in high-dust occupations up to 45 years of age has a 3.5 (95% CI 1.7 to 6.6) times higher odds of having a significant degree of emphysema at autopsy than a miner not in a dusty occupation when the coefficient for the cumulative dust index was used, and a 2.1 (95% CI 1.5 to 2.82) times higher odds when the coefficient for years in high-dust occupations was used. There were only four non-smokers with a significant degree of emphysema found in the cohort, and there was no such association found for nonsmokers. Oxman et al. (1993) has calculated that the cumulative exposure of a miner in this group with 20 years of exposure in high-dust occupations up to 45 years of age would be "roughly" 22 gh/m^3 respirable dust containing about 30 percent free silica. To provide an estimate of how this cumulative exposure might be acquired from an average exposure concentration, expressed in mg/m^3, OSHA performed the following calculations:

22 gh/m^3 = 22,000 mgh/m^3; 20 years x 2000 h/year = 40,000 hours total work; so,
22,000 mgh/m^3 / 40,000 h = an average concentration of 0.55 mg/m^3 respirable dust over the work tenure; so,
0.55 mg/m^3 respirable dust x 0.3 (percent silica) = 0.165 mg/m^3 average exposure to respirable silica.

This figure is less than twice the current OSHA permissible exposure limit (PEL). Thus, these findings suggest that workers exposed to average respirable silica levels in the range of the current OSHA PEL for 20 years may have an increased risk of developing emphysema. However, uncertainties concerning the exposure measurements in this study and the role of other respirable dust components of mine dust in the etiology of emphysema caution against drawing firm conclusions based on these data.

Hnizdo et al. (1994) conducted a retrospective cohort study, this time of only life-long non-smoking South African gold miners. The 242 miners had 23.1 mean years of mining (SD = 11.0, range 1-48) with a mean cumulative respirable dust exposure (mg/m^3-years) of 6.8 (SD 2.4, range 0.5-20.2). Only a minimal, insignificant degree of panacinar emphysema was found at autopsy and the degree was not associated with a statistically significant degree of lung function impairment nor with respirable dust exposure (years of gold mining or cumulative dust index). The degree of emphysema was also not associated with parenchymal silicosis but was associated with the degree of hilar gland nodules ($p < 0.05$), which the authors suggested might act as a surrogate for exposure to silica. The authors concluded that the slight degrees of emphysema found in lifelong non-smokers exposed for many years to silica dust at the level to which these miners were exposed is unlikely to cause a statistically significant impairment of lung function. However, based on their earlier study (Hnizdo et al., 1991), the authors also concluded that the statistically significant association between exposure to silica dust and the degree of emphysema in smokers suggested that tobacco smoking potentiates the effect of silica dust.

Hnizdo et al. (2000) conducted a longitudinal study of 724 South African gold miners. The main purpose of the study was to determine and quantify whether COPD determined at autopsy was related to lung function that had been measured years earlier. The study subjects were selected through a complex process. Subjects were selected from a database containing the results of autopsies of the hearts and lungs of miners and ex-miners on death. Subjects were selected only if they met these criteria: (1) autopsy between 1975 and 1986; (2) 80 percent of mining service in gold mines; (3) less than one year asbestos mining; (4) lungs inflated at autopsy; (5) tissue adequately preserved to enable histological assessment of bronchiolitis and bronchitis; and (6) lung function tests undergone within five years of death.

There were 8,462 subjects who satisfied the first four criteria and 6,035 who satisfied criteria one through five. Of this group of 6,305, 2,651 had COPD and 3,384 did not. A sample of 500 was drawn from the 3,384 who did not have COPD. From this group of 500 and the 2,651 that did have disease, the researchers excluded those without lung function tests within five years of death (criterion six) and cases of cardiac failure, leaving 724 subjects eligible for study. Results showed that emphysema diagnosed at autopsy was the main determinant of airflow impairment. The age- and smoking-adjusted emphysema score, however, decreased with increased categories of silicosis and cumulative respirable dust exposure. This was the opposite of the findings of other studies. The authors suggested that the complex selection process had resulted in an unrepresentative sample of miners and that this was likely to have affected the association between cumulative dust exposure and COPD outcomes, such as emphysema, but not to have affected the association between the autopsy findings and clinical findings for COPD.

The other studies that have examined the relationship of silica exposure to emphysema have been cross-sectional (prevalence) or case-control studies. Becklake et al. (1987) conducted an unmatched case control study of a cohort of white South African gold miners. There were 44 cases of emphysema (ascertained at autopsy) and 42 controls without emphysema. The presence and grade of silicosis was similar in both groups. This study showed that cases were, on average, older, had worked more high-dust exposure shifts, and had smoked more heavily (average daily cigarette use) than had controls throughout their lives. A multiple logistic regression analysis confirmed that the strongest predictors of emphysema at autopsy were number of shifts worked in high dust jobs, smoking, and age. Although the variables of presence or severity of silicosis were related to the total number of shifts worked in high dust jobs, these variables were not responsible for the predictive value of high dust mining in the model.

Using this model, Becklake et al. (1987) determined that a miner who had worked in high dust jobs for 20 years had approximately a 13-times greater chance of having grade 2 or higher emphysema at autopsy than a miner who had never worked in high dust. In a later study designed to examine the potential for selection bias, de Beer et al. (1992) added back a number of cases and controls that had been excluded from the original study due to missing data. The cases that had been originally excluded worked fewer shifts in high-dust jobs. There was no difference in number of shifts in high-dust

jobs between the controls in the initial data and those added back. The exposure of interest (high dust) was associated with poor initial information on cigarette smoking and medical examinations during which features such as cough, sputum, and rhonchi and/or wheezing were recorded. This resulted in the systematic exclusion of cases with none or low numbers of shifts in high-dust jobs. After including these new cases, miners who had worked in high-dust jobs for 20 years still had a statistically significantly greater chance of having emphysema at autopsy, but the odds ratio decreased from 12.70 (95% CI 3-52) to 3.06 (95% CI 1.14-8.23). The authors concluded that their study "highlights the need to maximize the inclusion of eligible subjects and the danger of differential exclusion of subjects in an analytical study."

One study of gold miners failed to demonstrate a relationship between number of years of employment in gold mines, an indicator of silica exposure, and emphysema. In a study of a random sample of 70 black underground gold miners, taken from a larger cross-sectional study (Cowie and Mabena, 1991, reviewed below in the section on bronchitis and above in Section V.B), Cowie et al. (1993) demonstrated, using computerized tomography, that 48 out of the 70 men who had worked underground for an average of 29 years in the gold mining industry had emphysema. There was no relationship between presence and grade of emphysema and number of years of mining. The association of presence and grade of emphysema with silicosis found in this study is discussed above in Section I.B.

Begin et al. (1995) studied the prevalence of emphysema in workers with simple silicosis or without silicosis and exposed to silica. Aspects of this study, especially those concerned with workers with silicosis, have been discussed above in section I.B. Briefly, the study population consisted of 207 workers evaluated for possible pneumoconiosis at Quebec Workman Compensation Board and who had a radiographic reading of pneumoconiosis in the category 0 or 1 of the ILO scale, as well as 5 control subjects. Emphysema was detected, typed, and graded on high-resolution CT scans. Age, work experience and industry, smoking habits, and pulmonary function test results were analyzed for possible associations. The subjects were 58 to 60 years of age and were exposed to mineral dusts for 25 to 27 years; 31 were lifetime nonsmokers and the others were either ex- or current smokers.

In lifetime non-smokers, emphysema was seen in 1 of 20 subjects without pneumoconiosis but in 8 of 11 patients with pneumoconiosis. In smokers without pneumoconiosis, emphysema was present in 55 percent of patients with silica exposure, and only in 29 percent of patients with asbestos exposure but comparable smoking histories ($p = 0.04$). In the workers without pneumoconiosis, age, smoking, and exposure to silica were significant predictors of reduced pulmonary function.

Experimental (animal) studies have suggested that silica dust-induced emphysema could precede silicosis and airway disease in humans. For example, it was shown that in rats exposed to silica dust, emphysema occurred at lower silica doses than did fibrosis in small airways or the appearance of early silicotic nodules (Wright et al., 1988).

I.D.1.a Summary and conclusions for emphysema.

OSHA has considered a series of longitudinal studies of white South African gold miners conducted by Hnizdo and co-workers. Hnizdo et al. (1991) found a significant association between emphysema (both panacinar and centriacinar) and years of employment in a high dust occupation (respirable dust was estimated to contain 30 percent free silica). There was no such association found for non-smokers, as there were only four non-smokers with a significant degree of emphysema found in the cohort. A further study by Hnizdo et al. (1994) looked at only life-long non-smoking South African gold miners. In this population, no significant degree of emphysema or association with years of exposure or cumulative dust exposure was found. However, the degree of emphysema was significantly associated with the degree of hilar gland nodules, which the authors suggested might act as a surrogate for exposure to silica. The authors concluded that the minimal degree of emphysema seen in non-smoking miners exposed to the cumulative dust levels found in this study (mean 6.8 mg/m^3, SD 2.4, range 0.5 to 20.2, percent free silica 30%) was unlikely to cause meaningful impairment of lung function.

From the two studies above, Hnizdo et al. (1994) concluded that the statistically significant association between silica dust and the degree of emphysema in smokers suggests that tobacco smoking potentiates the effect of silica dust. A later study by Hnizdo et al. (2000) of South African gold miners found, in contrast to their previous studies, that emphysema was decreased in relation to dust exposure. The authors suggested that selection bias was responsible for this finding.

The findings of several cross-sectional and case-control studies were more mixed. Becklake et al. (1987), in an unmatched case-control study of white South African gold miners, determined that a miner who had worked in high dust for 20 years had a greater chance of getting emphysema than a miner who had never worked in high dust. A reanalysis of this data, including added back cases and controls (because of possible selection bias in the original study), still found an increase risk for emphysema, although the odds ratio had decreased (de Beer et al., 1992). Begin et al. (1995), in a study of the prevalence of emphysema in silica-exposed workers with and without silicosis, found that silica-exposed smokers without silicosis had a higher prevalence of emphysema than a group of asbestos-exposed workers with similar smoking history. In non-smokers, the prevalence of emphysema was much higher in those with silicosis than in those without silicosis. A study of black underground gold miners found that the presence and grade of emphysema were statistically significantly associated with the presence of silicosis but not with years of mining (Cowie et al., 1993).

Several of the above studies (Becklake et al., 1987; Begin et al., 1995; Hnizdo et al., 1994) found that emphysema can occur in silica-exposed workers who do not have silicosis and suggest that a causal relationship may exist between exposure to silica and emphysema. The findings of experimental (animal) studies that emphysema occurs at lower silica doses than does fibrosis in the airways or the appearance of early silicotic

nodules (e.g., Wright et al., 1988) tend to support the findings in human studies that silica-induced emphysema can occur absent signs of silicosis.

Others have concluded that there is a relationship between emphysema and exposure to crystalline silica. Green and Vallyathan (1996) reviewed several studies of emphysema in workers exposed to silica. The authors stated that these studies show an association between cumulative dust exposure and death from emphysema. IARC (1997) has also briefly reviewed studies on emphysema in its monograph on crystalline silica carcinogenicity and concluded that exposure to crystalline silica causes emphysema. In their 2002 Hazard Review, NIOSH concluded that occupational exposure to respirable crystalline silica is associated with emphysema but that some epidemiologic studies suggested that this effect may be less frequent or absent in non-smokers.

Hnizdo and Vallyathan (2003) also conducted a review of studies addressing COPD due to occupational silica exposure and concluded that chronic exposure to silica dust at levels that do not cause silicosis may cause emphysema.

Based on these findings, OSHA preliminarily concludes that exposure to respirable crystalline silica or silica-containing dust can increase the risk of emphysema, regardless of whether silicosis is present. This appears to be clearly the case for smokers. It is less clear whether nonsmokers exposed to silica would also be at higher risk and if so, at what levels of exposure. It is also possible that smoking potentiates the effect of silica dust in increasing emphysema risk.

I.D.2. Chronic Bronchitis.

There were no longitudinal studies identified by OSHA that have examined the relationship between silica exposure and chronic bronchitis. However, a number of cross-sectional studies have reported finding a qualitative or semi-quantitative relationship between silica exposure and development of chronic bronchitis.

Sluis-Cremer et al. (1967) conducted a community-based study of 827 male residents of a South African gold-mining town. Occupational dust-exposed and non-exposed smokers and non-smokers were compared for prevalence of chronic bronchitis (as ascertained by questionnaire). There was a significant difference ($p < 0.01$) between the prevalence of chronic bronchitis in dust-exposed and non-exposed men among smokers only. The authors suggested that the increased prevalence of bronchitis in miners who smoke was the result of synergism between smoking and dust inhalation rather than just the dust inhalation alone.

Wiles and Faure (1977) conducted a cross-sectional study of 2,209 South African gold miners. The miners were 45 to 54 years of age and had 10 or more years of employment. There were 653 who had been ex-miners for one year or more. The gold mine dust was said to contain about 75-percent crystalline silica. Information was available on mean dust counts (expressed as respirable surface area) for each occupation and the number of shifts each miner had worked in an occupation. The prevalence of

chronic bronchitis (as assessed by questionnaire) increased with increasing mean dust concentration ($p < 0.001$) and with cumulative dust exposure in nonsmokers ($p < 0.05$), ex-smokers ($p < 0.05$), and smokers ($p < 0.001$). Holman et al. (1987) conducted a prevalence study of bronchitis in 1,363 gold miners in Western Australia in 1985. The overall prevalence of bronchitis in the cohort was 14 percent. Years of underground mining experience was used as a surrogate for dust exposure and the prevalence of bronchitis was compared to lifetime non-miners. After controlling for age and smoking the odds ratio for chronic bronchitis was 1.8 (95% CI, 1.0-3.3) for 1 to 9 years of underground mining, 2.5 (95% CI, 1.2-5.2) for 10 to 19 years of mining, and 5.1 (95% CI, 2.4-10.9) for more than 20 years of mining. The latter figure included miners with or without functional obstruction; for those miners having both chronic bronchitis and a restrictive disorder, the odds ratio was 8.2 (95% CI, 1.0-68.9).

Cowie and Mabena (1991) conducted a cross-sectional study of 1,197 black, male South African gold miners. They found that "chronic bronchitic symptom complex" reflected the intensity of dust exposure in the workplace. Chronic sputum production (a symptom of bronchitis) was common and most prevalent in those with the dustiest jobs (qualitative assessment). Chronic bronchitis was present in 62 percent of the workers and in 45 percent of those who had never smoked.

A prevalence study of chronic bronchitis among 239 granite quarry workers in Singapore was conducted by Ng et al. (1992b). Workers exposed to "high" levels of dust (rock drilling and crushing) were compared to those exposed to "low" levels (maintenance and transport) and both groups were compared to an external control group (postal delivery workers). A respiratory questionnaire found a significantly higher prevalence of symptoms of chronic bronchitis in the high exposure as compared to the low and control groups. These results were independent of smoking and age and were similar after excluding those with silicosis. The authors noted that in this prevalence study, the "survivor" effect would have tended to underestimate the effects of dust exposure. According to the authors, because of the strenuous and hazardous nature of quarry work, those who seek employment in the industry were likely to be a highly selected group in terms of physical fitness; this includes possibly a "superior" lung function (relative to the average lung function in the general population) to begin with. The authors further noted that, it is also likely that workers whose lung function were impaired as a result of their work will select themselves out of the work force, leaving the "survivors" in the work force.

A number of other cross-sectional studies failed to find an association between exposure to crystalline silica and chronic bronchitis. Symptoms of chronic bronchitis were not found to be statistically significantly more prevalent in a group of silicotic South African gold miners compared to non-silicotic miners, although the prevalence was slightly higher (Irwig and Rocks, 1978).

Samet et al. (1984) conducted a prevalence study of respiratory abnormalities in a population of 192 current underground uranium miners. Of the 192 current workers, 64 were less than 40 years of age, 116 were 40 to 50 years of age, and 12 were 60 years of

age or more. Duration of underground experience for these age groups is as follows: Less than 40 years of age—33 miners with less than 10 years underground, 31 miners with 10 to 19 years, no miners with 20 years or more; 40 to 59 years of age - 14 miners with less than 10 years, 35 miners with 10 to 19 years, 67 miners with 20 or more years; 60 or more years of age - no miners with less than 10 years, 4 miners with 10 to 19 years, 8 miners with 20 years or more. Since production was from sandstone deposits, silica exposure was anticipated. The authors reviewed available measurements taken by the State Mine Inspector during the years of the study (1969 to 1981). The authors reported that these measurements had shown that the crystalline silica content ranged from approximately 10 to 70 percent and dust concentrations were "on occasion above the Threshold Limit Value [of 0.1 mg/m^3 respirable quartz]." However, data were not available to adequately assess exposures for each individual. The cigarette smoking-standardized prevalence of the symptoms of chronic bronchitis (chronic cough and chronic phlegm) was not found to be associated with the number or years of mining. However, the authors commented that, because this was a prevalence study, they had no way to assess the potential bias that may have occurred if miners had left the workforce because they had respiratory diseases, potentially making the remaining study population unrepresentative.

A study of 281 hard-rock (molybdenum) miners and 108 non-miner residents of Leadville, Colorado also showed no association between the prevalence of chronic bronchitis and work in the mining industry (Kreiss et al., 1989). The mine had been temporarily closed for 5 months when the study began, so miners were not exposed at the time of the study. Personal silica samples had been taken during the period 1977 to 1981. At that time, 27 percent and 49 percent of the samples were greater than 100 $\mu g/m^3$ and 50 $\mu g/m^3$ respirable silica, respectively. In discussing the negative finding, the authors suggested that there may have been a differential out-migration of symptomatic miners and retired miners from the industry and Leadville, resulting in a survivor effect.

No increase in the prevalence of chronic bronchitis was detected in a study of a random sample of 342 workers in India whose job it was to chip and grind agate stones (Rastogi et al., 1991). The grinding process was a mechanical process that produced a lot of dust containing a high percentage of crystalline silica (70.4 percent). The chipping process involved the breakage and removal of cracked stones and produced a respirable dust concentration that was 6-fold less than that produced by the grinding process. There were 240 men and 102 women in the group. There were 158 grinders and 82 chippers among the men, while almost all the women were grinders. The controls (n = 149) were shopkeepers, washermen, rickshaw pullers, and hospital staff such as messengers, sweepers, and ward boys. They were matched with the study group for socioeconomic status, age, and smoking, and were considered never to have been exposed to silica. A large number (48.5 percent) of the agate workers had been exposed for less than 5 years, while a small number (17.5 percent) had been exposed for greater than 11 years. The mean exposure time was 10 ± 2.9 years for men and 8.9 ± 2.3 years for women. In contrast to the finding for chronic bronchitis, the prevalence of pneumoconiosis was significantly higher in agate workers as compared to controls ($p < 0.001$) and showed a significantly increasing trend with duration of exposure ($p < 0.01$). Also, although

neither gender was found as having an increased prevalence of chronic bronchitis, there was a statistically significantly higher prevalence of acute bronchitis in the female agate workers compared to controls ($p < 0.05$). NIOSH (2002) has commented that an association between silica dust exposure and chronic bronchitis may not have been detected because the workers in the control group (e.g. rickshaw pullers and sweepers) may have been occupationally-exposed to silica and the high prevalence of tuberculosis in both agate workers and controls may have masked an association for chronic bronchitis.

I.D.2.a Summary and conclusions for bronchitis.

There were no longitudinal studies available designed to investigate the relationship between silica exposure and bronchitis. However, several cross-sectional studies provide useful information. Studies are about equally divided between those that have reported a relationship between silica exposure and bronchitis and those that have not. Several studies demonstrated a qualitative or semiquantitative relationship between silica exposure and chronic bronchitis. Sluis-Cremer et al. (1967) found a significant difference between the prevalence of chronic bronchitis in dust-exposed and non-dust exposed male residents of a South African gold mining town who smoked, but found no increased prevalence among non-smokers. In contrast, a different study of South African gold miners found that the prevalence of chronic bronchitis increased significantly with increasing dust concentration and cumulative dust exposure in smokers, nonsmokers, and ex-smokers (Wiles and Faure, 1977). Similarly, a study of Western Australia gold miners found that the prevalence of chronic bronchitis, as indicated by odds ratios (controlled for age and smoking), was significantly increased in those that had worked in the mines for 1 to 9 years, 10 to 19 years, and more than 20 years, as compared to lifetime non-miners (Holman et al., 1987). Chronic bronchitis was present in 62 percent of black South African gold miners and 45 percent of those who had never smoked in a study by Cowie and Mabena (1991). The prevalence of what the researchers called “chronic bronchitic symptom complex” reflected the intensity of dust exposure. A higher prevalence of respiratory symptoms, independent of smoking and age, was also found for granite quarry workers in Singapore in a high exposure group as compared to low exposure and control groups, even after excluding those with silicosis from the analysis (Ng et al., 1992b).

Other studies found no relationship between silica exposure and the prevalence of chronic bronchitis. Irwig and Rocks (1978) compared silicotic and non-silicotic South African gold miners and found no significant difference in symptoms of chronic bronchitis. The prevalence of symptoms of chronic bronchitis were also not found to be associated with years of mining, after adjusting for smoking, in a population of current underground uranium miners (Samet et al., 1984). Silica exposure was described in the study to be “on occasion” above the TLV. It was not possible to determine, however, whether miners with respiratory diseases had left the workforce, making the remaining population unrepresentative. Hard-rock (molybdenum) miners, with 27 and 49 percent of personal silica samples greater than 100 and 55 $\mu g/m^3$, respectively, also showed no increase in prevalence of chronic bronchitis in association with work in that industry. However, the authors (Kreiss et al., 1989) thought that differential out-migration of

symptomatic miners and retired miners from the industry and town might explain that finding. Finally, grinders of agate stones (with resulting dust containing 70.4 percent silica) in India also had no increase in the prevalence of chronic bronchitis compared to controls matched by socioeconomic status, age and smoking, although there was a significantly higher prevalence of acute bronchitis in female grinders. A significantly higher prevalence and increasing trend with exposure duration for pneumoconiosis in the agate workers indicated that had an increased prevalence in chronic bronchitis been present, it would have been detected (Rastogi et al., 1991). However, control workers in this study may also have been exposed to silica and the study and control workers both had high tuberculosis prevalence, possibly masking an association of exposure with bronchitis (NIOSH, 2002). Furthermore, exposure durations were very short.

Thus, some prevalence studies supported a finding of increased bronchitis in workers exposed to silica-containing dust, while other studies did not support such a finding. However, OSHA believes that many of the studies that did not find such a relationship were likely to be biased towards the null. For example, some of the molybdenum miners studied by Kreiss et al. (1989), particularly retired and symptomatic miners, may have left the town and the industry before the time that the cross-sectional study was conducted, resulting in a survivor effect that could have interfered with detection of a possible association between silica exposure and bronchitis. This survivor effect may also have been operating in the study of uranium miners in New Mexico (Samet et al., 1984). Some of the controls used in the Indian agate worker study (Rastogi et al., 1991) may also have had occupational silica exposure. Additionally, tuberculosis in both study and controls may have masked an effect (NIOSH, 2002), and the exposure durations were very short. Several of the positive studies demonstrated a qualitative or semiquantitative relationship between silica exposure and chronic bronchitis.

Others have reviewed relevant studies and also concluded that there is a relationship between exposure to crystalline silica and the development of bronchitis. The American Thoracic Society (ATS) (1997) published an official statement on the adverse effects of crystalline silica exposure that included a section that discussed studies on chronic bronchitis (defined by chronic sputum production). According to the ATS review, chronic bronchitis was found to be common among worker groups exposed to dusty environments contaminated with silica. In support of this conclusion, ATS cited studies with what they viewed as positive findings of South African (Hnizdo et al., 1990) and Australian (Holman et al., 1987) gold miners, Indonesian granite workers (Ng et al., 1992b), and Indian agate workers (Rastogi et al., 1991). ATS did not mention studies with negative findings.

A review published by NIOSH in 2002 discussed studies related to silica exposure and development of chronic bronchitis. NIOSH concluded, based on the same studies reviewed by OSHA, that occupational exposure to respirable crystalline silica is associated with bronchitis, but that some epidemiologic studies suggested that this effect may be less frequent or absent in non-smokers.

Hnizdo and Vallyathan (2003) also reviewed studies addressing COPD due to occupational silica exposure and concluded that chronic exposure to silica dust at levels that do not cause silicosis may cause chronic bronchitis. They based this conclusion on studies that they cited as showing that the prevalence of chronic bronchitis increases with intensity of exposure. The cited studies were also reviewed by OSHA (Cowie and Mabena, 1991; Holman et al., 1987; Kreiss et al., 1989; Sluis-Cremer et., 1967; Wiles and Faure, 1977).

OSHA preliminarily concludes that exposure to respirable crystalline silica may cause chronic bronchitis and an exposure-response relationship may exist. Smokers may be at increased risk as compared to non-smokers. Chronic bronchitis may occur in silica-exposed workers who do not have silicosis.

I.D.3. Pulmonary Function Impairment.

In this section, OSHA reviews studies designed to evaluate relationships between exposure to crystalline silica and pulmonary function loss. Since it has been well-established that silicosis progression leads to reduced pulmonary function (see Section V.B.), this analysis focuses on studies of workers who did not exhibit progressive silicosis to evaluate whether exposure to silica has an effect on pulmonary function in the absence of silicosis.

Pulmonary function in workers exposed to silica has been examined in longitudinal studies of Vermont granite workers (Eisen et al., 1983, 1995; Graham et al., 1981, 1994), Swedish granite crushers (Malmberg et al., 1993), South African gold miners (Cowie, 1998; Hnizdo, 1992), and U.S. automotive foundry workers (Hertzberg et al., 2002).

Graham et al. (1981) conducted a longitudinal study of pulmonary function in currently employed and retired Vermont granite stone shed workers. Three groups of current workers were examined. One group was workers whose lung function had been tested in 1974 to 1975 and again in 1979. Another group included workers additionally tested in 1970 to 1971. The third group had worked for more than 20 years and had been tested in 1974 to 1975 and 1979. A group of retired workers whose lung function had been tested at all three times was also examined. In the group of all current workers who had been tested in 1974 and 1979, surprisingly to the authors, an increase was found in mean FVC and FEV_1 between 1974 and 1979. There were also increases in mean FVC in retired workers and those working more than 20 years. Mean FEV_1 in retired workers and those working more than 20 years either slightly increased or minimally decreased. Based on previous studies, pulmonary function losses had been predicted. The authors believed that there were technical deficiencies in the earlier studies, such as improper instructions to the workers during the test and perhaps a leaky spirometer, that accounted for inaccurate findings.

A follow-up study of Vermont granite workers was also conducted by Graham et al. (1994). Starting with the last test date in the previous study (1979), pulmonary

function tests were administered every two years up to 1987. In this study, quarry and office workers (presumably lower or negligible exposure, although no measurements were made) were included in addition to the stone shed workers. Estimated silica exposure for the shed workers was between 50 and 100 µg/m^3 based on 413 personal breathing zone measurements of total respirable dust taken in 1983 and 1984 and previous estimates of the quartz percentage of the dust. The average quartz dust exposure level was 60 µg/m^3, and only 10.5 percent of the samples were over 100 µg/m^3. The analysis of the longitudinal loss of pulmonary function was based on 711 workers who had been tested at least three times out of the five opportunities possible over the study period. According to the authors, loss of FVC and FEV_1 were not correlated with number of years employed in the granite industry, did not differ between shed, quarry, or office workers, and were similar to other blue collar workers not exposed to occupational dust.

Vermont granite workers have also been studied by Eisen et al. (1983, 1995). The main purpose of the study was to assess the chronic effects of long-term, low level exposure to granite dust and shorter-term effects of current exposure on pulmonary function. Another purpose of the study was to assess potential bias due to a healthy worker effect. This longitudinal study followed 618 white male granite workers hired after 1940 (when exposure controls were being implemented to reduce exposures), aged 25 to 65, employed a mean of 14.7 years, and who had annual pulmonary function testing during the period 1970 to 1974 (five years). The authors noted that granite used in the manufacture of monuments in the Vermont granite sheds is composed of approximately 11 percent quartz. The association between respirable granite dust exposure and FEV_1 was assessed in two sub-groups: "survivors" (353) who were in the study for the entire period and had all five annual exams, and "dropouts" (265) who did not participate in the final survey.

There was a significant exposure-response ($p < 0.05$) observed in the "dropout" group but not in the "survivor" group or in the total cohort. The dropout group lost 4 ml/year FEV_1 per mg/m^3-year of cumulative respirable granite dust exposure. The dropout group also had a steeper FEV_1 loss (69 ml/year vs. 44 ml/year) over the study period compared to the survivor group. Similar trends were reported for workers divided by smoking category. In fact, in the never-smoked category, the survivors had no excess pulmonary function loss while the non-smoking dropouts lost lung function just as rapidly as did their smoking counterparts. An examination of the effect of current exposure on annual FEV_1 loss showed that the dropouts had an additional annual loss of 100 ml (in addition to that due to smoking or age) for each additional mg/m^3 of current respirable granite dust exposure. This finding was of "borderline" statistical significance ($p = 0.086$). There was little evidence of such an association in the survivor group. The authors concluded that exposures of approximately half the current U.S. permissible exposure limit for silica-containing dusts are associated with measurable effects on lung function with a four ml/year excess loss among the dropout group. The authors also concluded that their study demonstrated the presence of a healthy worker effect in that no statistically significant decline in pulmonary function was found for "survivors."

Changes in lung function over a 12-year follow-up period (1976 to 1988) in 45 granite crushers and 45 age- and smoking-matched referents in Sweden were studied by Malmberg et al. (1993). Each granite crusher had an individual assessment of total and average dust exposure. In 1988 the granite crushers had worked an average of 22 years and had inhaled an average cumulative amount of 7 mg of respirable silica dust. Average exposure concentration over the follow-up period was 0.16 mg/m^3 of respirable silica dust. At the end of the follow-up period, granite crushers had significantly lower FEV_1/VC ($p < 0.01$) and FEF_{50} ($p < 0.05$) than referents ($p < 0.01$). There were 5 smoking granite crushers who had an $FEV_1 < 80$ percent of that predicted. Over the follow-up period, granite crushers had statistically significantly greater decreases in FEV_1, FEV_1/VC, maximum expiratory flow, and FEF_{50} than the referents. However, the change in lung function was not statistically significantly correlated with the inhaled dose of respirable quartz.

The authors reported that two of the most heavily exposed workers showed evidence of silicosis, but the others had changes in pulmonary function that did not suggest silicosis. The authors believed that these findings were consistent with other findings implying that airway obstructive changes may occur independently and precede silicosis. They also hypothesized that obstructive changes may occur at lower exposures than required for the development of silicosis and that tobacco smoke may aggravate the changes, since four of the cases with a clinically significant reduction in FEV_1 had a "fairly low" exposure to silica and all five were tobacco smokers or ex-smokers. However, the authors cautioned that the study group was too small to confirm the hypothesis.

Another finding of the study was that the decrease in lung function over the 12-year time period of the study seemed to be more pronounced in the group who had not been exposed to silica dust for the entire period. Some in this group had retired for reasons of age and some had left to take other jobs. The authors thought that the changes in lung function in retired workers may have been due to retained silica and that changes may continue for a long time after exposure to silica ends. The authors concluded that "exposure to silica at concentrations of about twice the present TLV [0.1 mg/m^3] was thus associated with airway obstruction and loss of elastic recoil rather than fibrosis and a restrictive function loss as seen in silicosis."

A study providing quantitative estimates of increased risk for clinically significant loss of lung function among South African gold miners was conducted by Hnizdo (1992). The 1,625 miners included in the study had been tested during the period 1968 to 1971 and were retested five years later. There were 232 never smokers and 1,393 current smokers. The average duration of exposure was 24 years and the average concentration of respirable dust for the cohort was 0.30 mg/m^3 (30 percent crystalline silica). (The authors measured respirable dust but presented their results in terms of silica dust and did not refer to or separately address the effect of the mixed dust). The cumulative exposure to dust up to the 1968 to 1971 examination was a significant predictor of most indices of lung function, including FEV_1 and FVC. A multiple linear regression analysis showed that the effects of silica exposure and smoking were additive. For a 50-year old miner,

the loss of lung function attributable to dust exposure was estimated to be 236 ml of FEV_1 (95% CI 135-338) and 217 ml of FVC (95% CI 110-324) for an average cumulative respirable dust exposure of 14.4 ghm^{-3}, and 364 (95% CI 207-501) of FEV_1 and 335 (95% CI 170-500) of FVC for those in the highest dust quartile of 22.2 gh/m^3. The loss in lung function for smoking alone (30 pack-years) for a 50-year old was estimated to be 552 ml (95% CI 461-644). Therefore, the authors estimated that loss in FEV_1 for a 50-year old smoking miner (30 pack-years) with an average cumulative dust exposure of 22.2 gh/m^3 would be 916 ml (95% CI 784-1042) based on the exam results from 1968 to1971. Cumulative dust exposure was not associated with loss of FEV_1 or FVC between the 1968 to 1971 and the 5-year follow-up exams, after adjusting for the initial (1968 to 1971) values. The variables, in order of significance, that were related to this loss were the initial (1968 to 1971) pulmonary function value, cigarette equivalent pack-years, the current smoking state in 1968 to 1971, and the years of follow-up. Nonetheless, when miners were compared to non-miners, the predicted FEV_1 values for 55 year-olds at the five-year follow-up showed that the miners experienced a steeper decline in pulmonary function. The authors concluded that exposure to silica dust among South African gold miners was associated with significant loss of lung function and that even though the contribution of smoking was substantially higher than that of exposure to dust, the combined effect had the potential to cause serious pulmonary disability. They attributed a 10 ml per year loss of FEV_1 to continued dust exposure.

A similar estimated loss of 13 ml per year was reported by Cowie (1998) after adjusting for age among South African gold miners without silicosis. Cowie (1998) studied lung function in 242 gold miners in a follow-up of a case-control study. He compared baseline chest x-rays and pulmonary function studies of an initial cohort to those obtained five years later. Before adjustment for age, annual loss of FEV_1 was 37 ml. in those without silicosis. A similar loss was noted for FVC. Results of an earlier study (Cowie et al., 1993) suggested that a loss of approximately 8 ml of FEV_1 per year would be expected due to continued exposure to the dusty mine environment, which when added to the expected loss of 24 ml/yr due to aging, would be equivalent to approximately 32 ml/yr. The findings of the second Cowie (1998) study approximate this expectation with the finding of an average of 37 ml/yr. loss of FEV_1 in the men who did not have silicosis on entry to the study. This loss is equivalent to a 0.35 percent loss of predicted FEV_1 annually. Cowie (1998) noted that this was "remarkably" similar to the loss of 0.38 percent per year attributed to silica dust exposure that was reported by Malmberg et al. (1993) for Swedish granite workers.

Hertzberg et al. (2002), in a study of U.S. automotive foundry workers, found a consistent association between increased pulmonary function abnormalities and estimated measures of cumulative silica exposure. The cohort consisted of 563 current employees and 473 retirees of a Midwest foundry who had been employed before January 1, 1986. Eight individuals whose race was listed as other than white or African American were excluded from the analysis of PFT results due to lack of accuracy from small numbers, bringing the study cohort to 1,028 individuals. None of these workers had evidence of parenchymal changes from exposure to asbestos or silica. Data collected from plant walk-through surveys, company and union industrial hygiene files, and employee

interviews were used to estimate silica exposures. Estimated levels of exposure by date, department, and job function were merged with personnel records to calculate the cumulative exposure level for each employee. Exposure measurements were found for 26 of the 30 years covered by the study. Cumulative exposure categories were established such that, over a 40-year working lifetime, for 286 workdays per year, the four average daily exposure groups were: 0.006, 0.04, 0.12, and 0.28 mg/m^3. Existing company medical records were reviewed and abstracted for all annual PFT results since the start of testing in 1978 as well as cigarette smoking histories.

Although there was no association among nonsmokers, there was a statistically-significant trend among smokers of an increasing percentage of individuals with a decreased FVC and a statistically significant relationship of decreasing percent-predicted FVC with increasing cumulative exposure ($p = 0.042$ and 0.0013, respectively). Similarly, there was a suggestion of a trend in the relationship between abnormal FEV_1 and a statistically significant pattern of decreasing percent-predicted FEV_1 with increasing cumulative silica exposure in smokers ($p = 0.062$ and 0.011, respectively). There was also a statistically significant pattern of decreasing FEV_1/FVC at the highest cumulative silica exposure ($p = 0.0013$). A multiple linear regression analysis demonstrated that, for each PFT endpoint, there was a statistically significant relationship between decreasing PFT results and increasing cumulative silica exposure.

Hertzberg et al. (2002) also calculated odds ratios for the incidence of an abnormal PFT for 20 and 40 years of exposure at a variety of time-weighted average exposure levels. For example, for 20 years exposure at 0.1 mg/m^3, the risk of developing an abnormal FEV_1 increased by 1.3 and an abnormal FVC by 1.19. At 40 years, the risk of an abnormal FEV_1 was 1.68 and an abnormal FVC was 1.42. At an exposure level of 0.05 mg/m^3, the risk was reduced to 1.14 for FEV_1 and 1.09 for FVC for 20 years and 1.3 for FEV_1 and 1.19 for FVC for 40 years. In addition, longitudinal data analysis of FEV_1 and FVC results over time showed a 1.1 and 1.6 mL/yr statistically significant decline, respectively, for each mg/m^3 of silica exposure ($p = 0.001$ and 0.0108, respectively). Finally, Hertzberg et al. (2002) used multivariate analyses to calculate that there would be a loss of 104.4 mL of FEV_1, 137.7 mL of FVC, and 1.49% of FEV_1/FVC for 40 years exposure at 0.1 mg/m^3. For exposure at 0.05 mg/m^3 , the losses were 52.2 mL, 68.8 mL, and 0.75%, respectively.

There are also a number of prevalence studies that have examined relationships between lung function loss and silica exposure. Theriault et al. (1974a) studied 792 granite shed workers in Vermont in a c ross-sectional study correlating lung function changes with changes in chest x-rays. In this series of studies, the authors attempted to discern whether a quantifiable relationship existed between decrements in pulmonary function and occupational exposure to respirable granite dust, and respirable quartz dust.

In this study (Theriault et al., 1974a), 784 full-shift, breathing-zone samples were obtained from workers in 113 different occupations in 49 granite sheds; total dust concentrations for all and respirable quartz for 483 of the samples were reported in micrograms per cubic meter. One dust-year was defined as exposure to 523 micrograms

per cubic meter for a 40-hour work week over a one-year period. One quartz-year was defined as exposure to 50 micrograms per cubic meter respirable quartz for a 40-hour work week for a one-year period. These concentrations were related to the occupational history of each worker, and total lifetime dust and quartz exposure for each worker was estimated.

The workers filled out questionnaires regarding exposures and smoking history at the time of their annual chest x-ray and pulmonary function test. The study population included exposed workers, non-exposed workers, smokers, and non-smokers. The authors controlled for age and smoking. The decrease in FVC due to dust exposure was estimated at 1.6 ml per dust-year; or 1.4 ml per quartz-year.

The same authors compared lung function with radiographic results for some of these same granite shed workers (Theriault et al., 1974b). On average, changes in pulmonary function testing could be detected after 32.5 dust-years of exposure. With chest x-rays, opacities were not seen until after 46 dust-years of exposure had accumulated. A similar analysis using quartz-years as the exposure metric was not presented. The authors concluded that early detection of silica dust effects was more proficiently accomplished by pulmonary function studies than by radiographs. These results suggest that airflow in silica-exposed workers is significantly reduced by the time disease is detectable on simple chest x-ray.

Irwig and Rocks (1978) studied 1973 white South African gold miners. Silicotic (n = 134) and nonsilicotic miners were compared. Mean FVC was the same. Those with silicosis (defined as pqr nodulation of 1/0 or greater profusion on chest radiograph, rated according to the ILO U/C International Classification of Radiographs of 1971) had significantly lower ($p < 0.01$) mean FEV_1 (5 percent lower) and mean $FEF_{25-75\%}$ (14 percent lower) than those without silicosis. An analysis of the effect of variables such as height, age, smoking history, and exposure to mining dust demonstrated that the difference in lung function was almost entirely accounted for by exposure. The authors concluded that silicosis, *per se*, seemed to have little effect on lung function but that there was a significant exposure-response relationship between exposure to dust in gold mines and both symptoms and lung function tests indicative of COPD.

In a study of airflow obstruction in South African gold miners (Hnizdo et al., 1990), the etiologic fractions for marked obstruction were 48 percent for dust, 82 percent for smoking, and 90 percent for the combined effects of smoking and dust. The preventable fractions were estimated as 8 percent for the elimination of silica dust alone, 42 percent for smoking, and 40 percent for the elimination of either silica dust or smoking. The joint effect of dust and tobacco smoking on lung function impairment was therefore found to be synergistic in this study. The authors concluded that smoking was found to "potentiate" the effect of dust on pulmonary impairment.

Cowie and Mabena (1991), in a cross-sectional study discussed in the section above on chronic bronchitis and in Section V.B., examined pulmonary function in a working population of 1,197 black South African gold miners. Statistically significant

reductions in FEV_1, FEV_1/FVC%, and MMEF were found to be associated with the duration of exposure to the underground environment, after controlling for silicosis and smoking. The reductions found attributable to 25 years of exposure were:

- FEV_1 200ml ($p = 0.006$);
- MMEF 0.55 L/s ($p = 0.0009$); and
- FEV_1/ FVC% 3.6% ($p = 0.0001$).

The average annual loss of FEV_1 attributable to the underground environment was calculated to be 8 ml. In contrast to the finding for duration of exposure, there was no reduction in lung function attributed to high intensity dust exposure. Rather, workers in the highest intensity of exposure had modest increases in some parameters. This finding was attributed to the healthy worker effect, with the strongest (and healthiest) workers tending to work in the hardest (and also the dustiest jobs). Other limitations of the study were the lack of good, specific exposure information and that the design of the study was intended to provide a strong contrast in silicosis as a determinant and, in the process, produced a poor contrast in duration of exposure with most of the men close to the study mean and few at the extremes. In the opinion of the authors, this aspect of the design would have resulted in a significant under-estimation of the influence of exposure.

Several other prevalence studies of pulmonary function have examined granite workers. Ng et al. (1992b), in a study also discussed above in the chronic bronchitis section, compared workers in rock drilling and crushing with workers in maintenance and transport in Singapore granite quarries and also compared those groups with postal delivery workers as an unexposed control group. The highly exposed rock drilling and crushing workers had a mean reduction of five percent in FEV_1, FVC, and percent FEV_1/FVC that was independent of other factors such as age and smoking, as compared to the low exposure or unexposed groups. This reduction was comparable in magnitude (e.g., for FEV_1) to that for a person smoking approximately 20 cigarettes a day for 45 years. The study also found an age- and smoking-adjusted two- to four-fold increase in the prevalence of obstructive impairment related to high dust exposure. Another cross-sectional study of quarry workers was conducted by Montes et al. (2004b). These investigators studied 378 aggregate workers from 27 companies in Spain. The workers were exposed to respirable concentrations of dust between 0.1 and 17.6 mg/m^3. Percentages of crystalline silica in this dust ranged between 0.1 and 75.8. Cumulative exposure was calculated for each worker. In a bivariate analysis, FEV_1 decreased significantly in relation to the cumulative exposure to respirable dust (gh/m^3) and tobacco use. Loss of FVC was only statistically significantly related to dust. In a multivariate analysis, FEV_1 was inversely related to the product of dust exposure times pack-years ($p = 0.005$), but not with each variable independently, controlling for age and the presence of radiological opacities. The authors concluded that there was evidence of dust-tobacco interactions for FEV_1.

Ng et al. (1987) studied respiratory symptoms, radiographic changes and lung function in a cross-sectional survey of 218 male gemstone workers in Hong Kong. Cutters and carvers had average respirable quartz concentrations of 60 and 30 $\mu g/m^3$, respectively. The high-exposure group had average respirable quartz exposures of 100 and 160 $\mu g/m^3$. Silica flour with quartz content often exceeding 90% was commonly used as an abrasive. The FEV_1 and FVC values were not associated with radiographic category after adjustment for years of employment. The authors concluded that there was an independent effect of respirable dust exposure on FVC, but silicosis graded as less than category 2 had no effect on lung function after dust exposure was accounted for.

Loss of lung function in concrete workers exposed to respirable silica was studied in a cross-sectional study by Meijer et al. (2001). There were 144 concrete workers from two factories in The Netherlands included in the study. The workers did not have radiographic evidence of silicosis. Exposure to respirable dust and silica was measured using personal samplers. Results were compared to a control group of 103 non-exposed workers from an office-equipment factory in the same geographic area. In both concrete factories, the average respirable dust and silica concentrations were 0.8 and 0.06 mg/m^3, respectively. The cumulative respirable dust and silica exposures were 7.0 and 0.6 mg/m^3, respectively. Statistically significant losses in lung function ($p = 0.02$) (as indicated by decreased FEV_1/FVC ratio) were observed overall for concrete workers compared to controls. These losses were independent of current smoking status and allergy history. However, there was no exposure-response relationship found between lung function loss and either current or cumulative dust exposure. The authors concluded that their study had demonstrated a small lung function loss in workers exposed to concrete dust at levels below 1 mg/m^3 respirable dust with a respirable crystalline silica content of 10% (TWA, 8 hr).

Lung function loss in the absence of radiological silicosis was also observed in Chinese refractory brick manufacturing workers in an iron-steel plant studied by Wang et al. (1997). FVC, FEV_1, and DL_{CO} decreased significantly or close to significantly in both smokers and non-smokers without the radiological presence of silicosis. The advent and progression of silicosis was also associated with a decrease in FEV_1/FVC in both smokers and nonsmokers. Pulmonary function was decreased more in workers with category I silicosis than in those without silicosis and decreased further as silicosis progressed to categories II and III. The authors concluded that functional abnormalities precede radiographic changes in silicosis.

Two studies examined the prevalence of pulmonary impairment in workers in the hard rock mining industry. Manfreda et al. (1982) studied 95 underground miners from two mining companies in Manitoba, Canada and 382 controls from the general population. Most of the workers were smokers or ex-smokers. Only one miner had a radiographic appearance consistent with silicosis. Although no historical exposure records were available, exposure measurements made shortly after the lung function testing indicated minimal, median, and maximal respirable dust exposure levels of 0.2, 0.5, and 4.8 mg/m^3, respectively, with 6 to 9 percent being silica. Changes in FVC, FEV_1, FEF_{25-75}, all Vmax rates except $Vmax_{25}$, and the slope of phase III were

significantly related to duration of employment ($p < 0.05$ for all except Vpeak which was $0.05 < p < 0.10$). Kreiss et al. (1989), in a study that has been described above in the bronchitis section, also examined the prevalence of pulmonary function impairments in a hard-rock mining community in Colorado. Cumulative dust exposure was associated with decreases in maximal expiratory flow rate when controlled for smoking, age, and height. The results suggested to the authors that exposures resulted in irreversible pulmonary function changes that appeared in smokers (not clear if this includes ex-smokers) as airflow limitation (obstructive impairment) and in never-smokers as restrictive impairment. Multiple regression analysis found an exposure-response relationship for airflow limitations.

Chronic airflow limitation in pottery workers in France was observed in a cross-sectional study by Neukirch et al. (1994). The pottery plant studied made bathroom fixtures. Two categories of workers were established. One was considered directly exposed and included 172 males and 42 females with the following jobs: maintenance and cleaning, assembly line, checking goods, laboratory, casting, in front of the oven, manufacturing, and stoneware, enameling, grinding, and glazing workshops. The other category was considered indirectly exposed and included workers in offices, warehouses, dispatching, and plaster, molding, and palletization workshops. This categorization represented a qualitative base for silica dust levels since quantitative information was not available. The controls worked in a pipeline-making factory with no exposure to silica dust or other lung hazards. Workers with silicosis were not included in the analysis. All the pottery workers, even the indirectly exposed, had significantly lower pulmonary function values (FVC, FEV_1, and most of the flows) than the controls. For directly exposed men there were statistically significant reductions in FEF_{25-75} ($p = .05$) and V_{50} ($p = .04$). For indirectly exposed men there were statistically significant reductions in FVC ($p < .001$) and FEV_1 ($.0001 < p < .004$). For women there were statistically significant reductions for those indirectly exposed in FVC ($p = .01$) and FEV_1 ($p = .03$), and, for those directly exposed, in FVC ($p = .001$), FEV_1 ($p = .0001$), FEF_{25-75} ($p = .004$), V_{50} ($p = .02$), and V_{75} ($p = .001$). The authors thought that the finding that pulmonary function values were significantly lower than in controls, even in those not directly exposed, could be either the result of the presence of vulnerable workers (e.g., asthmatics) choosing to work in areas with less exposure or the possibility that environmental silica dust levels were high enough in the areas of indirect exposure to still cause disease. An additional finding of the study was that there were no significant correlations found between the mean values for pulmonary function and the duration of exposure.

Potato sorters exposed to diatomaceous earth containing crystalline silica were the subject of a cross-sectional study by Jorna et al. (1994). The workers were from five potato sorting plants of the same agricultural cooperative in the Netherlands. The lung function of currently exposed (n = 72) and retired exposed (n = 16) was compared to that of 55 controls (office staff). Workers were exposed to dust mainly generated from clay adhering to the incoming potatoes. In the year of the study, extensive measurements (at least four (8-hour) personal samples per job) found that the geometric mean exposures for total inspirable dust exposure, respirable dust exposure, and respirable silica exposure in

were 9.9 mg/m^3 (range: 2.4 to 21.6), 2.21 mg/m^3 (range: 0.5 to 6.7), and 0.27 mg/m^3 (range: 0.09 to 0.84), respectively. Cumulative exposure to respirable dust and silica was estimated based on measurements for each job and each worker's job history. Chest radiographs found no silicosis in the study population. All spirometric parameters except FVC were significantly lower in the currently exposed workers as compared to controls, and this difference was even greater for retired exposed workers compared to controls. Cumulative dust exposure in workers with $FEV_1 \leq 80$ percent of that predicted (indicative of airflow limitation) was significantly higher than in those without airflow limitation (223.4 vs. 112.5 gh/m^3; $p \leq 0.001$). A multiple linear regression analysis of currently exposed workers, controlling for smoking, height, and age, revealed a significant difference in FEV_1 from controls, and FEV_1 was statistically significantly related to cumulative respirable dust exposure. The decrease in FEV_1 was found to be 10.5 ml/year of employment for currently exposed workers. The authors noted that their results do not allow for discrimination between the effects of exposure to total dust and exposure to respirable silica, or possible exposure to diatomaceous earth, organic dust, growth inhibiting agents, and herbicides.

Begin et al. (1995, also discussed in the emphysema section above and in Section V.B.) studied the possible associations of age, work experience and industry, and smoking habits with pulmonary function test results in a study population consisting of 207 workers exposed to silica and evaluated for pneumoconiosis at the Quebec Workman Compensation Board and who had a radiographic reading of pneumoconiosis in the category 0 or 1 of the ILO scale, as well as 5 control subjects. The subjects were 58 to 60 years of age and were exposed to mineral dusts for 25 to 27 years; 31 were lifetime non-smokers and the others were either ex- or current smokers. Regression analyses documented that age, smoking, and exposure to silica were significant predictors of reduced pulmonary function in workers without pneumoconiosis.

A cross-sectional community study of 26,106 Norwegian men aged 30 to 46 who had normal radiographs (i.e., were not silicotic) and had undergone spirometric testing was conducted by Humerfelt et al. (1998). Thirteen percent of the men had occupational quartz exposure with a mean duration of exposure of seven years. Among this exposed group, significant inverse linear relationships were observed between years of exposure and the level of FEV_1 and the FEV_1/FVC ratio. A decline of 4.3 ml (95% CI -1.1 to -7.5 ml; $p < 0.01$) was associated with each year of quartz exposure. In one analysis, exclusion of those who worked in foundries did not change the relationships between exposure and FEV_1 or FVC levels. However, the effect of duration of exposure on FEV_1 was reduced by 48 percent when those who worked as rock drillers were excluded. Rock drillers had significantly lower FEV_1 levels than foundry workers ($p < 0.05$).

Silica-exposed slate workers in Norway were studied by Suhr et al. (2003). The cross-sectional study compared the occurrence of chronic obstructive pulmonary disease (defined as the presence of coughing for greater than three months during a year, phlegm when coughing, breathlessness walking uphill, or wheezing, and FEV_1 less than 70 percent of FVC), lung function changes, and the prevalence of respiratory symptoms among slate workers exposed to silica for at least one year and a control group with no

present or previous dust exposure. An earlier study by the authors had measured quartz exposure in different parts of the slate industry. The average concentration of total quartz in the slate factory was 0.27 mg/m^3 and the average concentration of respirable quartz was 0.12 mg/m^3. Outside in the quarries the average levels of quartz were 0.58 and 0.13 mg/m^3 for total and respirable quartz, respectively. The authors noted that in the preceding ten years most of the quarry-workers had built "quarry halls" to protect themselves against a cold winter climate. Inside in these quarry halls the average levels were 1.74 mg/m^3 total quartz and 0.46 mg/m^3 respirable quartz. Assessment of historical exposure showed that 32 of the 45 quarry workers with available exposure history had a lifetime inhaled quartz dose of more than 10 g (Bang and Suhr, 1998). The present study did not state in which part of the industry each worker had been employed. Chest x-rays, lung function tests and self-administered questionnaires were used to determine respiratory health. The slate workers had a statistically significantly higher occurrence of most respiratory symptoms (adjusted for smoking) and peak expiratory flow was significantly lower ($p < 0.01$), but there were no other significant alterations in lung function. Significantly more of the slate workers were smokers compared to controls (χ^2, $p = 0.04$). COPD prevalence was not increased among slate workers.

Respiratory disease in a cohort of 2579 coal miners in Spain has been examined in a longitudinal study by Montes et al. (2004a). The workers were followed for 20 years, during which they received an initial and subsequent respiratory exams. According to the authors, some of the miners had to do a "great deal of rock work" to get to the coal and thus would have experienced relatively high silica exposure compared to the direct coal extractors. Average respirable dust levels (and silica fraction) for the rock workers and coal extractors were 2.5 mg/m^3 (17.5 percent silica) and 3.4 mg/m^3 (8 percent silica), respectively. A Cox model multivariate analysis found that accelerated FEV_1 decreases were statistically significantly related to rock work ($p = 0.044$) and tobacco use ($p = 0.001$).

I.D.3.a. Summary and conclusions for pulmonary function impairment.

OSHA has reviewed numerous studies on the relationship of silica exposure to pulmonary function impairment as measured by spirometry. There were several longitudinal studies available. Two groups of researchers conducted longitudinal studies of lung function impairment in Vermont granite workers and reached opposite conclusions. Graham et al. (1981, 1994) examined stone shed workers, who had the highest silica exposure (between 50 and 100 µg/m^3), along with quarry workers (presumed to have lower exposure) and office workers (expected to have negligible exposure). The longitudinal losses of FVC and FEV_1 were not correlated with years employed, did not differ among shed, quarry, and office workers, and were similar, according to the authors, to other blue collar workers not exposed to occupational dust.

Eisen et al. (1983, 1995) found the opposite. They looked at lung function in two groups of granite workers: "survivors" who were in the study the entire period (had all five annual exams) and "dropouts" who did not participate in the final exam. There was a significant exposure-response for silica exposure and FEV_1 decline in the dropouts but

not the survivors. The dropout group had a steeper FEV_1 loss, and this was true for each smoking category. The authors concluded that exposures of 50 ug/m^3 produced a measurable effect in the dropouts. Eisen et al. (1995) felt that the "healthy worker effect" was apparent in this study and that studies that only looked at "survivors" would be less likely to see any effect of silica on pulmonary function.

A 12-year follow-up of age and smoking-matched granite crushers and referents in Sweden found that over the follow-up period, the granite crushers had significantly greater decreases in FEV_1, FEV_1/VC, maximum expiratory flow, and FEF_{50} than the referents (Malmberg et al., 1993). A longitudinal study of South African gold miners conducted by Hnizdo (1992) found that cumulative dust exposure was a significant predictor of most indices of decreases in lung function, including FEV_1 and FVC. A multiple linear regression analysis showed that the effects of silica exposure and smoking were additive. Finally, another study of South African gold miners (Cowie, 1998) also found a loss of FEV_1 in those without silicosis. Finally, a study of U.S. automotive foundry workers (Hertzberg et al., 2002) found a consistent association with increased pulmonary function abnormalities and estimated measures of cumulative silica exposure within 0.1 mg/m^3. The Hnizdo (1992), Cowie et al. (1993), and Cowie (1998) studies of South African gold miners and the Malmberg et al. (1993) study of Swedish granite workers found very similar reductions in FEV_1 attributable to silica dust exposure.

A number of prevalence studies have described relationships between lung function loss and silica exposure or exposure measurement surrogates (e.g., duration of exposure). These findings support those of the longitudinal studies. Such results have been found in studies of white South African gold miners (Hnizdo et al., 1990; Irwig and Rocks, 1978), black South African gold miners (Cowie and Mabena, 1991), Quebec silica-exposed workers (Begin, et al, 1995), Singapore rock drilling and crushing workers (Ng et al., 1992b), Vermont granite shed workers (Theriault et al., 1974a, 1974b), aggregate quarry workers and coal miners in Spain (Montes et al., 2004a, 2004b), concrete workers in The Netherlands (Meijer et al., 2001), Chinese refractory brick manufacturing workers in an iron-steel plant (Wang et al., 1997), Chinese gemstone workers (Ng et al., 1987), hard-rock miners in Manitoba, Canada (Manfreda et al., 1982) and Colorado (Kreiss et al., 1989), pottery workers in France (Neukirch et al., 1994), potato sorters exposed to diatomaceous earth containing crystalline silica in The Netherlands (Jorna et al., 1994), slate workers in Norway (Suhr et al., 2003), and men in a Norwegian community (Humerfelt et al., 1998). Two of these prevalence studies also addressed the role of smoking in lung function impairment associated with silica exposure. In contrast to the longitudinal study of South African gold miners discussed above (Hnizdo, 1992), another study of South African gold miners (Hnizdo et al., 1990) found that the joint effect of dust and tobacco smoking on lung function impairment was synergistic, rather than additive. Also, Montes et al. (2004b) found that the criteria for dust-tobacco interactions were satisfied for FEV_1 decline in a study of Spanish aggregate quarry workers.

One of the longitudinal studies and many of the prevalence studies discussed above directly addressed the question of whether silica-exposed workers can develop

pulmonary function impairment in the absence of silicosis. These studies found that pulmonary function impairment: (1) can occur in silica-exposed workers in the absence of silicosis, (2) was still evident when silicosis was controlled for in the analysis, and (3) was related to silica exposure rather than to the presence or severity of silicosis. Other studies did not directly address this question but did not attribute lung function loss to silicosis.

Many researchers have concluded that a relationship exists between exposure to silica and lung function impairment. IARC (1997) has briefly reviewed studies on airways disease (i.e., chronic airflow limitation and obstructive impairment of lung function) in its monograph on crystalline silica carcinogenicity and concluded that exposure to crystalline silica causes these effects. In its official statement on the adverse effects of crystalline silica exposure, the American Thoracic Society (ATS) (1997) included a section on airflow obstruction. The ATS noted that, in most of the studies reviewed, airflow limitation was associated with chronic bronchitis. The review of Hnizdo and Vallyathan (2003) also addressed COPD due to occupational silica exposure. They examined the epidemiological evidence for an exposure-response relationship for airflow obstruction in studies where silicosis was present or absent. Hnizdo and Vallyathan (2003) concluded that chronic exposure to silica dust at levels that do not cause silicosis may cause airflow obstruction.

Based on the evidence discussed above from a number of longitudinal studies and numerous cross-sectional studies, OSHA preliminarily concludes that there is an exposure-response relationship between exposure to respirable crystalline silica and the development of impaired lung function. The effect of tobacco smoking on this relationship may be additive or synergistic. Also, pulmonary function impairment can occur in silica-exposed workers who do not show signs of silicosis.

I.D.4. Nonmalignant Respiratory Disease Mortality.

In this section, OSHA reviews two studies of gold miners, a study of diatomaceous earth workers, and a death certificate case-control analysis that provide information on the relationships between exposure to crystalline silica and NMRD mortality other than that related to silicosis. A number of researchers have examined nonmalignant respiratory disease (NMRD) mortality in workers exposed to silica. In many studies, silicosis or pneumoconiosis mortality was included in the definition of NMRD and made up a substantial portion of the excess mortality observed. These studies have not been included here; instead, the question being addressed in this review relates to the role of crystalline silica in producing excess mortality from NMRD other than silicosis.

A cohort of 3,971 currently-working white South African gold miners was studied by Wyndham et al. (1986). The cohort was followed for nine years. Two types of analysis were conducted. The first was an analysis of SMRs in the miners compared to the total white male population of the Republic of South Africa. This analysis found that there was a statistically significant excess mortality for chronic respiratory diseases

(SMR 165.2, 108.2-242.7). This category grouped together bronchitis, emphysema, asthma, pneumoconiosis due to silica and silicates, other pneumoconiosis and other related diseases, and pulmonary heart disease, because in comparing the cause of death certified on the death certificate with the best available information from medical examination records and other data from the Medical Bureau for Occupational Diseases, the authors found evidence demonstrating that none of the miners certified on the death certificate as dying from pneumoconiosis actually died from that disease. They found, instead, that when pneumoconiosis was found in the miners, it was always an incidental finding in those dying from some other cause, the most common of which was chronic obstructive lung disease. Similarly, chronic obstructive lung disease was always the primary cause of pulmonary heart disease. The second analysis was a case-referent study in which each case of chronic respiratory disease was matched with four referents selected at random from miners born the same year as the case and who survived the case. The analysis found that the major risk factor for chronic respiratory disease was smoking. However, cumulative dust exposure had a statistically significant additional effect on the risk of disease, with the relative risk estimated as 2.48 per ten units of 1,000 particle-years of exposure ($p = 0.03$).

Mortality from "chronic obstructive lung disease" ("COLD") (bronchitis, emphysema, or chronic airways obstruction) in white South African gold miners was studied by Hnizdo (1990). In the cohort were 2,209 miners who were aged 45 to 54 during the time period between 1968 and 1971, who started mining between 1936 and 1943, and who had received an annual medical exam between 1968 and 1971. They were followed up through December 30, 1986. Retired miners were included if they had sought a medical examination for compensation. A nested age-matched case-referent study design was used. The study examined whether silica dust exposure was related to COLD mortality and if so, sought to elucidate the shape of the exposure-response curve and evaluate whether the combined effects of smoking and silica exposure were additive or synergistic.

The odds ratios (ORs) showed a statistically significant increasing trend for dust particle years ($p = 0.003$) and for cigarette years of smoking ($p < 0.0001$). The analysis estimated that those with exposures of 10,000, 17,500, or 20,000 particle-years of exposure had a 2.5, 5.06, or 6.4 times higher risk of dying from COLD, respectively, than those with the lowest dust exposure (less than 5,000 particle-years). Analysis of various combinations of dust exposure and smoking variables found that the multiplicative model fit the data significantly better than the additive model, suggesting a synergistic effect. Attributable risks estimated for dust exposure, smoking, and dust and smoking combined were 64, 93, and 98 percent, respectively. Therefore, it follows that the relative contribution of dust, smoking, or the combination of the two in causing COLD mortality is 5 (98-93), 34 (98-64), and 59 (98-34-5) percent, respectively. The authors concluded that dust exposure alone did not result in COLD mortality but that either smoking alone or the combination of dust exposure and smoking were the main risk factors for COLD mortality. The authors also concluded that smoking was more dangerous for miners exposed to silica dust than for others because of this synergistic effect.

Park et al. (2002) studied a cohort of 2,342 workers in a diatomaceous earth plant (mining and processing). The cohort comprised all employees with at least one year of employment and active anytime during the period 1942 to 1994. The cohort was exposed to a mean concentration of respirable crystalline silica (mostly cristobalite) averaged over the years of employment of 0.29 mg/m^3. Cumulative exposures to respirable crystalline silica were estimated for each worker. The mean final cumulative exposure to respirable crystalline silica dust was 2.12 mg/m^3-years (62.52 mg/m^3-years maximum).

There were 67 deaths in the cohort with an underlying cause of death of lung diseases other than cancer (LDOC). Ten of those deaths were from silicosis. Two of the deaths were from asbestosis. Observation times with cumulative exposures over 10 mg/m^3-years (16 percent of the deaths from LDOC) were excluded from the Poisson regression analysis because a decline in exposure-response with increasing exposure had resulted, in the opinion of the authors, from "some form of survivor selection." The authors found a statistically significant exposure-response trend for LDOC mortality, from which they estimated lifetime risks. This analysis is further discussed in Section II (Preliminary Quantitative Risk Assessment).

Calvert et al. (2003) conducted a case-control analysis from death certificate data of mortality from various diseases and occupational silica exposure. Death certificates were obtained from 27 US states. A qualitative silica exposure category (super-high, high, medium, low/no) was determined for each individual based on industry/occupation found on their death certificate. A statistically significantly increased risk for COPD (ICD 490-492) mortality was observed for those in the super-high, high, and medium exposure categories combined (OR = 1.12 , 95% CI 1.10 to1.14), as well as for those in the high (OR = 1.29, 95% CI 1.25 to 1.33) and super-high (OR = 1.47, 95% CI 1.30 to 1.66) categories. There was also a statistically significant trend of increased risk for COPD mortality with increasing silica exposures ($p < 0.001$). In addition, when silicotics were compared to those without silicosis, the odds ratio for COPD mortality showed a statistically significantly increased risk (4.38, 95% CI 3.39 to 5.67). The authors concluded that there was an association between crystalline silica exposure and COPD mortality, based on the consistently increased odds ratios among those in the medium and higher crystalline silica exposure categories and the significant trend across those categories.

I.D.4.a. Summary and conclusions for NMRD mortality.

In this section, OSHA reviewed studies on NMRD mortality that focused on causes of death other than from silicosis. Two studies of gold miners, a study of diatomaceous earth workers, and a case-control analysis of death certificate data provide useful information.

Wyndham et al. (1986) found a significant excess mortality for chronic respiratory diseases in a cohort of white South African gold miners. Although these data did include silicosis mortality, the authors found evidence demonstrating that none of the miners certified on the death certificate as dying from silicosis actually died from that

disease. Instead, pneumoconiosis was always an incidental finding in those dying from some other cause, the most common of which was chronic obstructive lung disease. A case-referent analysis found that while the major risk factor for chronic respiratory disease was smoking, there was a statistically significant additional effect of cumulative dust exposure, with the relative risk estimated as 2.48 per ten units of 1,000 particle years of exposure.

A synergistic effect of smoking and cumulative dust exposure on mortality from "chronic obstructive lung disease" (COLD) was found in another study of white South African gold miners (Hnizdo, 1990). Analysis of various combinations of dust and smoking found a trend in OR that indicated this synergism. There was a statistically significant increasing trend for dust particle years and for cigarette years of smoking. For cumulative dust exposure, an exposure-response relationship was found, with the analysis estimating that those with exposures of 10,000, 17,500, or 20,000 particle-years exposure had a 2.5, 5.06, or 6.4 times higher mortality risk for COLD, respectively, than those with the lowest dust exposure of less than 5000 particle-years. The authors concluded that dust alone would not lead to increased COLD mortality but that dust and smoking act synergistically to cause COLD and were thus the main risk factor for death from COLD in their study.

In a study of diatomaceous earth workers, Park et al. (2002) described positive exposure-response relationships between exposure to crystalline silica and excess risk for mortality from lung disease other than cancer. In a case-control analysis of death certificate data drawn from 27 U.S. states, Calvert et al. (2003) found increased mortality odds ratios among those in the medium and higher crystalline silica exposure categories, a significant trend of increased risk for COPD mortality with increasing silica exposures, and a significantly increased odds ratio for COPD mortality in silicotics as compared to those without silicosis.

Green and Vallyathan (1996) also reviewed several studies of NMRD mortality in workers exposed to silica. The authors stated that these studies showed an association between cumulative dust exposure and death from the chronic respiratory diseases.

Based on the evidence presented in the studies above, OSHA preliminarily concludes that respirable crystalline silica increases the risk for mortality from nonmalignant respiratory disease (not including silicosis) in an exposure-related manner. However, it appears that the risk is strongly influenced by smoking, and the effects of smoking and silica exposure may be synergistic.

I.D.5. Preliminary Conclusions for Other Nonmalignant Respiratory Disease.

Based on the findings of studies of the relationship of silica exposure to morbidity from emphysema, bronchitis, and lung function impairment (as measured by spirometry), and mortality from NMRD (other than silicosis), OSHA preliminarily concludes that an exposure-response relationship exists for exposure to respirable crystalline silica and the risk of these conditions and that these conditions can occur in the absence of silicosis.

However, except for NMRD mortality, data are insufficient for quantitative risk assessment. For emphysema, silica exposure may not increase risk in non-smokers. For all conditions, the effect of smoking may be additive (except for NMRD mortality) or synergistic.

I.E. ***Renal and Autoimmune Effects.***

In recent years, evidence has accumulated that suggests an association between exposure to crystalline silica and an increased risk of renal disease. Over the past 10 years, epidemiologic studies have been conducted that provide evidence of exposure-response trends to support this association. There is also suggestive evidence that silica can increase the risk of rheumatoid arthritis and other autoimmune diseases (Steenland, 2005b). In fact, an autoimmune mechanism has been postulated for some silica-associated renal disease (Calvert et al., 1997). This section will discuss the evidence supporting an association of silica exposure with renal and autoimmune diseases. Several review articles (IARC, 1997; Lancet, 1978; NIOSH, 2002; Parks et al, 1999; SSDC, 1988; Steenland, 2005b) that cite evidence for effects on both systems were used by OSHA to identify key studies. These review articles and their conclusions are summarized briefly, after which OSHA presents its evaluation of the primary literature.

An editorial in the Lancet (1978) noted a number of case reports that suggested a role for silica exposure in the development of renal effects, including proteinuria, acute renal failure, and the appearance of excessive amounts of silicon in the kidney. The editorial concluded that inhaled silica dust should be considered as a rare cause of renal disease. The editorial also stated that it was apparent that the inhalation of crystalline silica can cause renal disease with no evidence of a wide-spread connective-tissue disorder. With regard to autoimmune disease, the editorial cited a report stating that 10 percent of workers with acute silicosis also showed evidence of connective tissue disorders such as scleroderma, systemic lupus erythematosus, and rheumatoid arthritis. In addition, the editorial noted that other immunological changes have been described in persons with silicosis.

Ten years later, the subject was reviewed again by the Silicosis and Silicate Disease Committee (SSDC), a committee of pathologists appointed by NIOSH to assess the understanding of the diseases resulting from the inhalation of a variety of nonfibrous crystalline mineral particulates (SSDC, 1988). The SSDC cited additional reports of glomerulonephritis and tubular lesions found in some patients with accelerated silicosis as well as those with no pulmonary disease but with a history of silica exposure. However, they pointed out that glomerular lesions and other renal changes found in Vermont granite workers with silicosis were similar to those found in control subjects with a variety of other diseases. Thus, they thought that the changes were nonspecific and their association with silicosis uncertain. Of the finding of excessive silica in the kidneys of the workers discussed in the Lancet editorial above, the SSDC noted that the levels of crystalline silica in the kidneys of workers with silicosis or normal individuals were not known. Finally, the SSDC believed that the limited number of animal experiments conducted up to that point failed to provide an experimental basis for silica-

related renal disease. However, they also commented that it was difficult to ignore the numerous case reports of acute glomerulonephritis occurring in persons with accelerated silicosis.

The SSDC also addressed the role of crystalline silica in producing autoimmune disorders. While commenting that the unique association between exposure to silica and autoimmune diseases had long been recognized, they believed that the significance of the observation remains a matter of debate. They reported on several studies and case reports describing scleroderma among silica-exposed workers, including stone masons, coal and gold miners (absent an increased prevalence of radiological silicosis and with intensity of silica exposure seeming to be more important than duration), potters, and foundry workers. However, the personal experience of one of the committee members failed to support these findings. Finally, the SSDC discussed a study that demonstrated that the rate of progression of silicosis and the likelihood of relatively large nodular pulmonary lesions in patients with rheumatoid arthritis was greater than in control subjects. However, silica dust exposure did not appear to predispose to rheumatoid arthritis.

The "extrapulmonary" effects of silica were addressed again by IARC in 1997. Its review focused primarily on those studies published since the 1988 SSDC review. With regard to renal effects, IARC (1997) discussed several studies. Findings of these studies include the following: an increased prevalence of abnormal renal function among silica-exposed individuals, both with and without silicosis; a positive relationship between length of exposure to silica and severity of renal dysfunction; a contradictory study in which silicosis was associated with renal alterations but there was no relationship between loss of renal function and length of exposure or severity of silicosis; persistence of renal effects after cessation of silica exposure; a relationship between rapidly progressive glomerulonephritis and silica exposure; an elevated odds ratio for end-stage renal disease among silica-exposed men; and a finding of crystalline silica within the renal tubules in a case study of silica-related glomerulonephritis.

Several studies of autoimmune effects of silica were also cited by IARC (1997), including reports of systemic sclerosis-like (scleroderma-like) disorders following exposure to silica, evidence of an increased incidence of rheumatoid arthritis among Finnish granite workers, and granulomas mimicking cutaneous sarcoidosis or granulomatous cheilitis believed to be associated with cutaneous silica exposure.

Parks et al. (1999) have reviewed the human evidence for the association of silica exposure with autoimmune diseases as well as studies describing possible mechanisms that explain the role of crystalline silica in the development of these diseases. They concluded that several studies of different designs conducted in a variety of exposed occupational groups suggest an association between exposure to silica and increased risk of systemic autoimmune disease. Based on an assessment of clinic-based case-series, occupational cohort studies, registry linkage studies, and case-control studies, many published after 1995, Parks et al. (1999) reported that the most common diseases associated with silica exposure included scleroderma, rheumatoid arthritis, SLE, and some of the small vessel vasculitidies with renal involvement.

The question of whether silica exposure is a risk factor for renal disease was also addressed in a review by Stratta et al. (2001). This review covered individual case reports, case series, and occupational population-based epidemiological evidence. Studies were divided into those looking for evidence of renal disease in workers exposed to silica and those looking at the occupational exposures of persons with renal disease. Based on their review of these studies, the authors drew several conclusions: 1) "The evidence for the nephrotoxicity of silica continues to mount"; 2) Nephrotoxicity induced by silica may develop in the absence of silicosis; and 3) "Silica toxicity may cooperate in progression of renal damage due to any cause."

An updated review of studies of silica-related renal and autoimmune disorders was provided by NIOSH in their 2002 Hazard Review of silica. NIOSH (2002) cited over 30 case reports published between 1914 and 1998 that describe various autoimmune disorders in workers or patients who were occupationally exposed to crystalline silica. The most frequently reported autoimmune diseases were scleroderma, systemic lupus erythematosus (SLE), rheumatoid arthritis, autoimmune hemolytic anemia, and dermatomyositis or dermatopolymyositis.

NIOSH (2002) also cited over 20 additional case reports describing health effects that may be related to the immunologic abnormalities in patients with silicosis. These health effects included chronic renal disease, ataxic sensory neuropathy, chronic thyroiditis, hyperthyroidism (Grave's disease), monoclonal gammopathy, and polyarteritis nodosa. NIOSH (2002) also provided details on 13 post-1985 epidemiologic studies of silica-exposed workers that reported statistically significant excess numbers of cases or deaths from known autoimmune diseases or immunological disorders (scleroderma, rheumatoid arthritis, and sarcoidosis), chronic renal disease, and subclinical renal changes. Furthermore, NIOSH (2002) reported that epidemiologic studies had found statistically significant associations between occupational exposure to silica dust and several specific renal diseases or effects, including end-stage renal disease morbidity (including that caused by glomerular nephritis), chronic renal disease mortality, and Wegener's granulomatosis (systemic vasculitis often accompanied by glomerulonephritis). NIOSH (2002) also cited several studies that addressed the pathogenesis of glomerulonephritis and other renal effects in silica-exposed workers as well as possible cellular mechanisms of silica-related autoimmume diseases.

Most recently, Steenland (2005b) cited five occupational cohort studies and one proportional mortality study that have consistently shown two- to three-fold excesses of renal disease among silica-exposed populations (although he noted that this was based on relatively small numbers), two population-based case-control studies of renal disease that had shown odds ratios of two or more for silica exposure, and his own analysis of renal disease mortality in three combined occupational cohorts that showed a strong exposure-response trend for both underlying and multiple cause mortality. Steenland (2005b) determined that the evidence overall was still too sparse to be summarized as conclusive, but that it seemed very probable that silica causes kidney disease. In comparing the risks of various diseases from silica exposure, Steenland (2005b) expressed the opinion that,

surprisingly, kidney disease appears to be perhaps the most common serious health effect of silica exposure after small opacities found on lung X-rays, although the kidney data is based on fewer studies than for X-ray opacities. However, he also believed that silicosis would represent the largest risk if X-ray opacities progress frequently to symptomatic silicosis. Steenland (2005b) also cited supportive studies that have pointed to plausible mechanisms by which crystalline silica may induce renal disease, which include a direct toxic effect of silica on the kidneys, deposition in the kidney of immune complexes (IgA) following silica-related pulmonary inflammation, or an autoimmune mechanism. Citing Parks et al. (1999), Steenland (2005b) also noted that there is increasing evidence that silica can cause other autoimmune diseases as well, particularly rheumatoid arthritis, SLE, and scleroderma. He suggested that it is possible that the strong immune response in the lung can trigger an autoimmune reaction.

In the discussion below, OSHA presents its evaluation of studies concerning the relationship of silica exposure to renal disease and the autoimmune diseases scleroderma, rheumatoid arthritis, systemic lupus erythematosus, and small vessel vasculitides.

I.E.1. Renal Disease.

A number of longitudinal and mortality studies have observed relationships between exposure to silica and an increased risk of renal disease. A proportionate mortality study of renal disease in granite cutters was conducted by Steenland et al. (1992). Death certificates of the granite cutters were examined for any mention of renal disease, whether it was as the underlying cause of death, contributory cause, or other significant condition. The authors developed a data base of U.S. mortality rates (age, sex, race, and calendar-time specific) and proportions, using multiple cause-of-death data for the years 1960 to 1989. These rates and proportions were then used to calculate the expected occurrence of renal disease in the cohort of granite cutters. The authors noted that multiple cause data reflect the prevalence of specific diseases at death. The diseases that are the best candidates for multiple cause analysis have a long course and are often not the cause of death, but are serious enough to be noted by the physician on the death certificate. Proportionate mortality ratios (PMR, the ratio of observed to expected) for underlying cause and for multiple causes were calculated for acute and chronic renal disease categories. For acute renal disease, neither PMR's for multiple cause of death nor underlying cause of death was statistically significantly elevated. For chronic renal disease, the PMR was statistically significantly elevated using multiple cause (PMR 2.18, 26 deaths, 95% CI 1.43-3.20) but not underlying cause data. The authors concluded that this finding confirmed an association between exposure to crystalline silica and renal disease as seen in case reports and a case-control study (Steenland et al., 1990).

A cohort of 3,971 currently-working white South African gold miners was studied by Wyndham et al. (1986). The authors stated that these miners were exposed to "low levels of dust containing a moderate amount of silica." The cohort was followed for nine years. An analysis of SMRs in the miners compared to the total white male population of the Republic of South Africa (based on causes of death given on the death certificates)

found that there was statistically significant excess mortality for acute and chronic nephritis (ICD 580-584) (SMR 381.0, 95% CI 164.4-750.9, 8 observed, 2.1 expected).

The incidence of end-stage renal disease (ESRD) was examined in a retrospective cohort study of a subcohort of 2,412 men drawn from a cohort of South Dakota gold miners (Calvert et al., 1997). The members of the Calvert et al. (1997) cohort with ESRD were identified through the ESRD Program Management and Medical Information System (a database maintained by the Health Care Financing Administration). The incidence rate in the miners was compared to the expected incidence of ESRD in the U.S. to obtain the standardized incidence ratio (SIR). The mean duration of employment was eight years, the average year of first employment was 1946, and 94 percent had twenty years since first employment. The mean, median, and range of cumulative silica exposure were 0.18, 0.39, and 0.008 to 4.32 mg/m^3-years, respectively. The median and mean intensity of exposure were 0.04 and 0.05 mg/m^3, respectively. The ESRD SIR for the entire cohort was not statistically significantly elevated. There were a total of eleven members of the cohort with ESRD. However, there was a statistically significantly increased incidence of the type of ESRD known as non-systemic ESRD, which is caused by glomerulonephritis and interstitial nephritis (SIR 4.22, 95% CI 1.54-9.18, 6 observed). Most of this increase appeared to be due to ESRD caused by glomerulonephritis (SIR 4.28, 95% CI 1.38-10.00). The SIRs for non-systemic ESRD with duration of underground employment and cumulative dust exposure were also determined. Miners with the highest duration of employment (10 or more years) had a statistically significantly increased SIR (7.70, 95% CI 1.59-22.48). The SIR for miners exposed to cumulative exposures of from 0.22 to less than 0.55 mg/m^3-year was statistically significantly increased at 11.05 (95% CI 3.01-28.30). The SIR for those miners exposed to 0.55 mg/m^3-year or more, however, was not statistically significantly increased.

The authors suggested that this finding may be explained by a limitation in the study. Since the database was only complete after 1977, cohort members who died before 1977 were excluded from the analysis, thus excluding those with a higher mean duration of employment and higher mean cumulative dust exposure. This reduced the power of the study to detect elevated risks in those with high cumulative dust exposures. To address this issue, the tertiles of exposure were redefined so that each had a similar number of expected cases of non-systemic ESRD. The tertile with the highest cumulative silica dust exposure (0.30 mg/m^3-years or more, with a median intensity of exposure of 0.04 mg/m^3) had the highest risk of non-systemic ESRD (SIR 8.11, 95% CI 2.20-20.77, 4 cases). An additional analysis examined a subgroup of workers first employed underground after 1950 when silica exposures had been reduced to a median of 0.02 mg/m^3. The risk for ESRD remained statistically significantly elevated (SIR 5.00, 95% CI 1.03-14.61) in this subgroup. The authors concluded that their study findings provide evidence that occupational exposure to silica is associated with an increased risk for ESRD, especially that caused by glomerulonephritis. Because the median level of exposure of the cohort was below the current OSHA PEL (0.09 mg/m^3 for this workplace), the authors also concluded that the PEL might not be adequately protective. However, the authors felt that they could not make strong conclusions about this due to the small numbers and wide confidence intervals in their study.

A similar study of ESRD was conducted on a cohort of 2,820 Italian ceramic workers (Rapiti et al., 1999). All workers were enrolled in a health surveillance program during the period 1974 to 1991 and were alive as of 1994. Data on employment history, smoking status, and silicosis status were available. As in the Calvert et al. study, each worker was matched to see whether they were in the regional ESRD registry as of 1994. Data in the regional registry was also used to compute expected rates of ESRD for the region. The total cohort of ceramic workers had a statistically significantly increased prevalence of ESRD with an O/E ratio of 3.21 (6 observed, 95% CI 1.17-6.98). Also, the prevalence of ESRD was statistically significantly increased for those with latency since first exposure of 10 to 19 years (4 observed, O/E 4.65, 95% CI 1.26-11.9), but not for those with latencies of less than 10 years, 20 to 29 years, or 30 years or greater. The six observed cases had cumulative respirable silica exposures ranging from 0.2 to 3.8 mg/m^3 -years. The authors concluded that their data confirmed the findings of Calvert et al. (1997) that exposure to silica is associated with an increased risk for end stage renal disease.

A study of North American industrial sand workers examined mortality from nephritis/nephrosis (McDonald et al., 2001). This study has been described in detail in Section C above [Carcinogenic Effects of Silica (Cancer of the Lung and Other Sites)]. Briefly, the cohort consisted of 2,670 men employed before 1980 for three years or more in one of nine North American sand plants and a large associated office complex. They were traced through 1994. The SMR for mortality from nephritis or nephrosis, calculated using state/provincial rates, was 212 (16 vs 7.56, $p = 0.002$). The excess was present only in workers employed for at least 10 years. The authors concluded that this finding of excess mortality from non-malignant renal disease was important because the evidence was fairly clear and consistent but that the scope of their study did not allow for further examination of this finding.

McDonald et al. (2005) updated this cohort mortality study of North American industrial sand workers by extending the follow-up to 2000. Mortality rates for the cohort were compared to state and national rates. A cause of death was available for each person who died. A nested case-referent analysis was conducted using quantitative estimates of silica exposure. The SMR at 20 or more years since hire as compared to the US rate for nephritis/nephrosis was still statistically significantly increased for the extended follow-up period (SMR 280, $p < 0.001$, 18 deaths). Also, the SMR for kidney cancer for the 20 or more years latency group, which was not statistically significantly increased in the previous study, was statistically significantly increased for both the 1995 to 2000 period (SMR 342, $p = 0.03$, 4 deaths) and the entire follow-up period (SMR 202, $p = 0.03$, 10 deaths). The comparison using the state cancer rates yielded lower but still statistically significantly elevated rates for nephritis/nephrosis (SMR 222, *p* value not provided) and kidney cancer (SMR 197, *p* value not provided) for the entire follow-up period. An analysis by year of hire found a generally decreasing trend over time for kidney cancer and nephritis/nephrosis, with the highest rates reported among pre-1950 hires. Looking at individual plants, an excess risk of mortality from nephritis/nephrosis was observed among workers in most plants, while excess kidney cancer mortality was

seen among workers mainly from plants in Pennsylvania and West Virginia. Case-referent analysis failed to demonstrate a relationship between either disease and cumulative exposure or average exposure intensity (as was consistently seen for silicosis and lung cancer). The authors suggested that biopersistent agents or those causing immune effects may show a different pattern of exposure-response relationships. They also commented that the size of their cohort did not allow for a more detailed analysis for duration and intensity of exposure. The authors concluded that their findings do not support a causal relationship between silica exposure and chronic renal disease or renal cancer but fail to explain the excess mortality observed.

Steenland et al. (2002a) combined three silica-exposed cohorts for a pooled analysis of renal disease mortality. The three cohorts were industrial sand workers, gold miners, and granite workers. For each cohort, underlying and multiple cause mortality data and a job-exposure matrix were available. The original gold miner (Steenland and Brown, 1995a) and industrial sand (Steenland et al., 2001b) studies will be discussed in turn, followed by a discussion of the pooled analysis. Results for renal disease mortality in the granite worker cohort (Costello and Graham, 1988) had not been published previously to Steenland et al. (2002a). This granite worker cohort is more fully described in Section C [Carcinogenic Effects of Silica (Cancer of the Lung and Other Sites)] and will be summarized below.

Steenland and Brown (1995a) conducted a mortality study of South Dakota gold miners exposed to silica. This study has been extensively described above in Section C [Carcinogenic Effects of Silica (Cancer of the Lung and Other Sites)]. Briefly, the cohort consisted of 3,328 gold miners who had worked underground for at least one year between 1940 and 1965. Status was followed up to 1990. A job exposure matrix was used to estimate dust exposure for each job over time and was based on dust measurements that were available for the years 1937 to 1975. For the entire cohort, there was no statistically significant increase in mortality from chronic renal disease. However, there was a statistically significant increase in mortality from chronic renal disease in those miners with a cumulative dust exposure of 48,000 dust days (one dust day is one day with exposure to a concentration of one mppcf dust) or greater (SMR 2.77, significant at the 0.05 level, 8 observed). Moreover, a chi square trend test indicated a statistically significant positive trend for chronic renal disease mortality with increasing cumulative exposure category (significant at the 0.05 level). In an analysis by year of hire, chronic renal disease mortality was statistically significantly elevated only for those hired prior to 1930 (SMR 2.39, 95% CI not reported, only that it excluded 1.00, 7 observed). Additionally, excesses of chronic renal disease mortality in a review of multiple cause mortality stratified by time of hire were shown to be concentrated in those hired prior to 1930 (SMR 2.14, 95% CI 1.05-4.04, 10 observed). The authors noted that exposures were known to be higher in earlier years. More than half (58 percent) of the cohort had been first employed before 1950, a period during which the authors stated that the exposures were “particularly high.” Follow-up of this cohort was extended six years to the end of 1996 for this pooled analysis.

Steenland et al. (2001b) also studied kidney disease morbidity and mortality in a cohort of industrial sand workers in the U.S. The cohort and study methods have been described in detail in Section C above (Lung and Other Cancers). The cohort consisted of 4,626 silica-exposed workers whose mortality experience was compared with that of the U.S. population. The workers were employed in 18 plants from the 1940s to the 1980s, most producing silica flour, a nearly 100 percent pure and finely ground quartz. Follow-up was until the end of 1996. As in the Steenland et al. (1992) study described above, underlying and multiple-cause mortality data were used (i.e., any mention of the disease on the death certificate). An exposure-response analysis was also conducted using a job-exposure matrix based on more than 4,000 industrial hygiene samples. The authors thought that their job-exposure matrix was probably reasonably accurate because silicosis and other unspecified pneumoconiosis as underlying causes of death showed an increasing trend in standardized rate ratios (SRRs) with cumulative exposure. Mortality from acute renal disease was statistically significantly increased using multiple-cause data (SMR 2.61, 95% CI 1.49-4.24, 16 observed deaths) but not using underlying cause data. Mortality from chronic renal disease, on the other hand, was statistically significantly increased using either underlying (SMR 2.22, 95% CI 1.06-4.08, 10 observed deaths) or multiple-cause (SMR 1.61, 95% CI 1.13-2.22, 36 observed deaths) data. An analysis was also done for multiple-cause mortality with cumulative exposure. Quartiles of exposure were >0 to 0.10, 0.10 to 0.51, 0.51 to 1.28, and 1.28+ mg/m^3-years. For both acute and chronic renal disease, standardized rate ratios increased with increasing quartile of cumulative exposure.

Steenland et al. (2001b) also matched their cohort to the national registry of treated end-stage renal disease (ESRD) (use of this data was described in Calvert et al., 1997, as detailed above) to determine incidence rate ratios. The SIR for ESRD was statistically significantly elevated at 1.97 (95% CI 1.25-2.96, 23 cases) as was the SIR for glomerulonephritis (3.85, 95% CI 1.55-7.93, 7 cases). Exposure-response analyses were also conducted for ESRD based on the same exposure quartiles used for the renal mortality analysis. The authors reported finding a "pronounced" trend of increasing ESRD risk by increasing cumulative exposure. In addition, case-control analyses by conditional logistic regression found rate ratios by quartile of cumulative exposure of 1.00, 2.68, 4.00, and 4.38. Use of the log of cumulative exposure provided the best fit to the data (coefficient = 0.84, 95% CI -0.04 to 0.66). The authors concluded that the exposure-response trends observed supported the finding of a causal relation between silica exposure and subsequent renal disease. They estimated that the excess lifetime risk of ESRD through age 75 for males exposed at 0.05 mg/m^3 respirable silica was 14 percent (95% CI -1% to 70%), based on the coefficient for log cumulative exposure from the nested case-control analysis restricted to ESRD cases. The authors noted that the background lifetime risk for a non-exposed male for ESRD is 2 percent.

The 5,408 Vermont granite workers (Costello and Graham, 1988) were exposed to silica in quarries or in sheds during the period 1950 to 1982. Follow-up for the cohort continued to the end of 1994. The combined cohort for the pooled analysis (Steenland et al., 2002a) consisted of 13,382 workers with exposure information available for 12,783. Exposure matrices for the three cohorts (gold miners, industrial sand workers, and granite

workers) had been previously validated by exposure-response data analysis for silicosis morbidity or mortality. The exposure estimates were validated by the monotonically increasing exposure-response trends seen in these silicosis analyses, since cumulative silica levels are known to predict silicosis. The mean duration of exposure, cumulative exposure, and concentration of respirable silica for the cohort were 13.6 years, 1.2 mg/m^3- years, and 0.07 mg/m^3, respectively. SMRs (compared to the U.S population) for renal disease (acute and chronic glomerulonephritis, nephrotic syndrome, acute and chronic renal failure, renal sclerosis, and nephritis/nephropathy) were statistically significantly elevated using multiple cause data (SMR 1.29, 95% CI 1.10-1.47, 193 deaths) and underlying cause data (SMR 1.41, 95% CI 1.05-1.85, 51 observed deaths). Renal disease mortality was also evaluated for the following quartiles of cumulative exposure: >0 to 0.15, 0.15 to 0.55, 0.55 to 1.67, and 1.67+ mg/m^3-years. There were highly statistically significant trends for increasing SMR with increasing cumulative exposure for both multiple cause ($p < 0.000001$) and underlying cause ($p = 0.0007$). Exposure-response analysis was also conducted as part of a nested case-control study with odds ratios determined for the same cumulative exposure quartiles noted above. The referent was the group of workers in the lowest exposure quartile. Statistically significant monotonic trends of increasing OR with increasing exposure were seen for multiple cause ($p = 0.004$ linear trend, 0.0002 log trend) and underlying cause ($p = 0.21$ linear trend, 0.03 log trend) analysis. The exposure-response trend was homogeneous across the three cohorts; addition of interaction terms did not increase the log likelihood of the model (e.g., the rate ratios by quartile of cumulative exposure using the multiple cause data were 1.00, 1.20, 1.36 and 3.31 for granite workers, 1.00, 1.15, 2.01 and 2.69 for gold miners, and 1.00, 1.56, 1.87 and 1.88 for industrial sand workers). Within the individual quartiles, statistically significantly increased odds ratios for multiple cause renal mortality were observed in the two highest cumulative exposure quartiles (for 0.55-1.67 mg/m^3-years OR = 1.77, 95% CI 1.10-2.85; for 1.67+ mg/m^3-years OR = 2.86, 95% CI 1.73-4.72). For underlying cause renal mortality, statistically significantly increased odds ratios were observed only for the highest exposure quartile (OR = 3.93, 95% CI 1.31-11.76). The authors used the exposure-response coefficient for the model with the log of cumulative exposure to calculate that the lifetime excess risk of death (underlying cause) from renal disease by age 75 for an exposure of 0.10 mg/m^3 over a working lifetime (age 20 to 65) was 1.8 percent (95% CI 0.8-9.7%) above a background risk of 0.3 percent.

The authors concluded that their study added to the evidence that renal disease is associated with exposure to crystalline silica. Noting that statistically significantly increased odds ratios and SMRs were seen primarily for cumulative exposures of >0.5 mg/m^3-years, the authors pointed out that this would come from working for five years at an exposure level of 0.1 mg/m^3 or 10 years at 0.05 mg/m^3. OSHA believes that the findings of this pooled analysis seem credible because the analysis involved a large number of workers from three cohorts with well-documented, validated job-exposure matrices and found a positive and monotonic increase in renal disease risk with increasing exposure for both underlying and multiple cause data.

Several mortality studies have not observed relationships between exposure to silica and renal disease mortality. Two studies of granite workers, one in the U.S. and

one in Finland, did not report finding a relationship. Davis et al. (1983) examined proportionate mortality during the period 1952 to 1978 for a cohort of 1,023 white male Vermont granite quarry and shed workers. In contrast to the studies of Steenland et al. (1992; 2001b; 2002a), only underlying cause of death was used. Comparisons were to mortality rates for U.S. white males. Estimates of lifetime exposure to silica were made and workers were grouped into four cumulative exposure categories. As has been noted above, dust controls were installed in the sheds between 1937 and 1940 and in the quarries by 1950. For the cohort as a whole, the observed-to-expected ratio (after excluding deaths from tuberculosis or silicosis) was not statistically significantly increased for "diseases of genitourinary system" (ICD 580-629) (O/E = 1.3, 95% CI 0.0-2.1, 15 deaths). Another analysis that used time of entry into the industry, either before or after implementation of controls, as a proxy for silica exposure resulted in an O/E of 1.4 (13 deaths, 9.0 expected) for diseases of genitourinary system, but the confidence interval was not reported. The authors noted that the post-exposure control group worked an average of 14 years and only nine had more than 25 years experience in the industry. The relative risk of mortality from genitourinary diseases was increased for those in the high (399-800 mppcf-years) and medium (199-400 mppcf-years) cumulative exposure categories (RR = 1.2 and 2.0, respectively) but not for the very high or low-exposure categories. Thus, no clear exposure-response relationship was seen (no information was provided on the statistical significance of the relative risk measures). Finally, an analysis by jobs ever worked found 5 deaths (1.8 expected) from genitourinary disease in "other quarry workers" (statistical significance not reported). The authors concluded that their findings do not provide consistent evidence of association between exposures in the granite industry and mortality.

Finnish granite workers were studied in a mortality study by Koskela et al. (1987). The cohort consisted of 1,026 workers hired between 1940 and 1971 and followed until the end of 1981. Mortality rates were compared to the general male population of Finland. There were 4 deaths (1.8 expected) where the main cause of death was "diseases of the urinary tract." Three of these deaths were from chronic pyelonephritis (0.6 expected) and one was from chronic nephritis. Renal disease was also reported in five other cases where it was not the primary cause of death. Three cases of urinary tract disease were associated with rheumatoid arthritis on the death certificates. The authors commented that a definite conclusion regarding an association of exposure to granite dust with glomerulonephritis was not possible because of the small number of cases.

Calvert et al. (2003) also did not find an increased mortality odds ratio for renal diseases with presumed silica exposure in a death certificate, matched case-control analysis of risks of mortality from various diseases and occupational silica exposure. Death certificates were obtained from 27 U.S. states. A qualitative silica exposure category (super high, high, medium, low/no) was determined for each individual based on industry/occupation found on their death certificate. Further details of this study can be found in Section C [Carcinogenic Effects of Silica (Cancer of the Lung and Other Sites)]. Calvert et al. (2003) found no significant association between crystalline silica exposure and several renal diseases, including acute and chronic renal failure and chronic

and membranous glomerulonephritis. In noting the contrast in their findings with other recent studies, Calvert et al. (2003) commented that death certificates can be an incomplete source of information (i.e., missing information may result in false negative findings). However, they pointed out that, if their study missed a true increase in risk, one would have to assume that renal diseases and/or silica exposed jobs are much more likely to be missing from death certificates of those with increased silica exposure compared to the general population.

Two mortality studies of lead and zinc mine workers in Sardinia, Italy, also failed to find an increased mortality for urinary tract diseases. Carta et al. (1994) studied cohorts (n = 906 and 835) from two mines, one with a higher silica content of the dust (n = 835), over the period 1973 to 1988. Mortality from urinary diseases was not increased for the combined cohort from the two mines. Data for cohorts from individual mines were not provided.

No statistically significant increase in mortality from urinary diseases was observed for silica-exposed women in a study of a cohort of women who appeared to have worked in the same two mines described above and were followed from 1951 to 1988 (Cocco et al., 1994). Cocco et al. (1994) noted that the average respirable quartz exposure in the two mines were 0.007 and 0.09 mg/m^3, respectively. No increase in mortality from urinary disease was found for the combined cohort or for cohorts from the individual mines. There was only one case observed among the cohort from the lower-exposure mine and two cases in the cohort from the higher-exposure mine. The authors noted that their study had low statistical power.

Several other studies, such as case series, case-control studies, cohort studies comparing exposed and non-exposed populations, and prevalence studies also support the finding of an effect of silica exposure on kidney disease. An early case series report studied morphologic alterations in the kidneys of silicotics. Kolev et al. (1970) conducted pathological examinations of the kidneys of 45 patients who had died of advanced silicosis at ages between 45 and 58. These were compared to 40 control patients who had died of obstructive emphysema and unspecific pneumosclerosis with cor pulmonale. The kidneys of about 51 percent of the patients who had died of silicosis displayed glomerular and interstitial lesions that the authors defined as a nonspecific glomerulonephrosis. None of the kidneys of the controls had these lesions. A lack of silica particles in the kidneys led the authors to suggest that a direct toxic effect was not involved. Since chronic lung diseases or conditions cause prolonged hypoxia, which leads to pulmonary hypertension resulting in cor pulmonale, the lack of effect in the controls with cor pulmonale argued against a pathological association of the kidney lesions with the hypoxia existing in advanced cases of silicosis. The authors believed that autoantibodies against altered tissue components and macrophages might be formed in the course of silicosis. They thought that the corresponding antigen-antibody complexes, when reaching the glomeruli, might bring about the described renal lesions.

Osorio et al. (1987) reported on a case of glomerulonephritis in a worker exposed to silica and seven other case reports from the literature. Their case was a foundry

coremaker with extensive silica exposure (up to 2.5 times the OSHA PEL was measured for the coremaker's job description) but no pulmonary disease, who developed nephrotic syndrome and renal failure over a three-month period and whose biopsy showed a proliferative glomerulonephritis. The seven other cases with glomerulonephritis and high silica exposure included a sandblaster, bricklayer, ceramic painter, ceramic glazer, foundry worker, tile factory worker, and coal mine driller. Three of the eight cases did not have clinical silicosis. Chest x-rays were normal and there were no pulmonary symptoms. For the authors, this suggested that some silica-exposed workers might get renal disease before chest x-ray changes or pulmonary symptoms were observed, and for some individuals, renal disease might be the dominant effect.

OSHA reviewed three case-control studies of renal disease. Steenland et al. (1990) conducted a study of 325 cases of ESRD selected from the Michigan Kidney Registry. Controls were selected by random-digit dialing in the four urban areas of the study and pair-matched to cases for age, race, and area of residence. Considered were history of having ever been exposed to silica and cumulative exposure. Odds ratios were statistically significantly elevated for exposure to silica overall (OR = 1.67, 95% CI 1.02-2.74), silica in brick and foundry work (OR = 1.92, 95% CI 1.06-3.46), and silica in sandblasting (OR = 3.83, 95% CI 0.97-15.19).

According to the authors, the only strongly positive trend of increasing risk with increased duration of exposure was for silica in sandblasting. The authors reported that the odds ratio for silica in sandblasting for 2.5 years for 40 hours a week was 2.74 (95% CI .69-9.97). When the five years preceding the date of diagnosis were excluded, the odds ratio for exposure to silica increased slightly from 1.67 to 1.81 (95% CI 1.09-3.02) and the coefficient for cumulative duration of exposure changed from -0.0039 to -0.0004. The authors concluded that their findings of an elevated risk of ESRD that was associated with self-reported exposure to silica in foundries, brick manufacturing, and sandblasting was consistent with other reports of renal disease resulting from acute exposure to silica.

A hospital-based case-control study found an association between silica exposure and rapidly progressive glomerulonephritis (RPGN) that was positive for antineutrophil cytoplasmic autoantibodies (ANCA, a marker for the small vessel vasculitides, an autoimmune disease) (Gregorini et al., 1993). The authors studied 16 patients with ANCA-positive RPGN who had been admitted to the hospital nephrology department. The 32 controls were taken from male patients admitted to the department and affected by nephropathies other than ANCA-positive RPGN. Interviews elicited information on occupational histories, and silica exposure was assessed by identifying those jobs known to be associated with silica exposure and by collecting and analyzing data related to "the sources of silica dust, protection equipment and department features." A total duration for silica exposure was estimated for each case and control. Seven of the 16 cases and 1 of the 32 controls were considered definitely exposed to silica dust. The mean duration of exposure for those considered definitely exposed was 26.3±8.8 years (range 10 to 34 years). For the cases with occupational history of silica exposure, the time to disease from first exposure ranged from 30 to 39 years (mean 32). Four of the seven cases definitely exposed to silica had pulmonary silicosis. For the cases and matched controls,

the conditional maximum likelihood point estimate of the OR for silica exposure was 14.0 (95% CI 1.7-113.8, $p < 0.001$). Renal biopsies available in six of the exposed cases showed a severe crescentic and necrotizing glomerulonephritis not different from those in unexposed patients. However, histological examination also showed, in three of the six exposed patients but none of the unexposed, a distinctive glomerular lesion consisting in peripheral nodular areas of glomerular sclerosis, in addition to the crescentic and necrotizing glomerulonephritis. The authors concluded that their study shows a strong relationship between silica exposure and ANCA-positive RPGN and that silica exposure, therefore, should be considered a risk factor for ANCA-positive RPGN.

Another case-control study demonstrated an association of occupational exposure to silicon compounds with Wegener granulomatosis with renal involvement. Nuyts et al. (1995) selected 16 patients from six Belgian renal units. For each patient, two age-, sex-, and region-matched controls were selected from the general population using lists of voters (all Belgians 18 years and older). Occupational histories were reconstructed from interviews and quantitatively scored by an industrial hygienist. Five of the cases had been employed as bricklayer, stone cutter, in a brickyard, or sandblaster. Two had worked on metal-turning tables, two as shoemakers and two in animal feed factories. Exposures of seven cases were to silica or silica-containing dusts such as cement, quartz, and grain dust. (The authors noted that rice husks may contain up to 20% crystalline silica.) Statistically significantly increased odds ratios were observed for exposure to silica (OR = 5, 95% CI 1.4-11.6) or silicon-containing compounds such as grain dust (OR = 6.5, 95% CI 1.3-13.5). The authors stated that exposure to grain dust resulted in an almost sevenfold increased risk of developing Wegener granulomatosis.

Two studies examined renal function as measured by excretion of specific high- and low-molecular weight proteins and enzymes in silica-exposed workers compared to workers not exposed to silica. These proteins and markers are used as markers of early glomerular and tubular disturbances. Ng et al. (1992c) measured urinary excretion of albumin, α-1-microglobulin (AMG), and β-N-acetyl-glucosaminidase (NAG) in 26 non-silicotic and one silicotic crushers and grinders currently working in one of three granite quarries in Singapore and six silicotic workers who had ceased exposure from three to 17 years before the study. The mean duration of exposure of the 33 was 16 years (range 1-33). Five of the silicotics had silicosis profusion category 1 and the others category 2. The non-exposed controls were 19 age-matched male hospital ancillary workers and community volunteers.

Excretion of albumin was statistically significantly increased ($p = 0.03$, *t* test) in the exposed as compared to non-exposed group with geometric means (SD, range) of 9.3 (2.6, 1.6-71.6) and 5.5 (2.0, 1.0-13.0) mg/g creatinine, respectively. Albumin excretion was raised above the 95^{th} percentile of the non-exposed subjects in 13 (39 percent) of the exposed workers, compared with 1 (5 percent) of the non-exposed group ($p < 0.001$ by χ^2 test). Excretion of AMG was also statistically significantly increased ($p = 0.002$, *t* test) in the exposed as compared to non-exposed group with arithmetic means (SD, range) of 7.5 (3.2, 1.6-17.1) and 4.6 (2.7, 1.7-12.0) mg/g creatinine, respectively. Increases for NAG

excretion in the exposed as compared to the non-exposed group were not statistically significant.

In an additional analysis, silicotics were compared to nonsilicotic exposed workers and non-exposed workers. Statistically significant increased excretion in silicotics was observed for albumin ($p = 0.05$), AMG ($p = 0.002$), and NAG ($p = 0.02$). An analysis restricted to workers 40 years and older found similar results (albumin, $p = 0.06$) (AMG, $p = 0.002$) (NAG, $p = 0.04$). These finding on silicotics suggested to the authors that these functional changes are not reversible upon removal from exposure given that all but one of the silicotics had not been exposed for many years (from 3 to 17 years before the study). The authors concluded that some degree of irreversible renal functional disturbance related to lesions in the glomeruli and proximal tubules, likely arising from prolonged exposure to silica, was demonstrated in seemingly healthy silica-exposed workers. However, the authors felt that further studies were needed to ascertain whether the urinary alterations observed are of clinical significance in reflecting early and asymptomatic glomerular or tubular disease in silica-exposed workers.

A similar study was conducted in quarry workers in Spain (Hotz et al., 1995). The differences were that none of the 86 silica-exposed workers had silicosis, and they were only exposed for an average of 15.2 months (range 11-20). The 86 controls were matched for age, smoking status, and body mass index. The workers were also younger by about fifteen years than those in the Singapore study. The rock in the quarry was made of quartzite with 90 percent silicon dioxide (SiO_2) and some aluminum oxide (Al_2O_3) and ferric oxide (Fe_2O_3). Twenty-five to thirty percent of the silica dust particles were less than six µm in diameter. The mean silica concentration ranged from 4 to 300 mg/m^3.

Urinary excretion of albumin, transferrin, retinol-binding protein (RBP), and NAG were all statistically significantly increased in exposed as compared to control workers. The prevalence of values above the reference range followed a similar pattern but only was statistically significantly elevated for RBP. Urinary silicon (mg/g creatinine) was also statistically significantly increased in exposed as compared to control workers ($p = 0.0001$). However, the authors noted that urinary silicon is only useful as an indicator of recent exposure and confirmed that exposure was occurring despite the use of personal protective equipment. The authors concluded that they had observed subclinical renal effects in nonsilicotic workers after less than two years of exposure to silica. The authors also concluded that the effects seen in their study may represent the start of a cascade of degenerative changes, ultimately leading to overt nephropathy and renal failure.

Boujemaa et al. (1994) conducted a cross-sectional study to examine these early indicators of renal dysfunction in silicotic workers. The study group consisted of 116 male underground mine workers who had silicosis compensated by the Belgian Occupational Disease Fund and who had been exposed to silica but whose exposure had stopped several years earlier. The mean duration of exposure was 14.9 years (range 2 to

35) and the average time since last exposure was 23.2 years (range 0 to 30). There were 61 age-matched referents from the general population.

The silicotic workers had statistically significantly higher excretion of several markers, including albumin, RBP, and NAG, than the age-matched controls. However, the prevalences of subjects with abnormally elevated values did not differ between the two groups. The markers were also not correlated with duration of exposure or severity of silicosis. The authors commented that markers of proximal tubule dysfunction measured in their study (RBP) and by Ng et al. (1992c) (AMG) were comparable, so the pattern of effects seen in the two studies were identical. Another similarity was seen in the study of workers who were not currently exposed, confirming the suggestion that renal alterations associated with silica exposure may be irreversible. Boujemaa et al. (1994) concluded from their findings that silicosis is associated with infraclinical renal alterations but also determined that a conclusion that silica caused these alterations could not be drawn at the present time in the absence of an identified relationship with length of exposure or severity of silicosis.

The prevalence of kidney disease was studied in a cohort of individuals with silicosis by Rosenman et al. (2000). Silicotic patients were identified from a mandatory reporting system in Michigan. Reports came from hospitals, physicians, the state workers' compensation bureau, and from death certificates. Each report was followed up with a telephone interview questionnaire to the case or next of kin, gathering historical information on lifetime work, cigarette smoking, medical care, medication, and symptoms limited to respiratory conditions. Creatinine records were abstracted from all medical records with a mention of kidney disease. By the time the reports were received, most of the individuals were no longer exposed to silica. The study reviewed 583 confirmed cases of silicosis reported from 1985 to 1995. Seventy-nine percent had had their exposure to silica in a foundry. Progressive massive fibrosis was reported for twenty-nine percent. Seventy-four percent had had more than twenty years of exposure to silica. Only 283 of the reports had medical records with creatinine levels.

Silicotics were statistically significantly more likely to have a serum creatinine level greater than 1.5 mg/dl (considered elevated) within age and race strata than results in the general population, based on the third National Health and Nutrition Examination Survey data. Age-adjusted relative risks were 2.49 (95% CI 1.72-361) for whites and 1.68 (95% CI 1.18-2.40) for African-Americans. Presence of kidney disease or elevated creatinine levels were not associated with increased profusion of silicosis or increased duration of exposure to silica either in the overall group or by age- and race-specific strata. The authors concluded that their findings confirmed an association between kidney disease and exposure to silica and that chronic kidney disease should be considered a potential complication in patients with silicosis.

Steenland et al. (2002b) conducted a study to determine the incidence of end-stage renal disease (ESRD) among workers with silicosis. The study population of 1,328 workers with silicosis and adequate work history information was drawn from the silicosis surveillance systems of Michigan (discussed above) and two other states (New

Jersey and Ohio). The cohort was then linked with the ESRD register as discussed by Calvert et al. (1997). The workplaces or jobs of the cases were distributed as follows: in Michigan, foundries (79 percent) and sandblasting (26 percent); in New Jersey, vitreous plumbing fixtures (30 percent), foundries (21 percent), ceramic tile (11 percent), sand and gravel mining (11 percent), iron ore mining (10 percent), and porcelain electrical supplies (10 percent); and in Ohio, foundries (45 percent), production of stone/clay/concrete (23 percent), and sandblasting (22 percent). Data describing severity of silicosis were available only for Michigan, where 69 percent of cases had simple silicosis, 25 percent exhibited progressive massive fibrosis, and 3 percent had normal chest x-ray films but were identified as silicotics from autopsy evidence. Exposure measurements were available in 48 workplaces in Michigan where exposures exceeded 0.05 mg/m^3 in 63 percent of the workplaces, and in 29 workplaces in Ohio where exposures exceeded 0.05 mg/m^3 in 69 percent. The overall cohort had an average of 27 years of exposure. However, there were relatively few person-years at risk (23,945) because person-years could only be accumulated from the ESRD registry beginning in 1977. None of the analyses performed yielded an increased SIR for ESRD among the silicotics, including an analysis of glomerular nephropathy incidence, an analysis of trends by duration of exposure, and analyses that varied the start date for accumulating person-years at risk (e.g., using the date of entry into the silicosis register vs. the date of first exposure to silica).

The authors concluded that, while their results did not show that silicotic patients have an excess of ESRD, the results did suggest an excess of glomerular ESRD (a two-fold excess was found but it was not statistically significant). The authors did allow that their analyses were limited by the small numbers and possible selection biases. For example, some subjects with silicosis may have died due to their renal disease before being entered into silicosis registers.

I.E.2. Autoimmune Effects.

Several cases of autoimmune diseases have been reported in employees engaged in occupations known to have high silica exposures. The most commonly reported autoimmune diseases are scleroderma and rheumatoid arthritis. In 1914, Bramwell described scleroderma in five masons, one coppersmith, and one coalminer (Bramwell, 1914). Although he attributed the scleroderma to use of hand tools in cold weather, it is interesting that these cases manifested in workers of occupations with known silica exposure. Erasmus (1957) described 17 cases of scleroderma in European underground miners who were applying for financial benefits due to the onset of silicosis. All cases exhibited skin lesions and pulmonary symptoms due to scleroderma.

Cutaneous silica granuloma was reported in a 57-year-old stonemason (Mowry et al., 1991). The patient had reported that he used a rock saw and often returned home at the end of each workday with lacerated, stinging, and bleeding forearms. A biopsy specimen from one of his lesions showed fibrosis and innumerable crystalline structures. Mulloy (2003) reported a case of systemic vasculitis in a former Department of Energy employee. The employee was assigned to two jobs in which silica exposure was likely.

However, throughout his career, he held many other positions which exposed him to other hazardous chemicals such as solvents, heavy metals, beryllium, depleted uranium, and ionizing radiation.

Twenty-four cases of scleroderma were reported among South African gold miners between 1981 and 1988 (Cowie and Dansey, 1990). The incidence of scleroderma was 25 times higher among silica-exposed miners than in the general population.

Rodnan et al. (1967) described 60 cases of scleroderma in men of various occupations, of which, 26 were in occupations known to have high silica exposures. Onset of symptoms among these cases ranged from 5 years to 41 years. This study also matched these cases with controls and found the frequency of silica exposure was higher among cases than controls ($p < 0.01$). However, actual exposures were not reported in this study. Finally, this study also estimated the prevalence of scleroderma to be 17/100,000 among coal miner hospital discharges compared to 6/100,000 in non-miner hospital discharges among males.

Klockars et al. (1987) conducted a retrospective study examining the incidence and prevalence of subjects awarded pensions and benefits due to rheumatoid arthritis among Finnish granite workers. The study group comprised 1,026 Finnish granite workers hired in quarries for at least three months between 1940 and 1971 and followed until 1981. New disability pensions awarded between 1969 and 1981 were studied and prevalence calculated at the end of 1981. Lifetime occupational histories were obtained for surviving participants or next of kin (for deceased participants) via questionnaire. Representative silica exposures were used from a separate study of Finnish quarries completed in 1970 to 1972 by the Finnish Institute of Occupational Health. Using data from the Institute of Occupational Health from 1970 to 1972, exposures to silica, vibration, and noise were determined. Exposures to silica ranged from 0.2 to 4.9 mg/m^3 with a geometric mean of 0.82 mg/m^3.

The results showed that 10 subjects received compensation for rheumatoid arthritis, compared to an expected 1.6 ($p < 0.001$). The number receiving free medicines was 19, compared to an expected 7.5 ($p < 0.001$). The study concludes that there is an association between silica exposure and rheumatoid arthritis.

Brown et al. (1997) examined the mortality of persons hospitalized for silicosis in Sweden from 1965 through 1983 and in Denmark from 1977 through 1989. Subjects with incomplete medical records or confirmed cases of asbestosis were excluded from the study. Subjects were followed, beginning with the first hospitalization for silicosis and ending either with the subject's death, emigration, or the end of the study (1983 for Sweden and 1989 for Denmark).

During the follow-up, six deaths due to autoimmune diseases were recorded: three with rheumatoid arthritis, two with systemic lupus erythematosus, and one with Sjogren's syndrome. The SMR for these causes of death combined compared to the

general population was reported as 5.9 (95% CI 2.2 - 2.9). Although the temporal relationship between the diagnosis of silicosis and onset of autoimmune diseases cannot be determined from this study, it nevertheless demonstrates an increased mortality rate from autoimmune disease among silicotic men compared to the general public.

Another mortality study (Calvert et al., 2003) showed that those with silicosis were more likely to have rheumatoid arthritis than those without silicosis (mortality odds ratio 3.75, 95% CI 1.92-7.32). This study also showed an association between rheumatoid arthritis and silica exposure (mortality odds ratio 1.19, 95% CI 1.12-1.25). However, when exposures were stratified into medium, high, and super high exposures, no trend or dose-response was observed. The study design is discussed in more detail in Section C (Lung and Other Cancers).

A recent preliminary study provides evidence suggesting a mechanistic association between silica exposure and autoimmune disease. Carlsten et al. (2007) conducted a cross-sectional study of 16 mason apprentices and 26 electrician apprentices. Although self-reported, the mason apprentices had significantly higher silica exposures ($p < 0.05$) than the electrician apprentices. This study focused on differences in key cytokines and lymphocyte cell surface makers and found statistically significantly ($p < 0.05$) higher levels of key cytokines, and lower CD25+ and CD69+ lymphocyte cell surface markers in the masons than in the electricians. The author concluded that since increased levels of key cytokines and lower lymphocyte cell surface markers can lead to autoimmune diseases, those exposed to silica may be at risk for such diseases. The one major limitation of this study was the inability to fully characterize silica exposures.

In an earlier study, Haustein et al. (1990) reviewed scleroderma in 120 patients in East Germany between 1981 and 1988. The study revealed the presence of silica particles between 1 and 20µm in diameter lodged in the skin of heavily exposed areas. (The authors noted that silica is chemically inert, cannot be digested, and remains in the tissue.) The authors explained that because silica is toxic to macrophages, the macrophages die and silica is again exposed for ingestion and the phagocytotic process. Fibroblasts are permanently stimulated by lymphokines and monokines, increasing immune activity. This is believed to be the mechanism for development of silica-induced scleroderma.

The majority of studies conducted that have examined the association between silica exposure and autoimmune diseases are retrospective in nature. Major limitations of these studies include the lack of detailed exposure characterization and the lack of a demonstrated temporal relationship between silica exposure or silicosis and the onset of autoimmune diseases. However, most studies do provide evidence of an association between the presence of silicosis and autoimmune diseases. This suggests an association between exposure to silica and autoimmune disease.

A recent case-control study was conducted to examine the association between silica exposure and rheumatoid arthritis in Sweden (Stolt et al., 2005). From hospital-based and private rheumatology units, 276 male cases of rheumatoid arthritis diagnosed

between 1996 and 2001 were identified that meet the diagnostic criteria set by the American College of Rheumatology. Cases were selected from a larger study population in a specific geographical area. Matching for age, sex, and residential area, 276 controls were selected from the larger study population. Silica exposure was assigned via questionnaire for both cases and controls.

Upon analysis, the study showed that the odds of having rheumatoid arthritis were 2.2 times higher (95% CI 1.2-3.9) for those exposed to silica (adjusting for age and smoking). This odds ratio increased to 2.7 (95% CI = 1.2-5.8) when analyzing subjects from 50 to 70 years-old separately. No statistically significant increase in risk was seen in 18 to 49 year-old men. Based on job categories, the odds ratio for rock drilling and stone crushing was reported to be 3.0 (95% CI = 1.2-7.6). The authors conceded that misclassification of silica exposure could have occurred since exposures were ascertained via questionnaire. In addition, since vibration is also a hazard associated with rock drilling and stone crushing, it is unclear what effect, if any, vibration exposure had on developing rheumatoid arthritis.

Haustein and Anderegg (1998) sent questionnaires to 298 dermatology clinics between 1980 and 1981 in the former East Germany, requesting occupational information for all cases of scleroderma and exposures to silica of greater than six months duration. A total of 454 females and 137 males were registered for the study and the assessment period ran from 1980 to 1997.

The reported incidence and prevalence of scleroderma in the general population were 11.7 per million and 53.7 per million respectively (population of 1.4 million). Although no information was given regarding the determination of silica exposures, the study reported that relative risk for developing scleroderma was increased 12-fold for silicosis patients and 5.7-fold for silica-exposed persons compared to the “healthy” population over 40 years of age. The study also found the average latency period between the beginning of exposure and onset of scleroderma to be 24.3 years in those cases that did not have silicosis. The majority of cases with both silicosis and scleroderma found that silicosis preceded the onset of scleroderma.

Rosenman and Zhu (1995) examined the association between pneumoconiosis and connective tissue disease among men and women using Michigan hospital discharge data between 1990 and 1991. From the discharge data, 155 cases of silicosis in men and 5 cases of silicosis in women were identified for review and analysis. Anyone under the age of 20 and diagnosed with cystic fibrosis was excluded from the study. A standardized incidence ratio (SIR) was calculated comparing actual cases to expected cases.

The study yielded a significant SIR of 3.2 (95% CI 1.1-9.4) for rheumatoid arthritis in silicotic men. The association was not statistically significant among women. This study does not account for smoking nor does it specify if silicosis or rheumatoid arthritis was first diagnosed among the cases. However, these data do suggest a higher incidence of rheumatoid arthritis among silicotic men.

In a later study, Rosenman et al. (1999) showed an association between silicosis and rheumatoid arthritis in men. This retrospective cohort study reviewed medical records and questionnaires from 583 confirmed silicosis cases reported to the Michigan state surveillance system between 1987 and 1995. Rheumatoid arthritis was self-reported via questionnaire and was verified by medical records when available.

The results showed a relative risk of 2.73 (95% CI 1.75-4.06) for rheumatoid arthritis prevalence among silicotics as compared to the general population. Although not statistically significant, the study reported a relative risk of 15.65 (95% CI = 0.21-87.03) for scleroderma prevalence in silicotics compared to the general population and a relative risk of 11.37 (95% CI = 0.15-63.23) for systemic lupus erythematosus. Although the onset of either silicosis or the autoimmune disease with respect to each other was not discussed, the study highlights the importance of considering connective tissue disease as an additional complication when evaluating patients for silicosis.

Sluis-Cremer et al. (1985, 1986) conducted two case-control studies examining the association between silica exposure, silicosis, rheumatoid arthritis and systemic sclerosis in South African gold miners. In the first study (Sluis-Cremer et al., 1985), 79 cases of systemic sclerosis were selected from the Medical Bureau for Occupational Diseases (MBOD), South Africa through 1984. Controls were matched and selected from miners attending MBOD examinations between 1970 and 1971. To estimate the silica exposures, the authors reviewed occupational records, multiplied the number of shifts worked by a weighting factor proportional to the silica dust concentration of that occupation. Weighting factors were highest for underground high dust exposure, followed by underground low-dust exposure, and finally, all dusty surface operations. No other information on exposure characterization was available.

Results showed no statistical significance in the number of silicosis cases among cases of systemic sclerosis and controls when controlled for cumulative silica exposure. Although no odds ratios were reported, the study did report that cases of systemic sclerosis had significantly higher life time exposures to crystalline silica. The authors also reported that the difference in cumulative silica dust exposures was due to intensity of exposure rather than duration of exposure. The authors believed that intensity of exposure may have been a more important risk factor than duration of exposure.

In a second study (Sluis-Cremer et al., 1986), the association between silicosis and rheumatoid arthritis was examined. From the same database of patients, 91 definite and 66 probable cases of rheumatoid arthritis were identified. Cases were selected and matched by year of birth with controls not having rheumatoid arthritis. Medical records were reviewed to identify all subjects with silicosis. Silica exposures were calculated in the same way as in the previous study (Sluis-Cremer et al., 1985). Definite and probable cases of rheumatoid arthritis combined were found to be more likely to also have silicosis (OR = 2.84, 95% CI 1.36-4.32). When definite and probable cases were analyzed separately, only definite cases of rheumatoid arthritis were more likely to also have silicosis (OR = 3.79, 95% CI = 1.72-8.36). The authors concluded that miners with

rheumatoid arthritis and exposed to silica were more likely to develop silicosis than miners without rheumatoid arthritis. This study found no significant differences in silica exposures between cases and controls, but the authors believe that if an association between exposure to silica and the development of rheumatoid arthritis exists, it is unlikely to be a strong one.

Walsh (1997) evaluated scleroderma mortality rates among the general population and those exposed to silica between 1985 and 1992. The results indicated that the number of observed deaths (128) due to scleroderma among men exposed to silica was no different than that expected in the general population (ratio = 1.0, 95% CI = 0.6-1.2). No other information was provided in the abstract from this study.

In 1995, Bovenzi et al. conducted a case-referent study examining the association between chemical exposures and scleroderma. Five hundred twenty seven cases of musculoskeletal disorders or connective tissue disease were selected from hospitals from 1976 to 1991. Clinical records were verified for diagnoses. Two age- and gender-matched controls were selected from patients who were discharged from the same hospital the same day as the cases but who were not affected with either disease. Interviews were conducted to determine exposure to various chemicals, including solvents and silica. Those indicating exposure durations of less than six months were excluded from the study.

Although not statistically significant, the odds ratio of 5.2 (95% CI 0.48-74.1) indicated that men with scleroderma were more likely to have been exposed to silica. One possible explanation for this data is the small sample size; of the original 527 cases, only 21 cases of scleroderma (16 women and 5 men) were selected for analysis with 42 matched controls.

I.E.3. Preliminary Conclusions for Renal and Autoimmune Effects.

Overall, there is substantial evidence suggesting an association between exposure to crystalline silica and increased risks of renal and autoimmune diseases. In addition to a number of case reports, epidemiologic studies have found statistically significant associations between occupational exposure to silica dust and chronic renal disease (e.g., Calvert et al., 1997), subclinical renal changes (e.g., Ng et al., 1992c), end-stage renal disease morbidity (e.g., Steenland et al., 1990), chronic renal disease mortality (Steenland et al., 2001b, 2002a), and Wegener's granulomatosis (Nuyts et al., 1995). In other findings, silica-exposed individuals, both with and without silicosis, had an increased prevalence of abnormal renal function (Hotz et al., 1995), and renal effects have been reported to persist after cessation of silica exposure (Ng et al., 1992c). Possible mechanisms suggested for silica-induced renal disease include a direct toxic effect on the kidney, deposition in the kidney of immune complexes (IgA) following silica-related pulmonary inflammation, or an autoimmune mechanism (Calvert et al., 1997; Gregorini et al., 1993).

An analysis of renal disease mortality and silica exposure showed strong exposure-response trends for both underlying and multiple cause mortality (Steenland et al., 2002a). Steenland (2005b) estimated excess lifetime risks (age 75) after 45 years exposure to 0.1 mg/m^3 respirable crystalline silica to be 5.1 percent (3.3-7.3) for end-stage renal disease incidence, based on 23 cases (Steenland et al., 2001b), and 1.8 percent (0.8-9.7) for kidney disease mortality (underlying), based on 51 deaths (Steenland et al., 2002a). OSHA believes that these findings are credible, as they are based on large numbers of workers and the exposure information has been validated. However, there are considerably less data, and thus the findings based on them are less robust, than what is available for silicosis mortality or lung cancer mortality. Nevertheless, OSHA preliminarily concludes that the underlying data are sufficient to provide useful estimates of risk and has included the Steenland et al. (2002a) analysis in its Preliminary Quantitative Risk Assessment.

Several studies of different designs, including case series, cohort, registry linkage and case-control, conducted in a variety of exposed groups suggest an association between silica exposure and increased risk of systemic autoimmune disease (Parks et al., 1999). Studies have found that the most common autoimmune diseases associated with silica exposure are scleroderma (e.g., Sluis-Cremer et al., 1985); rheumatoid arthritis (e.g. Klockars et al., 1987; Rosenman and Zhu, 1995); and systemic lupus erythematosus (e.g., Brown et al., 1997). Mechanisms suggested for silica-related autoimmune disease include an adjuvant effect of silica (Parks et al., 1999), activation of the immune system by the fibrogenic proteins and growth factors released as a result of the interaction of silica particles with macrophages (e.g., Haustein and Anderegg, 1998), and a direct local effect of non-respirable silica particles penetrating the skin and producing scleroderma (Green and Vallyathan, 1996). However, there are no quantitative exposure-response data for the association between exposure to silica and autoimmune diseases, making quantitative risks assessments for these diseases not possible at this time.

Therefore, OSHA preliminarily concludes that there is substantial evidence that silica exposure increases the risks of renal and autoimmune disease. The positive and monotonic exposure-response trends demonstrated for silica exposure and renal disease risk more strongly suggest a causal link. There are two studies of renal disease that provide quantitative exposure-response data. There are no quantitative exposure-response data with regard to autoimmune diseases. OSHA preliminarily concludes that the available exposure-response data on silica exposure and renal disease is sufficient to allow for quantitative estimates of risk.

I.F. *Physical Factors That May Influence Toxicity of Crystalline Silica.*

OSHA has preliminarily concluded that epidemiologic studies provide ample evidence that exposure to respirable crystalline silica increases the risk of lung cancer among workers (see Section V.C. above). OSHA has also preliminarily concluded that it is established that exposure to respirable crystalline silica causes silicosis. IARC (1997) has also determined that "crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is carcinogenic to humans." In making this determination, the

IARC Working Group noted that "carcinogenicity was not detected in all industrial circumstances studied." The Working Group also stated that "carcinogenicity may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs." Thus, while IARC has determined that cristobalite and quartz are both carcinogenic to humans, there has been considerable discussion among researchers as to whether the toxicologic potency of crystalline silica might vary depending on crystalline structure or surface chemistry of the particles.

Much research has been conducted to investigate the influence of various physical factors on the toxicologic potency of crystalline silica. Such factors include crystal polymorphism, the age of fractured surfaces of the crystal particle, the presence of impurities on particle surfaces, and coating of the particle. These factors may vary among different workplace settings suggesting that the health risk to workers exposed to a given level of respirable crystalline silica may not be equivalent in different work environments. These findings are discussed in this section.

I.F.1. Mechanism of Action.

Physical characteristics relevant to the toxicity of crystalline silica primarily relate to the surface of silica particles, which researchers believe play an important role in the mechanism by which silica causes lung damage. Thus, any factor that influences or modifies these surface characteristics may alter the toxicity of silica by affecting the mechanistic process. There have been many studies that have examined possible mechanisms of action for silica, and these studies are discussed in this section. First, the overall proposed basic mechanism of action will be described. This will be followed by a discussion of studies which have examined in further detail, and at the cellular and molecular level, specific parts of the process by which silica is proposed to cause silicosis and cancer.

Before a discussion of the possible mechanisms by which a silica particle entering the lungs could cause lung damage, a brief review of the pharmacokinetics of silica deposition and clearance will be presented. IARC (1997) reviewed studies on the pharmacokinetics of crystalline silica in humans and animals. However, at the time of the IARC review there were only a few studies that had investigated retention of crystalline silica particles in the human lung. Although these studies described finding quartz particles in the bronchoalveolar macrophages and sputum of silicotic patients, there was generally no correlation between lung quartz content and severity of pathological changes in the lung. For example, one study of hard-rock miners with 14-36 years of exposure reported lung silica burdens of 25-264 mg per single lung (Verma et al., 1982). The miners had variable amounts of pathological response that was not correlated with lung burden.

These early studies also found that the dissolution of quartz did not appear to contribute substantially to its clearance or to changes in its biological activity. In fact, the quartz component of dust residing in the lung was generally found to be greater than that

of the dust in the air, suggesting that crystalline silica was not cleared as well as the other components of the dust (IARC, 1997). A study in which silica particles were counted in the bronchoalveolar fluid of people occupationally exposed to silica (Pairon et al., 1994), further confirmed that silica is one of the most persistent mineral particles in the lung.

It is difficult to rely on animal studies to describe the pharmacokinetics of crystalline silica in humans because rodents are obligate nasal breathers and have a different pattern (cycle period and tidal volume) of breathing. Also, there are differences between species in terms of quartz clearance rates with the clearance rates of humans being slower than that of rats and hamsters. Nonetheless, animal studies reviewed by IARC (1997) have demonstrated that clearance from the lung periphery is slow and incomplete, resulting in a captured fraction of silica that is never cleared. In rats, it was observed that quartz particles that had deposited on the terminal bronchiolar and alveolar duct surfaces had moved into epithelial cells and to the interstitium. The quartz then moved to the lymph nodes, where accumulation continued up to 150 days after exposure has stopped. Particle removal via macrophages was found to be severely inhibited due to a direct toxic effect of silica on macrophages.

Since the IARC review, Kuempel et al. (2001) have developed a toxicokinetic/dynamic model to predict the relationship between occupational quartz exposure and lung burden. The researchers used the toxicokinetic/dynamic model fit to lung burden and pulmonary response data from a subchronic inhalation study in rats to estimate the minimum critical quartz burden associated with reduced pulmonary clearance and increased neutrophilic inflammation in humans. The minimum critical quartz lung burden estimated by the model that would be associated with reduced pulmonary clearance and increased neutrophil inflammation in humans was 0.39 mg/g lung tissue. Although the model was originally developed for respirable coal mine dust (with approximately five percent respirable quartz), it was extended to describe quartz clearance and retention in the lungs. In the study to evaluate the model, lung burden of quartz was measured at autopsy of the coal miners. The model predicted a lung burden 1.7 times greater than the observed quartz lung burden, but this was within the confidence interval. Thus, the model was used to predict the human internal dose (lung and lymph node quartz burdens, at age 75 years, following a 45-year working lifetime, beginning at age 20 years, plus 10 years retirement) associated with exposure to a given airborne concentration of respirable silica. The model was also used to predict the average quartz concentration associated with a given internal dose. The average exposure concentration over a 45-year working lifetime, predicted from the model to be associated with the critical quartz lung burden (0.39 mg/g) associated with reduced pulmonary clearance and increased neutrophilic inflammation was 0.036 mg/m^3. The lung burdens associated with exposure concentrations of 0.05 and 0.1 mg/m^3 were 0.54 and 1.08 mg/g, respectively.

This lung dosimetry model was also used by the authors to estimate quartz lung burdens in a study of early pulmonary inflammatory responses in coal miners (Kuempel et al., 2003). The miners were exposed to a mean respirable crystalline silica (quartz) concentration of 0.046 (± 0.029) mg/m^3. The mean years working in mining was 16.7 (± 4.8). The model predictions of quartz lung burden were evaluated using data available on

quartz mass recovered from the lungs of two individuals who volunteered for whole lung lavage (WLL). The observed lung quartz burdens of the two were consistent with the predictions of the lung dosimetry model (0.46 observed vs 0.66 predicted). The authors suggested that, since quartz may be sequestered in the lung (e.g. in granulomatous lesions in the alveolar lumen or in the interstitium), the total lung burden is likely to be higher than that lavageable by WLL and that this was consistent with the somewhat higher predictions of the model. They also noted that the dosimetry model assumes very slow alveolar clearance, such that nearly all the quartz deposited in the deep lung is predicted to be retained in the alveoli, or in the interstitium, or transferred to the lung-associated lymph nodes. The actual and predicted lung burdens could also differ because particle deposition and clearance could differ among individuals and thus differ from the average values assumed in the models. Also, uncertainties in exposure estimates could account for the differences from predicted to actual lung burdens. The authors concluded that, given these issues, the lung dosimetry model seemed to provide adequate predictions of lung burdens associated with exposure concentrations. Cumulative exposure to or estimated lung burden of respirable quartz was a highly statistically significant predictor of an inflammatory response, as measured by increased polymorphonuclear leukocyte (PMN) count in bronchoalveolar lavage fluid. Estimated quartz lung burden was a highly statistically significant predictor of radiographic category of small opacities ($p < 0.0001$). Both PMN count and estimated quartz lung burden were statistically significantly predictive of radiographic category in a model with both covariates (p-values < 0.04). The statistically significant relationship between estimated quartz lung-burden and early radiographic categories (including 0/1 and 1/0) suggested to the authors that these changes represent early stages of pneumonconiosis. The authors pointed out that these miners had relatively low working lifetime dust exposures, having worked on average 17 years and almost entirely under U.S exposure limits for coal and quartz. Even under these conditions, some showed evidence of early pulmonary response to the inhaled particles, including inflammation and radiographic small opacities.

It has been proposed that silicosis results from a cycle of cell damage, oxidant generation, inflammation, scarring, and fibrosis (Brown and Donaldson, 1996; Castranova, 2004; Fubini et al., 2004; Nolan et al., 1981; Shi et al., 1989, 1998). A silica particle entering the lung could cause lung damage by three major mechanisms. One mechanism is that silica could cause direct damage to lung cells due to its unique surface properties. Silanol groups are present on the surface of silica particles. Hydrogen from silanol groups forms bonds with oxygen and nitrogen groups in biological membranes, resulting in the loss of membrane integrity, lysosomal enzyme leakage, tissue injury, and lung scarring. Silica also has reactive sites on its surface consisting of silicon-based free radicals. When a silica particle is fractured, siloxyl radicals form on the fracture plane. These free radicals react with aqueous (water-based) constituents in the lung, generating reactive oxygen species, or ROS, that can react with and damage cellular constituents such as DNA, proteins, lipids, and carbohydrates. It is hypothesized that cellular response, and particularly macrophage activation and death, is mediated by strong interactions between reactive sites on the particle surface and cell membrane components (Brown and Donaldson, 1996; Castranova, 2004; Fubini et al., 2004; Nolan et al., 1981; Shi et al., 1989, 1998).

The second basic mechanism for silica-induced lung damage is the activation or stimulation, by silica particles, of alveolar macrophages (after phagocytosis) and/or alveolar epithelial cells leading to (1) release of cytotoxic enzymes, ROS, reactive nitrogen species (RNS), inflammatory cytokines, and chemokines, (2) eventual cell death with the release of the silica particle, and (3) the recruitment and activation of polymorphonuclear leukocytes (PMN) and additional alveolar macrophages. The elevated production of ROS/RNS would result in oxidative stress and lung injury that stimulates alveolar macrophages and/or alveolar epithelial cells to produce growth factors and fibrogenic mediators, resulting in fibroblast activation and pulmonary fibrosis. Basically, a continuous ingestion-reingestion cycle, with cell activation and death, is established. The prolonged recruitment of macrophages and PMN causes a persistent inflammation, regarded as the primary step in the development of silicosis. ROS generated from silica particles directly or by stimulated cells that may damage the lung epithelia may also play a role in silica-induced DNA damage or cell proliferation contributing to carcinogenesis. The third basic mechanism involves negative surface charge as a significant contributor to the cytotoxicity of silica. At pH 7.4, 1 in 30 of the silanol (SiOH) groups on the silica surface exist as SiO-. Contact with the negative surface charge on the silica surface has been proposed to cause lysis of cell membranes. Binding of some metal ions (Al^{+3}, Fe^{+3}, Zn^{+3}) to ionized silanol groups on the quartz surface has been shown to neutralize this surface charge and decrease toxicity by interfering with the interaction between quartz particles and components of the cell membranes (Brown and Donaldson, 1996; Castranova, 2004; Fubini et al., 2004; Nolan et al., 1981; Shi et al., 1989, 1998).

Additional proposed mechanisms involved in silica-induced carcinogenesis include direct DNA damage, inhibition of tumor suppressor gene p53, loss of cell cycle regulation, stimulation of growth factors, and production of oncogenes. In rat models of particle-induced lung cancer, hyperplasia of alveolar type II epithelial cells has been viewed as a precursor to metaplasia and tumor formation (Brown and Donaldson, 1996; Castranova, 2004; Fubini et al., 2004; Nolan et al., 1981; Shi et al., 1989, 1998).

Castranova (2004) has reviewed the studies examining components of the proposed mechanisms by which silica exposure leads to silicosis and cancer and has summarized the findings to arrive at a description of the proposed mechanistic process. The discussion that follows is derived from this review, unless otherwise noted.

As described above, the first step in the process involves the action of the ROS that either occur on the surface of silica or that are generated by the activation of macrophages upon phagocytosis of the silica particle. These ROS cause the activation of nuclear factor κB (NF-κB), a transcription factor that controls the gene expression of chemokines, cytokines, adhesion molecules, and growth factors. Before it is activated, NF-κB is in the cytoplasm as an inactive form bound to an inhibitory protein (IκB). NF-κB is activated when IκB is phosphorylated. Silica has been shown to induce the phosphorylation of IκB and thus the activation of NF-κB. Both the phosphorylation and activation are blocked by antioxidants, suggesting that silica-induced oxidants activate

phosphorylation of IκB. It has also been demonstrated that IκB is phosphorylated by protein tyrosine kinase (PTK), and that PTK inhibitors block the silica-induced phosphorylation of IκB and the activation of NF-κB. Thus, silica-induced oxidants activate phosphorylation of IκB by PTK, which results in NF-κB activation.

Silica also induces the activity of phosphoinositide 3-kinase (PI3-kinase) in macrophages. This activation was inhibited by antioxidants, suggesting to the authors that ROS are involved. Also, the inhibition of PI3-kinase partially inhibited the silica-induced activation of NF-κB, suggesting that PI3-kinase is involved. Thus, crystalline silica particles can activate NF-κB by two routes: (1) by inducing phosphorylation of IκB, which then activates NF-κB; and (2) by inducing P13 kinase, which appears to have a role in NF-κB activation. After activation, NF-κB translocates to the nucleus where it binds to gene promoters on DNA. This binding activates transcription of mRNA, which induces translational production of chemokines, cytokines, and growth factors.

Tumor necrosis factor-α (TNF-α) is a cytokine that is thought to be a key mediator in the pathogenesis of silicosis, in particular in silica-induced inflammation and fibrosis. A direct relationship has been demonstrated between silica-induced production of TNF-α by alveolar macrophages and infiltration of inflammatory cells into the lungs (Driscoll and Guthrie, 1997). Also, mice that have been immunized with antibody to TNF-α have an attenuated increase in lung chemokine mRNA expression and a markedly reduced inflammatory response to silica exposure (Driscoll and Guthrie, 1997). The translational production of TNF-α is activated by NF-κB. It has been shown that an inhibitor of NF-κB translocation to the nucleus can decrease NF-κB binding to DNA, NF-κB activation of the TNF-α gene promoter, and TNF-α production. Nitric oxide, produced by macrophages upon stimulation by silica, may also play a role in the activation of NF-κB, and thus TNF-α. In silica-exposed mice lacking the gene for nitric oxide production, there was a decrease in the amount of TNF-α produced as well as a decrease in histological evidence of silica-induced lung damage and inflammation (Srivastava et al, 2002; Zeidler et al., 2004). The release of TNF-α appears to occur at non-cytotoxic doses of silica. This suggests that the activation of cells to produce these factors is as important as, or possibly more important than, direct cytotoxicity in the response to silica (Driscoll and Guthrie, 1997).

TNF-α itself does not act directly to attract inflammatory cells. Inflammatory cells are attracted by chemotactic cytokines called chemokines. The infiltration of inflammatory cells that results from TNF-α production appears to be related to the production of macrophage inflammatory protein (MIP-2), which is a chemokine for neutrophils. Silica exposure of rats has been shown to increase lung expression of MIP-2 as well as MIP-1α, which is a chemokine for neutrophils, macrophages, and lymphocytes (Driscoll and Guthrie, 1997). Treatment with an antibody to TNF-α has been shown to decrease MIP-2 production, inflammation, and the resulting pulmonary fibrosis. An experiment in which rats were exposed to silica by intratracheal instillation demonstrated an association between silica-induced induction of NF-κB, neutrophil recruitment, and MIP-2 production. According to Driscoll and Guthrie (1997), TNF-α (in general, not necessarily when it is a result of silica exposure) induces a number of processes that

contribute to inflammatory and immune responses including expression of adhesion molecules on endothelial cells, production of other chemokines such as interleukin-8 (IL-8) and monocyte chemotactic protein-1 (MCP-1), production of ROS by phagocytic cells, arachidonic acid metabolism (i.e., prostaglandin E2, prostacyclin), and hepatic acute phase response.

The activation of NF-κB has also been associated with an exposure-dependent increase in production of the cytokine interleukin-1 (IL-1) by the bronchoalveolar cells of rats exposed by inhalation to silica. IL-1 appears to also play an important role in the pathogenesis of silicosis. IL-1 has been demonstrated to affect inflammation in the lung by stimulating the production of chemokines and adhesion molecules (which allow for adhesion of neutrophils to vascular endothelial cells). Also, an experiment was conducted in which mice that did not have functional IL-1 (IL-1 knockout) were exposed to silica. At 1, 6, and 12 weeks post-exposure, the number and size of granulomas were dramatically decreased compared to normal mice (Srivastava et al., 2002).

Other chemotactic or inflammatory factors are also thought to influence inflammatory cell recruitment in response to silica exposure. These factors are as follows, with the cellular target in parentheses: leukotriene B4 (neutrophils), platelet activating factor (neutrophils, monocytes), complement C5a (neutrophils, monocytes) and transforming growth factor-β (monocytes) (Driscoll and Guthrie, 1997).

As discussed in Section V.B. above, epidemiological studies have shown that silicosis can develop or progress even after exposure to silica dust has ended. Porter et al. (2004, 2006) and Scabilloni et al. (2005) have examined the progression of lung inflammation and damage in rats after the cessation of silica exposure. Rats were exposed to silica by inhalation for 20, 40, or 60 days, and a portion of each group was examined for 36 days post-exposure. Inflammation, as indicated by bronchoalveolar lavage polymorphonuclear leukocytes (PMNs), increased in all groups during exposure, but remained increased in the 36-day post-exposure period in rats exposed for 40 or 60 but not 20 days. The authors concluded that in the two higher-exposure groups, recruitment of PMNs into the lung continued without further silica exposure. Fibrosis, on the other hand, was present in all exposure groups over the 36-day post-exposure period but appeared earlier in the 40- and 60-day exposure groups than in the 20-day exposure group. The observation that the PMN influx did not progress in the rats exposed for 20 days, while fibrosis did, suggested to the authors that lavagable PMNs do not predict fibrogenicity. The authors also pointed to the consistency of this finding with the lack of PMN influx seen in human chronic silicosis cases despite the progressive nature of the disease.

Porter et al. (2006) found that the severity of oxidative stress and the magnitude of the increase in lung nitric oxide, which may participate in silica-induced pulmonary inflammation, damage, and fibrosis production, also increased during the post-exposure period. Future research to determine whether the levels of the other mediators discussed above (e.g., IL-1 and/or TNF-α) also increase after cessation of silica exposure in parallel to inflammation and fibrosis was proposed (Porter et al. 2004).

As noted above, it has been proposed that ROS, either directly from silica or from activated cells, may also play a role in the carcinogenic process. Shi et al. (1998) have described general mechanisms of carcinogenesis thought to involve ROS and reviewed evidence suggesting that silica-induced carcinogenesis may also follow this pattern. According to the investigators, the general mechanisms of carcinogenesis that may result from ROS include: direct DNA damage leading to mutation (e.g. strand breaks); excessive cell proliferation involving oncogenes, cytokines such as IL-1 and TNF-α as mediators of growth and differentiation, and transcription factors such as NF-κB and activator protein 1 (AP-1,); loss of growth regulation via loss of tumor suppressor function by mutation of tumor suppressor genes, such as p53; and division of damaged cells with injury caused by lipid peroxidation products and a rise in intracellular calcium.

Shi et al. (1998) reviewed the evidence suggesting that DNA damage can be induced by silica. Silica has been shown to cause DNA strand breaks *in vitro*. This action is blocked by hydroxyl radical scavenging agents, indicating a role for ROS. Studies have demonstrated that silica binds to DNA by the formation of hydrogen bonds between the DNA phosphate backbone and silanol groups on the silica surface, thus bringing the DNA strand close to the sites of ROS production on the silica surface. It has also been demonstrated that silica, via interaction with hydroxyl radical, produces 8-hydroxydeoxyguanine—a modified DNA base important in mutagenesis and carcinogenesis.

Driscoll et al. (1997) examined mutation in rat alveolar epithelial cells. Rats were exposed to saline or saline suspensions of silica by intratracheal instillation. Fifteen months later alveolar epithelial cells were isolated from bronchoalveolar lavage (BAL) cells and cultured in 6 thioguanine-containing media to select for mutations in the *hprt* gene. Mutations were increased in alveolar epithelial cells taken from rats exposed to silica as compared to cells taken from rats exposed to saline only. In addition, to examine the role of inflammatory cells in inducing mutations, a cultured line of rat alveolar epithelial cells were exposed *in vitro* to BAL cells (macrophages and neutrophils) taken from rats exposed to silica. Mutations were caused in the cultured alveolar cells by the silica-exposed BAL cells. BAL cells enriched to have more neutrophils were more mutagenic then those enriched to have more macrophages, although both were mutagenic. When these cultured cells exposed to BAL were also treated with the antioxidant enzyme catalase, which promotes the conversion of hydrogen peroxide to water and molecular oxygen, mutation was inhibited. The authors suggested that these study results supported a role for these inflammatory cells and their cell-derived oxidants in the *in vivo* mutagenic effects of silica exposure. However, in a further study, these authors determined that there were other key factors in silica-induced alveolar epithelial cell mutagenesis in addition to the inflammatory response.

Johnston et al. (2000) exposed rats to crystalline or amorphous silica by inhalation for 13 weeks. Lung burdens for both forms of silica were similar. At the end of the 13-week exposure period, neutrophils were increased in BAL following exposure to both crystalline and amorphous silica but more so for amorphous silica. Cytotoxicity was

twice as high for amorphous as for crystalline silica. MIP-2 was also increased in both exposure groups. After a post-exposure recovery period of eight months, however, these measures remained increased in rats exposed to crystalline but not for those exposed to amorphous silica. Mutation frequency at the end of the exposure period, on the other hand, was significantly increased only with crystalline silica. Thus, genotoxic effects in alveolar epithelial cells occurred only in response to crystalline silica, despite the presence of an inflammatory response to both forms of silica. This result suggested to the authors that, in addition to an inflammatory response, particle biopersistence, solubility, and direct or indirect epithelial cell cytotoxicity may be key factors for mutation induced by crystalline silica. It should be noted that Castranova (2006, personal communication) has expressed the opinion that solubility is not critical and that, rather, amorphous silica is less toxic to alveolar macrophages and can be more readily cleared.

As noted above, Shi et al. (1998) discussed factors involved in possible mechanisms of carcinogenesis. Shi et al. (1998) identified various cytokines, such as IL-1 and TNF-α, as important mediators of growth and differentiation and transcription factors, such as NF-κB and activator protein-1 (AP-1) as being involved in the expression of and response to growth factors and oncogenes. TNF-α has been shown to act as a tumor promoter in BALB/3T3 cell transformation.

Castranova (2004) discussed AP-1 activation as controlling the production of inflammatory mediators, growth factors, and oncogenes. Activation of AP-1 has been reported to be involved in neoplastic transformation, tumor progression, and metastasis. AP-1 is composed of dimers of the protein products of individual member within the Jun and Fos immediate-early response gene families. AP-1 can bind to the TPA response elements in the promoter or 5' flanking regions of a number of target genes, such as those encoding collagenase and transforming growth factor-β, and a number of other genes involved in both inflammation and carcinogenesis. Silica-induced activation of AP-1 has been reported in rat lung type II epithelial cells, mouse epidermal cells, and macrophages.

As for other activations induced by silica, oxidants also appear to play a role in activation of AP-1. The signaling pathway appears to begin with the ROS-induction of the translocation of protein kinase C (PKC) from the cytosol to the cell membrane (Ding et al., 2006). The subsequent phosphorylation of mitogen-activated protein kinase (MAPK) family members is PKC-dependent. The MAPK family members undergoing phosphorylation are p38 and extracellular signal-related protein kinases (ERKs). Inhibition of PKC has been shown to decrease silica-induced phosphorylation of ERKs and p38 as well as inhibit silica-induced AP-1 activation. Direct inhibition of ERKs and p38 also directly inhibits silica-induced AP-1 activation.

The p53 tumor suppressor gene is believed to act by preventing the passage of genetic lesions in cells with DNA damage to a new generation of cells (Shi et al., 1998). It does this by upregulating the expression of several genes that control growth inhibitory and apoptotic (controlled cell death) pathways. Mutational inactivation of p53 is a frequent alteration seen in human cancers. Studies have shown that ROS can also damage p53. Liu et al. (2000) have studied p53 and K-ras genes in lung cancer patients

with silicosis to evaluate whether p53 and K-ras mutations were correlated with occupational silica dust exposure. Ras gene products are proteins that bind guanine nucleotides with high affinity and are involved in signal transduction pathways in many cell types. K-ras is a commonly activated oncogene in human lung cancer with predominant structure alterations of the 12^{th} codon. The study examined p53 and K-ras mutations in primary lung cancers in 36 workers occupationally exposed to crystalline silica and who had silicosis. It was observed that the majority of p53 gene mutations clustered on exon 8—a pattern distinct from that for non-occupational lung cancer. Also, the p53 mutation incidence distributions among histological lung cancer types (small cell vs. adenocarcinoma) differed from that for non-occupational lung cancer. For K-ras, it was noted that in common lung adenocarcinoma, such as is seen in smokers, K-ras mutations are detected in 30 percent of cases. Mutational activation occurs primarily in codon 12 of the K-ras gene (in 70-100 percent of total mutations). This is true for both Europeans and Chinese. In contrast, in the workers studied, no mutations were detected in codon 12. Instead mutations were found in codons 7, 15, 20, and 21 and were clustered in 15. Also, the spectrum of base substitutions was G to C in these workers as opposed to G to T in non-occupational lung cancer. The authors noted that mutations with lung cancer caused by smoking differ from those that develop in response to defined chemicals (e.g., as seen in uranium miners). The authors concluded that the unusual pattern of p53 and K-ras mutations may serve as molecular evidence of silica as a "special" human carcinogen. They also concluded that their findings support a carcinogenic effect of silica at the DNA molecular level.

I.F.1.a. Relationship between silicosis and lung cancer.

As described above, the early steps in the proposed pathways that lead to silicosis and lung cancer seem to share some common features. This, among other things, has led some researchers to suggest that silicosis is a necessary prerequisite to developing lung cancer in silica-exposed individuals. According to Castranova (2004), ROS generated directly from the silica surface and/or during phagocytosis of those particles seem to trigger critical signaling events for both NF-κB and AP-1 activation. Therefore, oxidative stress has been proposed to play a key role in the pathogenesis of silicosis and silica-induced lung cancer. Driscoll and Guthrie (1997) pointed out that there is limited evidence for a direct genotoxic effect of silica. They suggested that any increased lung cancer risk associated with silica may be a consequence of the inflammation and increased epithelial cell proliferation associated with the development of silicosis.

According to these authors, ROS released from inflammatory cells could damage DNA, representing a potential indirect mechanism by which silica exposure could result in damage to DNA. The increased epithelial cell proliferation associated with silica exposure was also noted as a possible contributor to increased lung cancer risk. This is because increased cell proliferation may increase the probability that a spontaneous genetic error or a genotoxic effect from ROS would be fixed in a proliferating cell and be clonally expanded. However, as discussed above, Driscoll and Guthrie (1997) completed a further study and determined that there were other key factors in silica-induced alveolar

epithelial cell mutagenesis in addition to the inflammatory response (Johnston et al., 2000).

A review of epidemiologic studies has also attempted to answer the question of whether silicosis is a necessary precursor of lung cancer in silica-exposed individuals. (See also Section I.C.4) Checkoway and Franzblau (2000) reviewed 17 studies of lung cancer mortality among silicotics. Although they found that the association between silica exposure and lung cancer was generally stronger among silicotics than non-silicotics, there were a number of issues that they believed complicated the analysis. One issue was the relative insensitivity of chest radiographs that might have resulted in underascertainment of silicosis cases. Also, for most studies, researchers did not have access to serial radiographs over a worker's lifetime, thus making it difficult to determine the temporal relationship between silicosis and lung cancer. One of the studies (Checkoway et al., 1999) appeared to show evidence of an exposure-response relationship for lung cancer with cumulative silica exposure among workers without radiographic evidence of silicosis. However, in that study, there was a shorter interval between date of hire and date of final radiograph in non-silicotics compared to silicotics, providing another occasion for underascertainment of cases.

Perhaps the biggest issue is the strong correlation between exposure and silicosis, suggesting that silicosis may be functioning as a marker for silica exposure, which is, in turn, also correlated with lung cancer risk. Checkoway and Franzblau (2000) believed that the best information on this question would be derived from well-designed animal studies. They concluded that the question of whether silicosis is required for elevated lung cancer risk in silica-exposed individuals is "virtually unanswerable" from currently available epidemiologic literature, and is unlikely to be addressable in future epidemiologic studies. Finally, the authors concluded that risk assessments should consider silicosis and lung cancer in silica-exposed individuals as separate entities whose cause/effect relations are not necessarily linked.

I.F.2. Toxicity of Crystalline Polymorphs.

Most studies of crystalline silica toxicity concern quartz, which is the predominant crystalline form involved in occupational settings. Other major polymorphs of crystalline silica occur less frequently and include cristobalite and tridymite. Early animal studies appeared to suggest that the crystalline polymorphs cristobalite and tridymite were more toxic to the lung than quartz. The earliest animal study (Gardner, 1938) showed that experimental animals injected with cristobalite showed a more severe response than that produced by quartz and that the resulting fibrosis that followed was diffuse rather than nodular. King et al. (1953), who exposed rats by single intratracheal injection to quartz, cristobalite, or tridymite, confirmed the earlier study and described the action of cristobalite as "perhaps slightly faster than quartz," and tridymite as having a "spectacular" fibrotic effect.

Another study with rats also demonstrated significantly more tumors in rats treated with tridymite as compared with those treated with cristobalite or quartz (Wagner

et al., 1980). In this study, groups of 32 rats were treated by single intrapleural injection with tridymite, cristobalite, or one of four different types of quartz. The rats were then allowed to live until natural death, at which time they were examined for the occurrence of malignant lymphomas of histiocytic type (MLHT). The numbers of tumors in each group of 32 rats were as follows: tridymite, 16; Min-U-Sil (quartz), 11; D&D (quartz), 8; Snowit (quartz), 8; DQ12 (quartz), 5; cristobalite, 4; and saline control, 0. These differences were statistically significant ($p < 0.01$). These results were in contrast to a previous similar experiment (Wagner, 1976) in which cristobalite was found to be the most carcinogenic. However, a further analysis (Wagner et al. 1980) showed that the discrepancy did not reflect a difference between the two experiments in the carcinogenicity of cristobalite, but rather that Min-U-Sil and Snowit proved more carcinogenic in Wagner et al. (1980). *In vitro* cytotoxicity to mouse peritoneal macrophages was also examined with the polymorphs and quartz samples (Wagner et al., 1980). There was a correlation between this cytotoxicity and the rat tumor potency, except for DQ12. The authors suggested that cristobalite may have shown little *in vitro* cytotoxicity because it is relatively unstable. They also thought that since tridymite is a "denser" particle and thus of smaller particle size and greater surface area than cristobalite, differences in surface area and perhaps surface charge might have accounted for its higher toxicity.

Hemenway et al. (1990) examined the comparative clearance, from rat lungs, of quartz from two sources and pure cristobalite. Clearance kinetics and biological response were determined after short-term exposure. The clearance of cristobalite was much less than either of the quartz samples. There was little or no clearance of cristobalite after the first 30-day post-exposure period. Cristobalite also exhibited the greatest cellular biological response. The response was early and sustained as evidenced by elevated numbers of macrophages, neutrophils, and lymphocytes in bronchoalveolar lavage through 180 days post-exposure. One quartz sample showed a response of about 30 percent that of cristobalite, while the response of the other quartz sample was no different from control.

Jakab and Hemenway (1992) examined the interaction of quartz or cristobalite with influenza virus infection (also known to cause pulmonary fibrosis) in mice. Mice were intratracheally instilled with quartz or cristobalite followed three days later by infection with influenza by aerosol inhalation. Several parameters indicative of pulmonary reaction were examined at 30, 60, and 90 days after infection. In mice that were not infected with influenza virus, cristobalite caused more of a fibrotic reaction than quartz. The influenza infection increased the fibrogenic response to both forms of silica suggesting that the response was additive.

Fubini et al. (1995) explored altered surface physicochemical properties of several polymorphs in an effort to examine their implications for biological responses. Building on the observation that freshly ground silicas have shown a higher degree of toxicity than aged particles and that this phenomenon has been attributed to the presence of reactive radicals on the newly cut surfaces (see section below for further discussion of this issue), the authors compared the amount of surface radicals for several silica polymorphs after a

very mild grinding in a ball mill. The overall number of surface radicals after grinding was higher for cristobalite than for quartz.

Warheit et al. (1995) compared pulmonary responses in rats after short-term (3 days) inhalation exposure to cristobalite or quartz. Indices studied were measures of pulmonary inflammation and cytotoxicity. Inflammation was increased over controls in animals exposed to both cristobalite and quartz ($p < 0.05$). The inflammatory reaction at 30 days post-exposure appeared greater for exposure to cristobalite than quartz. At 90 days, this difference was much smaller and not statistically significant. Indices of cytotoxicity were much greater for cristobalite than for quartz at both time periods. For example, bronchoalveolar lavage levels of lactate dehydrogenase at 90 days post-exposure were elevated 12-fold for cristobalite and 4-fold for quartz. The authors also cited a previous study (Hemenway et al., 1986) in which rats were exposed for 8 days to aerosols of cristobalite, quartz, or amorphous silica. Cristobalite caused the most lung injury, causing substantial inflammation and fibrosis. Quartz produced intermediate effects and amorphous silica produced minimal effects.

DNA strand breakage, production of thymine glycol (a DNA damage product of oxidative mutagens) and hydroxyl radical generation induced *in vitro* by cristobalite, tridymite, or several different quartz samples was studied by Daniel et al. (1995). The relative order of the different polymorphs and quartz samples in assays for oxygen consumption and hydroxyl radical production differed from the order in which they caused DNA strand breakage or altered thymine glycol production. Cristobalite, tridymite, and some of the quartz samples showed stronger activity in some assays but less activity in others. The cristobalite sample exhibited rapid molecular oxygen consumption and was the most active sample when hydrogen peroxide was used in the assay but was less active than some quartz samples when hydrogen peroxide was omitted. Cristobalite showed less ability to generate hydroxyl radicals from hydrogen peroxide compared to the quartz samples. This suggested to the authors that the different polymorphs may vary with respect to the mechanisms by which they generate oxygen radicals and thereby damage DNA. However, the authors drew no conclusions concerning relative potency of the polymorphs, but rather concluded that the mechanisms of crystalline silica carcinogenesis needed to be further investigated in relation to the underlying physicochemical characteristics.

In contrast to the studies discussed above, several authors have concluded that cristobalite and tridymite are not more potent than quartz in their toxicities. Guthrie and Heaney (1995) reviewed studies examining mineralogical characteristics of silica polymorphs in relation to their pathogenic effects. In their opinion, tridymite and cristobalite generally appeared to have pathogenic effects comparable to quartz. Bolsaitis and Wallace (1996) reviewed studies showing the effect of different polymorphs on hemolytic activity and on inflammation and fibrosis in mouse lungs induced by quartz, cristobalite, or tridymite. The results showed that hemolytic activities were within the range of experimental error and development of lung fibrosis was essentially the same among the three polymorphs. In noting that the mechanisms of action and particle characteristics that cause silicosis and other silica-related diseases have not been

precisely defined, NIOSH (2002) determined that additional research was needed, including further *in vivo* and *in vitro* studies on the pathogenicity and toxicity of quartz compared to its polymorphs.

A difference in toxicity between cristobalite and quartz has not been observed in epidemiologic studies. (Exposure to tridymite has not been the subject of epidemiologic study.) In some workplaces, such as ceramics, pottery, or brick manufacture, exposure may involve more than one polymorph. In such cases, epidemiologic studies have not usually identified specific exposure to quartz or cristobalite. Therefore, excess lung cancer mortality observed in these studies cannot be attributed to a specific polymorph but only to crystalline silica in general (NIOSH, 2002).

IARC (1997) also addressed whether there were possible differences in carcinogenic potential among polymorphs. Among the studies considered by IARC (and reviewed in Section V.C above), most studies were of populations principally exposed to quartz. Only the study of U.S. diatomaceous earth workers (Checkoway et al., 1997) examined workers exposed predominantly to cristobalite. The IARC Working Group concluded that although there were some indications that cancer risks varied by type of industry and process in a manner suggestive of polymorph-specific hazards, available data did not permit differentiation of the cancer hazard between quartz and cristobalite. In their study of diatomaceous earth workers, whose predominant exposure was to cristobalite, Rice et al. (2001) reiterated that differential polymorph toxicity had not been confirmed by results of epidemiological studies. However, citing results from studies of pottery workers, they also believed that there may be some evidence of increased mortality from lung cancer among workers in industries with high-temperature processes. These authors concluded that differences in the carcinogenic potential of various crystalline silica polymorphs have not been established and therefore cancer risks from workplace exposure to crystalline silica cannot yet be attributed or limited to a particular polymorph. Steenland et al. (2001a) further addressed this issue and found that the exposure-response trends observed within the diatomaceous earth cohort did not differ notably from those derived from other studies involving exposure to quartz.

OSHA preliminarily concludes, based on epidemiologic and experimental evidence, that the crystalline silica polymorphs quartz, cristobalite, and tridymite have similar toxicity and carcinogenic potency.

I.F.3. Freshly Fractured vs. Aged Silica.

When crystalline silica is subjected to high energy forces, as occurs in work processes such as abrasive blasting, rock drilling, tunneling, stone carving and the production of silica flour, it is said to be “freshly fractured.” Silica that is not fractured by the work process is said to be “aged.” For example, workers in the glass industry and those who work with paint fillers do not work in processes that fracture silica particles. A number of studies have examined the question of whether freshly fractured silica is more toxic than aged silica. It has been noted that acute silicosis is typically associated

with the generation of freshly fractured silica dust in these occupations (Castranova et al., 1996). Studies addressing these issues are described in this section.

I.F.3.a. *In vitro* studies.

The surfaces of freshly fractured silica particles have a greater number of silicon ($Si^{\bullet}$) and siloxyl ($SiO^{\bullet}$) radicals than do those of aged silica. After four weeks, silica stored in air will still have 20 percent of the surface-free radicals that were present immediately after grinding. These free radicals can react with water to form hydroxyl radicals through the production of hydrogen peroxide (H_2O_2) (Shi et al., 1989).

Early *in vitro* studies demonstrated that freshly fractured silica caused more cytotoxicity in cells than did aged silica. The significantly increased cytotoxicity of freshly fractured silica over aged was evidenced by a decrease in cell membrane integrity as measured by induction of lipid peroxidation (three-fold), an increase in release of lactate dehydrogenase from macrophages (1.5-fold), and an increase in hemolytic activity (36-fold) (Vallyathan et al., 1988).

Studies have also demonstrated that freshly fractured silica has an increased ability to activate respiratory bursts in alveolar macrophages. During the respiratory burst, the macrophage produces superoxide anion (O_2^-), which is then converted to hydrogen peroxide (H_2O_2). Respiratory bursts in macrophages after *in vitro* exposure were monitored by measuring superoxide anion, hydrogen peroxide secretion and nitro blue tetrazolium (NBT) reduction to formazan. Superoxide secretion decreased by 16 percent and 27 percent after storage of ground silica for 24 and 96 hours, respectively. Hydrogen peroxide secretion decreased by 65 percent after 24 hours of storage. After 48 hours, NBT reduction was 39 percent as compared to 69 percent immediately after grinding (Shi et al., 1989).

Vallyathan et al. (1988) noted that silica aged for years still retained the ability to stimulate alveolar macrophages, decrease membrane integrity, and cause lipid peroxidation, suggesting that silicon-based ROS on the crystalline surfaces can only partly explain the biologic reactivity of silica. They found that substances, such as superoxide dismutase, that blocked the activity of ROS were only partially effective in decreasing lysis. In contrast, there was a significant or complete inhibition of H_2O_2 release and lipid peroxidation by several hydroxyl scavengers. The authors suggested that the ability of these scavengers to inhibit the freshly fractured silica-induced lipid peroxidation and H_2O_2 release provided evidence of a direct correlation between hydroxyl radical generation and cellular injury. These authors suggested that freshly fractured silica is more potent due to surface formation of newly generated silicon-based radicals as well as the propagation of other oxygenated radicals in aqueous environments. They suggested that these radicals plus the ones generated by macrophages may overwhelm the cell's defense mechanisms. They also proposed that these mechanisms should be viewed as particularly relevant to the pathogenesis of acute silicosis.

In a further study of the increased activity of freshly fractured silica, Vallyathan et al. (1992) demonstrated that the biological reactivity of silica was reduced when it was coated with an organosilane material. In this study, the cytotoxicity of freshly fractured and aged silica to macrophages was determined by measuring membrane integrity. Freshly fractured silica was 4.2-fold more potent in decreasing membrane integrity than aged silica. The ability of silica to activate macrophages was measured by the secretion of hydrogen peroxide or the generation of chemiluminescence (reactive species react with a light-emitting probe and the light is detected with a luminometer*)*. Freshly fractured silica was 50 percent more potent than aged silica in inducing hydrogen peroxide secretion and 4.6-fold more potent in stimulating chemiluminescence. When freshly fractured silica was coated with the organosilane, its cytoxicity to macrophages was decreased by 53 percent for a one-hour exposure and 73 percent for a five-hour exposure. Also, chemiluminescence generated from silica-exposed macrophages was decreased by 58 percent when the silica particles were coated. The authors concluded that these findings suggest that surface radicals may be an important factor in the induction of disease by silica.

The generation of free radicals from macrophages and polymorphonuclear leukocytes (PMN) upon induction of the respiratory burst by silica has also been directly measured by electron spin resonance (Vallyathan et al., 1992). Freshly fractured silica induced an enhanced radical generation with an increased dose of silica. Silica aged for 14 days induced a weaker radical generation response.

Elias et al. (2000) studied the cytotoxic and transforming potencies of various silica samples on Syrian hamster embryo cells. Upon grinding in a wet atmosphere, the cytotoxic and transforming potencies of quartz particles were greatly reduced compared to those of the quartz that was dry-ground. The authors concluded that wet grinding resulted in the amorphization of the external layers of the quartz particles. Thus, the surface functionalities (such as silanol patches and iron sites active in ROS generation) involved in the induction of cytotoxicity were deactivated.

I.F.3.b. *In vivo* studies.

Several *in vivo* studies have also been done to compare the effects of freshly fractured and aged silica. Vallyathan et al. (1995) (also reported in Shoemaker et al., 1995) exposed rats to an average of 20 mg/m^3 freshly fractured or aged silica for 2 weeks by inhalation. Biochemical and pathological changes in the lavagate (fluid used to wash out the lungs) and lungs were examined.

In exposed rats, there were increases in the total number of cells, red blood cells (indicative of damage at the alveolar blood-air barrier level) and lymphocytes and neutrophils (indicative of an inflammatory response) found in the lavagate. These increases were significantly greater ($p < 0.05$) in the rats exposed to freshly fractured as compared to aged silica. Histopathology done on the lungs confirmed the findings of inflammation. As with the lavagate, the changes found were significantly increased ($p < 0.05$) in those exposed to freshly fractured as compared to aged silica. Similarly, lipid

peroxidation was significantly increased ($p < 0.05$) (indicative of damage at the membrane level). The fluid of the lavagate from rats exposed to freshly fractured silica also had significantly more albumin and protein (indicative of damage at the alveolar blood-air barrier) and β-*N*-acetyl glucosaminidase (indicative of damage at the cell level) than that from those exposed to aged silica ($p < 0.05$). Cells in the lavagate showed significantly greater biochemical changes (due to membrane injury, disruption of the integrity of lysosomes and increased production of ROS) in the rats that had been exposed to freshly fractured as compared to aged silica ($p < 0.05$), which, in turn, produced a significantly greater response as compared to controls ($p < 0.05$). The authors suggested that this was probably because quartz causes persistent acute biologic toxicity in the lung by repeated cycles of phagocytosis and macrophage injury.

This study also demonstrated that there was a decrease in antioxidant defense indices in animals exposed to freshly fractured, as compared to aged silica. The authors suggested that their study results indicated that the pulmonary reactions of rats to short-duration exposure to freshly fractured silica mimic those seen in acute silicosis in humans. These reactions in the rat include inflammation, blood-air barrier damage, activation and generation of ROS by pulmonary phagocytes, and increased lipid peroxidation. The authors cited studies of human acute silicosis which have demonstrated increases of phospholipid and inflammatory cells in lavage fluid, damage to the blood-alveolar air barrier, and activation of oxidant production by pulmonary phagocytes (Goodman et al., 1992).

In a follow-up to this study, the investigators altered the level of iron contamination of the freshly fractured silica (Castranova et al., 1997). As discussed above, surface radicals on freshly fractured silica are thought to generate hydroxyl radicals upon contact with water. Since iron chelation reduces the number of hydroxyl radicals on the particle surface, it was thought that trace contamination of silica with ferrous iron could enhance hydroxyl radical generation via a Fenton-like reaction. The finding that both the production of hydroxyl radicals and silica-induced biological reactions decrease in a similar fashion with time after fracturing suggested that a relationship exists between hydroxyl radical generation and toxicity. Thus, the investigators believed that trace contamination with iron would increase the pulmonary responses to inhaled silica.

In this study, animals were exposed as in the previous study but low- and high-iron contamination of the silica was accomplished by altering the length of the polyethylene delivery tube of the stainless steel screw feeder. The iron contamination was correlated with length of contact time of the silica with the stainless steel before going into the mill. The study found that silica with high-iron contamination produced more reactive species than did silica with low-iron contamination. Pulmonary responses were also increased with the high- vs low-iron silica. Silica with high-iron contamination produced significantly more damage to the alveolar air-blood barrier, more inflammation, increased macrophage activity, and a greater level of lipid peroxidation in the lung tissues. The authors concluded that the results support the hypothesis that trace iron contamination can augment the generation of oxidants by silica and enhance its

inflammatory and cytotoxic potency in the lung. They suggested that trace contamination of silica with iron may occur in occupational circumstances such as rock drilling and sandblasting, leading to increased lung damage and inflammation in workers in these occupations.

Interestingly, Vallyathan and Shi (1997) have noted that chemical etching of silica particles with hydrochloric acid to remove metal ion impurities and reactive centers that were created by fracturing the particle surface resulted in markedly diminished ability to cause DNA double strand breakage *in vitro*. They also noted that these *in vivo* studies agree with the *in vitro* studies that confirm the presence of reactive sites on the surface of freshly fractured silica and the significant role they may play in the pathogenesis of acute silicosis.

In a recent study, Porter et al. (2002) compared low doses of aged and freshly fractured silica on pulmonary inflammation and damage in rats. In this study rats were treated by intratracheal instillation with either vehicle, aged, or freshly fractured silica, at a dose of either 5 or 20 μg once a week for 12 weeks (for a total of 60 and 240 μg silica). These doses were chosen to approximate human exposures of between 270 and 1,000 $\mu g/m^3$, 8 hr/day, 6 days/week for 10 years, which are in the range of mean 8-hour time-weighted-average levels of respirable quartz (340 to 490 $\mu g/m^3$) reported for high wall drillers, bulldozer operators and back fillers in U.S. surface mines. These estimates of equivalent human exposures were made with the following assumptions: (1) total ventilation in a person performing light work is approximately 10 m^3/8-hour work day, (2) alveolar deposition in humans of inspired particles 1 μm in aerodynamic diameter is approximately 20 percent, (3) the ratio of alveolar surface area in humans versus rats is approximately 255, and (4) adjusted for lifespan, 12 weeks in the rat is approximately equivalent to 10 years for humans. Exposure to 60 μg silica caused the same inflammatory response and alveolar macrophage activation whether the silica was aged or freshly fractured. However, at the 240 μg dose, freshly fractured silica was significantly more potent ($p \leq 0.05$) than aged silica in stimulating the activation of alveolar macrophages, but the amount of pulmonary damage did not differ between aged and freshly fractured silica. These results showed that silica induced pulmonary inflammation in rats at levels much lower than had previously been demonstrated. The authors suggested that the difference in potency between aged and freshly fractured silica is apparent only after a threshold lung burden of silica is reached.

I.F.3.c. Human studies.

A few human studies with workers presumed to be exposed to freshly fractured silica have demonstrated similar effects to those seen in animal studies. Goodman et al. (1992) studied a worker with acute silicosis who had worked as a rock driller at a quarry and also at surface coal mines. Although much of his work in the past had been done with a wet process in which water was applied to reduce dust generation, in the period just prior to getting acute silicosis, he had worked primarily as a driller at a surface coal mine using a dry process. The worker had described the dust during this dry drilling as being so dense that he “couldn’t see anything.” Similar to results seen in animals

exposed to silica, bronchoalveolar cells from this worker exhibited an increased level of activity (as measured by resting and stimulated chemiluminescence) as compared to those observed in individuals without histories of occupational dust exposure.

Castranova et al. (1998) demonstrated that in rats, exposure to silica by intratracheal instillation or by inhalation results in an increase in levels of mRNA for inducible nitric oxide synthase in bronchoalveolar lavage cells, elevated nitric oxide production by bronchoalveolar lavage cells, and an increase in nitric oxide-dependent chemiluminescence from alveolar macrophages. Freshly fractured silica was a more potent stimulant of nitric oxide-dependent chemiluminescence than aged silica. These authors also compared similar endpoints in a healthy volunteer, a silica-exposed coal miner with a normal chest x-ray, and a silica-exposed miner with an abnormal chest x-ray with an ILO reading of 1/0. There was some mRNA for inducible nitric oxide synthase in the bronchoalveolar lavage cells of the miner with the normal chest x-ray. However, there was much more in the cells of the miner with the abnormal chest x-ray. There was also more nitric oxide-dependent chemiluminescence seen in cells from the miner with the abnormal chest x-ray compared to the miner with the normal x-ray. For the miner with the normal x-ray, both of these endpoints were increased above control.

I.F.3.d. Discussion and conclusions.

Many animal and *in vitro* studies have demonstrated that crystalline silica that is freshly fractured in the laboratory shows greater biological activity than aged silica. A few studies have demonstrated similar inflammatory and cellular effects in workers whose jobs result in exposure to freshly fractured silica and experimental animals exposed to freshly fractured silica.

In the studies described above, silica was fractured by several different methods, such as crushing or grinding in an agate mortar and pestle or generating in an air jet mill fitted with a polyurethane liner and stainless steel jets. However, it has been reported that the toxicity of silica can be changed according to the method of preparation. Shi et al. (1989) found that the toxicity of quartz particles increased when the sample was ground in a mill rather than in a press and suggested that after crushing in a press, the particle has a smooth surface, while the milled particle has sharp edges and a larger surface area. Thus, it appears that the methods used to generate fractured surfaces can affect toxicity by alteration of surface characteristics. Occupational exposure to freshly fractured silica can occur in many different work processes. However, there is insufficient information available at this time on the surface characteristics of the freshly fractured silica generated in these varied work processes to enable a process-specific characterization of the potential toxicity of the silica to which workers are exposed.

I.F.4. Metal Impurities/Clay Encapsulation.

Metal impurities can also modify the surface reactivity of silica (IARC, 1997). Iron, depending on the quantity and ionic state, has been shown to either enhance or decrease the toxicity of crystalline silica. Aluminum has been shown to reduce the

toxicity of silica in several studies. Another physical factor relevant to the toxicologic potency of silica is the presence of a mineral coating, or "occlusion" of the silica surface, which may affect the biological availability of the quartz component of the dust. Research has suggested that contaminants on the surface, such as aluminosilicate clay, may diminish the biological availability of surface active sites affecting toxicity by gross occlusion of the silica surface. It is thought that contamination by this clay may leave aluminum ions at the abraded quartz surface and that this may be the mechanism of action for inhibition of silica toxicity. There have also been a number of studies of the effect on toxicity of coating silica with non-naturally occurring materials, such as polyvinylpyridine-N-oxide (e.g., Albrecht et al., 2004; Knaapen et al., 2002; Schins et al., 2002). This topic will not be discussed here. Studies of the effect on silica toxicity of iron, aluminum, other metal contaminants, and occlusion with aluminosilicate clay will be discussed below.

There have been a number of studies in which the presence of iron was shown to enhance the toxicity of crystalline silica. For example, as described above, Castranova et al. (1997) altered the level of iron contamination of freshly-fractured silica and demonstrated that trace iron contamination augmented the generation of oxidants by silica and enhanced its inflammatory and cytotoxic potency in the lung. This finding led the authors to suggest that trace contamination of silica with iron may occur in occupational circumstances, such as rock drilling and sandblasting, leading to increased lung damage and inflammation in workers in these occupations.

Donaldson and Borm (1998) and Fubini (1998) reviewed studies on the effect of iron on the toxicity of silica (quartz). They reported that in contrast to the findings described above, other studies have shown that iron can reduce the toxicity of quartz. Iron salts have been shown to protect against quartz-mediated damage to erythrocyte membranes. One study found that metallic iron diminished the ability of quartz to cause inflammation in the lungs of rats, measured as the mean number of neutrophils in the bronchoalveolar lavage (BAL) 7 days following instillation. Donaldson and Borm (1998) pointed out, however, that the ionic state of iron may be important. Contamination with ferrous or ferric iron, as opposed to metallic iron, was involved in the Castranova et al. (1997) study showing increased toxicity. This may be due to the generation by ferrous or ferric iron of Fenton-derived hydroxyl radicals on the silica particle surfaces, which would increase oxidative stress. The quantity of iron may also be important, with trace amounts increasing toxicity by assisting ROS generation, and large excesses decreasing toxicity by detoxifying the surface of silica particles. The authors concluded that further research would be needed to fully understand the phenomenon.

Fubini (1998) discussed the possible role of physicochemical factors in the sequence of events leading to silicosis and silicosis-induced cancer. Trace amounts of iron, which are very common in mineral samples, are thought to lead to the prolonged generation of Fenton chemistry-derived hydroxyl radicals which can cause DNA damage and induce transformation in epithelial cells, resulting in cancer. Fubini (1998) stressed that this effect does not usually relate to the actual amount of iron but to small fractions with particular redox and coordination states.

In reviewing other studies of the effects of iron, Fubini (1998) noted that iron-contamination is probably responsible for the pathogenic effects of crystalline silica of biogenic origin such as diatomaceous earth that becomes cristobalite upon heating. Iron is always present in these kinds of materials formed from living matter. Fubini (1998) cited other studies as demonstrating iron enhanced toxicity. For example, Saffiotti and Ahmed (1995) found that iron ions increased silica-induced cell-free damage as well as DNA damage and cell transformation. On the other hand, Nolan et al. (1981) demonstrated that iron reduced silica-induced cytotoxicity and membranolysis *in vitro*, probably by surface modification of silanols. Other studies cited by Fubini (1998) on the protective effects of iron include decreased silica-induced *in vitro* cytotoxicity and membranolysis and DNA damage and transformation in cells by a bulk iron oxide (hematite) mixed with quartz (Saffiotti and Ahmed, 1995) as well as reduced *in vivo* inflammation and fibrosis by metallic iron (Cullen et al., 1997). Fubini (1998) suggested that the latter result (Cullen et al., 1997) may be due to reduction of surface sites or the annealing of radicals.

As an additional point of information, Fubini (1998) noted that, among epidemiologic studies not finding increased cancer mortality (as reported in IARC, 1997), the sources of quartz are all from metal mines—gold, zinc, and tungsten. Fubini (1998) suggested that contact of the quartz with metals that are reducing agents could have modified the nature of the silica surface sites that otherwise are involved in the carcinogenic mechanism. A possible explanation is that such metals assist the annealing of surface radicals, thus eliminating particle-generated ROS, reducing the oxidative stress, and thus reducing damage to epithelial cells. Another possibility suggested is that metal-ion binding to silanols reduces membranolysis and cytotoxicity, which would favor clearance of silica particles.

Elias et al. (2000) examined the cytotoxic and transforming effects of silica particles with regard to various surface properties. The assay used was the Syrian hamster embryo (SHE) cell transformation assay, which is used as an appropriate *in vitro* model for screening for tumorigenic potential. Several different silica samples were used, including two quartz and three cristobalite samples. Cytotoxic and transforming potencies of the various silica samples were related to the composition and structure of surface functionalities. Specifically, the cytotoxic effects were related to the distribution and number of silanol groups and to the presence of trace amounts of iron on the surface. SHE cell transformation was induced by silica particles with iron-active sites that were able to generate ROS. Furthermore, it was determined that redox activity of the surface iron sites was different among the silica samples, likely dependent on the organization of the surface silanols and whether the surface silanols were isolated or in pairs. The different transforming potencies of trace iron-contaminated silica samples could be partially explained by the different potentials of surface iron to play a role in ROS generation.

The investigators then continued and expanded this line of research using the SHE cell transformation assay. Fubini et al. (2001) compared the cytotoxicity and

transforming potency of a series of different silica samples, all derived from the same original batch of Min-U-Sil. Each original sample was treated differently in order to generate a collection of samples, each of which differed in one physicochemical property that was being evaluated for its ability to inhibit or enhance the cytotoxic and transforming potency. Modification of surface iron content was accomplished by either treating the sample with deferoxamine, which extracts free iron, or enriching the sample with iron. The sample treated with deferoxamine showed a large decrease in, but not the elimination of, hydroxyl radicals and cytoxicity. Cellular transforming potency was decreased in a dose-related fashion as compared to the original quartz at the same doses. This result suggested to Fubini et al. (2001) that intrinsic iron was involved in the induction of cell transformation. It has also been suggested that this effect could be due to neutralization of surface charge (Castranova, personal communication, 2006). The sample enriched with iron also greatly decreased hydroxyl radical yield and the cell-transforming potency compared to the unmodified quartz. These results suggested to the authors that not all iron at the silica surface is active in free radical release but that only some isolated iron ions that are bound to the crystal lattice in a particular redox and coordination state are active. Also, a silica surface fully covered with iron exhibits an opposite effect of a silica surface with only trace amounts of iron.

The roles of iron and free radical generation in silica toxicity were further explored by Fenoglio et al. (2001). Three different samples of quartz were tested. One was Min-U-Sil, which contained trace levels of iron. Another was a sample of pure quartz dust, obtained from quartz chips that were purified by melting and ground in an agate mortar. The last sample was the Min-U-Sil treated with deferroxamine to remove iron. Two radical generating mechanisms, hydroxyl radical from hydrogen peroxide and cleavage of a C-H bond, were studied. The untreated Min-U-Sil was the most active, because it contained traces of iron, followed by the Min-U-Sil sample treated with deferroxamine and then the pure quartz. These results suggested to the authors that there were active sites other than iron but that at the active iron sites, the iron speciates at the surface giving rise to two kinds of surface centers where ROS is produced. The authors believed that iron speciation was one of the possible causes of the variability seen in the toxicities of silica samples of different origin. It has also been suggested that the temperature used in producing the quartz chips for this study could have deformed the crystalline surface, thus decreasing toxicity (Castranova, personal communication, 2006).

In another investigation (Clouter et al., 2001; Donaldson et al., 2001), actual workplace quartz samples were compared to a standard research quartz sample (DQ12) for their ability to damage erythrocyte membranes *in vitro* (as a measure of the direct reactivity of the quartz surface), cause inflammation following instillation into rat lung (as measured by total cells, PMN, protein, and LDH in the BAL fluid), and generate hydroxyl radicals. One workplace sample labeled OM, as described by Clouter et al. (2001), represented sand that was produced from medium-hard sandstone, crushed, processed, and then milled in a rotary ball mill to produce silica flour. Another workplace sample, labeled RH1, was from a similar site location although the feedstock to the plant was a soft, loosely consolidated sand where no crushing was required to produce the sand product and the only grain breakage was due to the milling circuit.

Although iron was present at a concentration of less than 0.5% in the samples, RH1 released 10 times more iron than either the other workplace sample or the DQ12 in both acid and neutral pH environments. The authors hypothesized that workplace sample RH1 would cause the most damage in the toxicity assays if iron played a role in mediating the toxicity of quartz. However, that did not turn out to be the case. Only the DQ12 sample caused significant erythrocyte membrane damage and lung inflammation in rats. There was also no relationship between the ability to release iron and the ability to generate free radicals. In fact, both workplace samples showed a greater ability to generate hydroxyl radicals than DQ12. Also, the ability of any sample to generate hydroxyl radicals was not predictive of the ability to cause hemolysis or lung inflammation. The authors concluded that workplace quartz species can be substantially less biologically active than standard quartz (DQ12) and that releasable iron was not a factor in this activity.

Fenoglio et al. (2003) examined the role of cysteine (CYS) and glutathione (GSH) in silica toxicity. GSH is essential for the protection of cells against oxidative stress. When it is depleted by a toxic substance such as quartz, nearby cells may be damaged. The quartz-induced depletion of GSH as well as the depletion of CYS are due to the oxidation of their thiol groups by a radical mechanism triggered by Fe(III) ions trapped on the silica particle surface. All quartz contains some iron in traces and this will cause the above-described reaction. Fenoglio et al. (2003) looked at the activity in a system of silica samples that were either native or that had been treated by grinding or by other mechanisms that altered the amount or state of the iron at the particle surface. The results demonstrated that the presence and quantity of iron and its state in various silica samples was correlated with GSH and CYS depletion.

There have been a number of studies in which aluminum has been shown to decrease the toxicity of silica. For example, Brown et al. (1989) assessed the inflammatory and fibrogenic potential in rats of silica as modified by pretreatment with aluminum lactate. The mode of action of the aluminum in reducing quartz toxicity was also investigated. The effect on inflammation was assessed by measuring the total number of leukocytes and the percentage of polymorphonuclear leukocytes (PMN) in the bronchoalveolar lavage (BAL). Silica was administered by intratracheal instillation into the lung. One week after administration of silica, the total number of leukocytes had increased 7-fold. This increase peaked at 4 weeks post-administration and was then sustained for 12 weeks. In the rats treated with silica plus aluminum lactate, there was only a small, nonsignificant increase in the total number of leukocytes at one week post-administration and then the number returned to the control level. In control rats there were no PMN in the BAL. In rats administered silica, PMN made up 45 to 55 percent of the BAL leukocytes, while in rats administered aluminum lactate along with silica, this was reduced to 10 to 20 percent. Functional status of the silica-exposed BAL leukocytes, as measured by their ability to degrade fibronectin, was also reduced by co-treatment with aluminum lactate. When administration of aluminum lactate was delayed until one month after silica administration, total leukocytes and percentage of PMN were significantly reduced at one month post-aluminum treatment, but not at one week. Functional status of leukocytes was not affected. Co-administration of silica and aluminum lactate also minimized areas of alveolar lipoproteinosis with septal hyperplasia

seen at one month. At 4 months, co-administration lessened the severity and reduced the percent of tissue involved from 80 to 5 percent. An inflammatory response to treatment with bacteria was not attenuated by co-administration of aluminum lactate. This finding suggests that in the case of co-administration with silica, aluminum lactate affects the silica particle itself rather than the inflammatory cell. If aluminum lactate were acting directly on the inflammatory cell, it would have affected the inflammatory cell upon co-administration with bacteria, resulting in an attenuation of the inflammatory response to the bacteria.

Brown et al. (1989) also cited several earlier studies demonstrating that co-administration of aluminum and crystalline silica attenuated the inflammogenicity and fibrogenicity of silica, markedly reducing the pathogenicity of silica in rats, guinea pigs, mice, sheep, and rabbits. Additionally, research was cited that demonstrated that a clay mineral, a potential source of aluminum in mixed dusts, co-administered with silica, reduced the biological activity of silica.

Donaldson and Borm (1998) and Fubini (1998) reviewed studies on the effect of aluminum on the toxicity of silica (quartz). They reported on a study that demonstrated that aluminum is better at neutralizing silica's negative surface charge than iron (Brown and Donaldson, 1996). Donaldson and Borm (1998) also reported that several studies have shown that aluminum salts, which are commonly found in minerals that are associated with quartz, lower the toxicity of quartz. In one study (Daniel et al., 1970), rats were exposed to 300 mg/m^3 quartz by inhalation for 12 months. During that period, a group of the rats were also exposed, by inhalation, to aluminum hydroxide or aluminum chlorohydroxyallatoinate for 30 minutes per day. The fibrogenic response to quartz was decreased in the rats that were also treated with aluminum. The accumulation of quartz was similar in all treatment groups.

In another study (Bégin et al., 1987b), sheep were instilled with quartz, aluminum lactate, or quartz together with aluminum lactate. Co-treatment with aluminum lactate decreased pathology scores and inflammation, as indicated by reduced cellular activity in BAL fluid. Donaldson and Borm (1998) proposed that the biological effects of quartz, such as silicosis and cancer, could be understood in terms of surface reactivity and noted that a range of substances, including minerals, could modify the ability of quartz to generate free radicals and cause oxidative stress. They proposed that the hazard posed by quartz is not constant but may vary depending on the origin of the silica sample and its contact with other chemicals and minerals.

Fubini (1998), in discussing the possible role of physicochemical factors in the sequence of events leading to silicosis and silica-induced cancer, reported that aluminum and other metal ions are thought to modify silanol groups on the silica surface. This decreases the membranolytic and cytotoxic potency and allows greater particle clearance from the lung before damage can occur. Fubini (1998) noted that the protective effect of aluminum is demonstrated by studies in which aluminum ions or kaolin reduced *in vitro* cytotoxicity and membranolysis and *in vivo* inflammation and fibrosis. Fubini (1998)

suggested that the aluminum ions acted by replacing the hydrogen in SiOH and the kaolin acted by the release of aluminum ions.

More recent studies continue to demonstrate the protective effect of aluminum on silica-induced toxicity. Duffin et al. (2001) (also reported in Donaldson et al., 2001) instilled rats with 250 µg quartz or the same amount of quartz treated with aluminum lactate. Bronchoalveolar lavage was performed 18 hours later. The degree of inflammation was measured by counting the number of PMN in BAL fluid. Instillation with quartz caused a large inflammatory reaction, whereas instillation with aluminum lactate caused almost no inflammatory reaction. Similarly, the levels of macrophage inflammatory protein-2 (MIP-2) tracked with the inflammatory reaction. There was much less MIP-2 mRNA and protein in the BAL of rats instilled with aluminum lactate than those instilled with untreated quartz. BAL protein and gamma glutamyl transpeptidase, both indicators of epithelial cell (Type II and Clara) damage, were increased with quartz but not with aluminum lactate. Additionally, BAL cells from rats instilled with aluminum lactate showed minimal change in DNA binding of NF-κB, in contrast to the marked increase in binding induced by quartz. As discussed earlier, NF-κB is believed to be involved in the regulation of proinflammatory gene expression and plays a role in the mechanism of action of silica toxicity. Duffin et al. (2001) demonstrated that aluminum lactate had a greatly decreased ability to signal via the NF-κB pathway for transcription of the key proinflammatory cytokine, MIP-2. Additionally, it was demonstrated *in vitro* that aluminum lactate had a reduced surface activity as indicated by a 60 percent decrease in the ability to generate hydroxyl radicals as well as a reduced hemolytic potential.

Schins et al. (2002) examined the effect of coating silica with aluminum lactate on silica toxicity, uptake, and silica-induced DNA damage in the human lung cell epithelial cell line, A549. These cells have structural and biochemical characteristics of human type II cells and are known to ingest particles. Two assays determined cytoxicity: the MTT assay as an indicator of metabolic competence and the LDH assay a measure of plasma membrane leakage. Measurements of DNA damage were DNA strand breakage and the hydroxyl radical-specific DNA lesion 8-hydroxydeoxyguanosine (8-OHdG).

Coating with aluminum lactate significantly inhibited the cytotoxicity of quartz in the MTT assay. Only uncoated quartz caused a significant increase in LDH at 4 hours. However, at 24 hours LDH was significantly increased with both coated and uncoated quartz, although this effect was less pronounced with aluminum lactate coating. The formation of DNA strand breaks was also significantly reduced (χ^2, $p < 0.01$) for the coated quartz compared to uncoated quartz. Oxidative DNA damage was increased only by the non-coated quartz. Lastly, cellular uptake of quartz particles coated with aluminum lactate was markedly less than that seen with uncoated particles.

The authors concluded that the aluminum coating, which could easily occur naturally, was shown to eliminate the ability of quartz both to generate hydroxyl radicals and exert critical genotoxic effects that very likely play a role in quartz carcinogenesis. The authors also believed that these data, along with previous data obtained in their

laboratory, provided further support for a role of surface-mediated ROS-formation and intracellular oxidant generation in the genotoxicity of quartz. The authors also noted that the coating appeared to affect the acidity and the solubility of the quartz, perhaps explaining its membranolytic potential. The coating was reported to hinder the formation of surface radicals and block surface charge formation caused by grinding.

Knaapen et al. (2002) also examined the effect of aluminum treatment on the DNA-damaging potential of silica in rat lung epithelial cells *in vivo*. Rats were exposed to quartz or quartz treated with aluminum lactate by intratracheal instillation. After three days, DNA strand breakage was measured in lung epithelial cells. In order to assess the role of inflammatory cells in DNA strand breakage, the DNA damage was measured in relation to the presence and activation of macrophages and neutrophils. BAL fluid was used to determine macrophage and neutrophil influx. Neutrophil activation was measured by myeloperoxidae (MPO), and total antioxidant capacity of the BAL fluid was measured by the TEAC (trolox equivalent antioxidant capacity) assay. The authors hypothesized that coating the silica surface with aluminum would prevent DNA damage in the epithelial cells by inhibiting inflammatory cell influx into the lung. Uncoated silica was shown to cause acute induction of DNA strand breaks. This effect was completely inhibited by treatment of the silica with aluminum. Treatment with aluminum reduced neutrophil influx and completely inhibited macrophage influx. MPO, the marker of neutrophil activation, was increased only by uncoated silica. TEAC assay results showed that both Al-treated and untreated silica resulted in an increased total antioxidant capacity, but to a lesser extent with aluminum-treated silica. These results suggested to the authors that the reactive particle surface plays an important role in silica-induced DNA damage *in vivo*. The data also provided support for the possible role of inflammatory cells in silica-induced genotoxicity.

The time course of silica-induced inflammation and the impact of coating with aluminum were also investigated by Albrecht et al. (2004). These researchers intratracheally treated rats with quartz or quartz coated with aluminum. Markers of lung toxicity, inflammation, and oxidative stress (total protein, LDH, and alkaline phosphatase in the BAL; total number of cells, macrophages and neutrophils, PMN percentage, β-glucuronidase, and MIP-2 levels in the BAL; MPO and TEAC activities, respectively) were determined at 3, 7, 21, and 90 days after quartz instillation. The authors hypothesized that the inhibition of subacute inflammation by the coating of silica with aluminum might reduce the onset and extent of epithelial hyperplasia (as preneoplastic lesion) as well as fibrosis. Thus, the purpose of their study was to evaluate the inflammatory response elicited by aluminum-coated quartz up to 90 days after instillation. Quartz induced both an acute and subchronic inflammatory and oxidative stress response. Quartz increased the total number of cells (alveolar macrophages, neutrophils, PMN) in the BAL fluid and total number of macrophages and neutrophils over time up to the 90-day point. The neutrophilic inflammation induced by quartz was inhibited at various time points by aluminum coating (by 48 to 86 percent) but the PMN percentage was significantly reduced ($p < 0.01$) only at 7 days. Aluminum coating also reduced the quartz-induced increase in total protein in the BAL fluid seen at 28 and 90 days from 64 to 53 percent. The increase in LDH level in the BAL was also reduced by

aluminum between 42 and 83 percent, although this level of LDH was still significantly increased ($p < 0.05$) as compared to controls. Alkaline phosphatase (an indicator of cytotoxicity) showed a significant increase only at 7 days after quartz instillation and this was reduced by aluminum coating by 31 percent. Aluminum coating significantly reduced the quartz-induced β-glucuronidase increase at all time periods (reduction between 74 and 83 percent). However, at 90 days, the level of β-glucuronidase induced by aluminum-coated quartz was still significantly increased over controls. The quartz-related increase in MIP-2 levels, which continued throughout the 90-day period, was reduced by aluminum coating until day 28 (by 32 to 43 percent). MPO and TEAC activity was increased at all time periods by quartz and this increase was inhibited by aluminum coating (MPO by 78 to 100 percent; TEAC by 43-57 percent). However, as with β-glucuronidase, even with aluminum-coated quartz, a significant increase in TEAC ($p < 0.05$) was still seen at the 90 day time point.

Albrecht et al. (2004) also measured activation of NF-κB in rat lung by quartz and quartz coated with aluminum, using the indicators of degradation of the inhibitor protein IκBα and immunohistochemistry for the p65 subunit of NF-κB. Treatment with aluminum-treated quartz resulted in less degradation of IκBα and lesser amounts of p65 subunit of NF-κB than untreated-quartz at both 3 and 90 days after administration. Both indicators, however, were still significantly different from controls after administration of aluminum-coated silica. Aluminum coating also completely inhibited the translocation to the nucleus of NF-κB upon treatment of RLE cells *in vitro* with BAL fluid taken at 3 days from rats treated with quartz. From their results, the authors concluded that aluminum coating reduced the acute inflammatory and toxic effects of quartz but did not inhibit the persistent inflammation.

It has been noted that treatment of silica with aluminum lactate has been used as a model to study the protective effects of aluminum silicate clays on the quartz surface (Clouter et al., 2001). There are several studies on the protective effect of occlusion with aluminum silicate clays. The research group of Fubini et al. (along with the research group that conducted the studies just discussed above) has published a series of studies relating the state of the surface of quartz to biological activity *in vitro* and *in vivo* (Bruch et al., 2004; Cakmak et al., 2004; Fubini et al., 2004). They examined the surface properties of four commercial quartz flours. Two of the samples had been shown to cause inflammation *in vivo* and to activate macrophages *in vitro*. The two active samples were also genotoxic *in vivo*. The other two samples, which were mostly inert, contained a higher content of impurities, including aluminum, potassium, carbon, and iron. The authors suggested that their results were consistent with a model in which the difference in behavior of the four dusts are mainly caused by different levels and dispersion of contaminants on the silica surfaces (mainly aluminum and potassium, but possibly also iron), which changed the silanol patches that correlate with cell damage. They proposed that the aluminum may have originated from kaolinite that might either remain as intact grains on the quartz surfaces or be spread on the harder quartz surface during grinding, thus providing reactive aluminum ions located in prominent positions. The more extended the aluminum dispersion, the less ordered the silanol patches would be. They suggested that the presence of aluminum may favor the clearance of the quartz before it

could damage cells. The two toxic quartzes, having ordered silanol patches, would initiate the macrophage ingestion-reingestion cycle. According to the authors, several differences found between the two low- and two high- toxicity quartzes may be explained on the basis of the low-toxicity samples having a high level of poorly coordinated aluminum ions at the surface. The authors cited the Duffin et al. (2001) study discussed above, suggesting that the aluminum ions on their samples may act similarly to those deposited from aluminum lactate in that study. Finally, the authors, citing studies that have demonstrated that kaolin contamination reduces quartz toxicity, suggested that kaolin contamination may leave aluminum ions at the abraded quartz surface during grinding.

Wallace et al. (1990) have examined the issue of aluminosilicate clay occlusion of quartz and its effect on toxicity. They noted that in mining and some other dusty workplaces, the measurements of quartz content are not always accurate predictors of the prevalence of silica-related disease. The authors suggested that the biologically available quartz surface may not be equivalent to the conventionally-measured quartz content of the respirable dust in such settings. Wallace et al. (1990) devised an analytical method and examined samples of settled and airborne dust from a clay mine and mill. They determined that some of the respirable quartz particles were occluded with aluminosilicate. The question arose as to whether clay would remain attached to a respirable quartz particle after deposition in the lung. To simulate this situation, quartz samples were mixed with lecithin surfactant for 3 hours. The particles retained the clay occlusion on their surfaces, suggesting that after deposition in the lung, and before phagocytosis by pulmonary macrophages, some quartz particles would present themselves as clay-surfaced. The authors suggested that the longer-term fate of such coatings during phagolysosomal events and clearance or sequestration would determine if and when unoccluded quartz surfaces of the particle became biologically available to tissue.

Wallace et al. (1996) cited research that has indicated that clay-occluded silica particles show comparable *in vitro* cytotoxicity to the same amount (size and surface area comparable) of pure quartz. They noted that comparisons of pathologic potential and silica exposure must, therefore, be made on the basis of worker population epidemiological data, for which surface properties of dust exposures typically are not investigated, or on the basis of *in vivo* animal model studies. Commenting on the results of the earlier 1990 study, the authors expressed the opinion that relatively soluble clay occlusion would be expected to persist at least until phagocytosis but that longer-term persistence under conditions of residence in interstitial tissue or the lymphatics was an open question. The authors, therefore, called for additional research to detail the nature of such occluded particle surfaces, the geological and processing factors which affect such occlusion, and the durability of such particles in tissue.

Stone et al. (2004) have studied whether water soluble extracts of standard clay samples also block the reactivity of pure quartz samples both *in vivo* and *in vitro.* DQ12 samples were treated with water soluble extract of high aluminum clays (kaolin and attapulgite) or low aluminum clays (hectorite and montmorillonite). The effect of these

treatments on DQ12-induced hemolysis of sheep erythrocytes *in vitro* and inflammation *in vivo* as indicated by increases in the total cell numbers, neutrophil cell numbers, MIP-2 protein, and albumin content of the BAL fluid was examined. Treatment with the extracts of either of the high aluminum clays completely inhibited DQ12-induced hemolysis. Addition of a cation chelator to the kaolin extracts significantly prevented the inhibition. Extracts of the low aluminum clays had no inhibitory effect. Treatment of the DQ12 with either a high aluminum clay extract (kaolin) or the low aluminum clay (hectorite) significantly inhibited the increases in total inflammatory cell number, neutrophil cell number, and protein in the BAL. The authors suggested that, since hectorite did not prevent hemolysis but did prevent inflammation, either there was a difference in sensitivity of the two assays to the silica surface or a difference in the mechanism by which hectorite inhibits silica activity compared to the other sample extracts. According to the authors, the kaolin extract inhibition of inflammation supports the hypothesis that aluminum salts within aluminum-rich silicate clays may dampen the potency of the silica surface. However, the observation that hectorite was also inhibitory suggested that substances other than aluminum can reduce the reactivity of the silica surface. Hectorite had relatively high levels of MgO and CaO.

Several studies have examined the role of surface-modified silica in human silica-related disease or in workplaces where silica occurs. For instance, Tourmann and Kauffman (1994) studied the contents of dusts recovered from lungs of coal miners with silicosis. They used an analytical technique that could distinguish between pure quartz particles and an admixture of quartz and clay particles. Citing other studies showing that the fibrogenicity of some quartz-rich samples of coal mine dusts correlated better with the incidence of pure quartz particles than with the gross quartz content, they hypothesized that there would be a positive correlation of silicosis grade with the pure quartz content of recovered lung dusts. However, no such correlation was observed. In fact, even for one sample that had a high gross quartz content, only a minute fraction of pure quartz particles could be detected. Most of the quartz of the dusts recovered from silicotic lungs was still contaminated with clay minerals. The authors concluded that the aluminosilicate layers on quartz do not dissolve completely and thus do not reveal new quartz particles with free surfaces. Furthermore, protective layers persist, even during long-term contact with human lung tissues (up to 40 to 50 years). The preliminary results suggested that the fibrosis caused by these coal mine dusts may be correlated with the release of iron from iron-containing mineral particles.

Several epidemiologic studies have examined the risks of silicosis and other respiratory diseases in industries where the workers would be presumed to be exposed to silica subject to aluminosilicate clay occlusion. Love et al. (1999) conducted a cross-sectional study of the risk of silicosis and other respiratory diseases in the heavy clay industry in the United Kingdom. Although ninety-seven percent of all quartz concentrations were less than 0.4 mg/m^3 respirable quartz, 10 percent were higher than this among the groups of workers exposed to the most dust. The profusion of small opacities in the chest radiographs classified as ≥ ILO category 1/0 was 1.4% (25 workers) and 7 of those workers had radiographs rated ≥ category 2/1. A logistic regression of risk of median profusion of small opacities category ≥ 0/1 for a 25 year old non-smoker with

a cumulative respirable quartz exposure of 1 mg/m^3-year found that a doubling of cumulative quartz exposure increased the risk by a factor of 1.33 (95% CI 1.05 to 1.68) The prevalence of chronic bronchitis and breathlessness were 14.2 and 4.4 percent, respectively and both were significantly related to dust exposure with ORs of 1.5 (95% CI 1.1 to 2.0) and 1.5 (95% CI 1.1 to 2.2), respectively. The authors called the prevalence figure for silicosis "relatively low" and suggested that the accompanying clay minerals, and specifically the release of aluminum, had modified (reduced) the toxicity of the quartz.

A retrospective cohort epidemiologic study has examined the risk of silicosis in Chinese tin and tungsten miners and pottery workers with regard to the clay occlusion of the silica in those workplaces (Chen et al. 2005; Harrison et al., 2005). This study is reviewed in detail in Section VI, Preliminary Quantitative Risk Assessment, and is briefly described here. The cohorts included 4,028 tin miners, 14,427 tungsten miners, and 4,547 pottery workers selected from 20 Chinese mines and potteries. Respirable silica particles from these three types of workplaces were analyzed for occlusion of the silica particle surfaces. According to the authors, the cumulative risk of silicosis for a given level of cumulative respirable silica exposure was significantly lower for the pottery workers compared to tin and tungsten miners. Analysis of the silica surfaces showed that 55 percent of surfaces of the silica particles from the potteries were not occluded, compared to 82 percent from the tin mines, and 87 percent from the tungsten mines. When cumulative exposure was adjusted for silica surface availability, much of the difference in the exposure-response relationships between the pottery cohort and the miner cohorts was resolved. The authors concluded that differences in clay occlusion of silica particles was a factor in the differences in silicosis risk observed between the pottery workers and miners. They suggested that silica particle surface occlusion by aluminosilicate clay may have partially but substantially diminished fibrogenic activity of pottery workplace silica dusts.

I.F.5. Preliminary Conclusions on Factors Affecting the Toxicity of Crystalline Silica.

OSHA has reviewed evidence concerning potential effects on silica-related toxicity of physical factors such as crystal polymorphism; the age of fractured surfaces of the crystal particle; the presence of impurities, particularly metals, on particle surfaces; and clay occlusion of the particle. These factors likely vary among different workplace settings suggesting that the risk to workers exposed to a given level of respirable crystalline silica may not be equivalent in different work environments.

The modification of surface characteristics by the physical factors noted above may alter the toxicity of silica by affecting the physical and biochemical pathways of the mechanistic process. Thus, OSHA has reviewed the proposed mechanisms by which silica exposure leads to silicosis and lung cancer. It has been proposed that silicosis results from a cycle of cell damage, oxidant generation, inflammation, scarring and fibrosis. A silica particle entering the lung can cause lung damage by two major mechanisms: direct damage to lung cells due to the silica particle's unique surface

properties or by the activation or stimulation of alveolar macrophages (after phagocytosis) and/or alveolar epithelial cells. In either case, an elevated production of ROS/RNS results in oxidant damage to lung cells. The oxidative stress and lung injury stimulates alveolar macrophages and/or alveolar epithelial cells to produce growth factors and fibrogenic mediators, resulting in fibroblast activation and pulmonary fibrosis. A continuous ingestion-reingestion cycle, with cell activation and death, is established. The mechanism of silica-induced carcinogenesis may also involve the generation of ROS that may damage the lung epithelia and play a role in DNA damage and cell proliferation (Castranova, 2004; Fubini et al., 2004; Shi et al., 1989, 1998).

Thus, the early steps in the proposed pathways that lead to silicosis and lung cancer seem to share some common features, leading some researchers to suggest that silicosis is a prerequisite to lung cancer in silica-exposed individuals. Oxidative stress has been proposed to play a key role in the pathogenesis of silicosis and silica-induced lung cancer (Castranova 2004). Driscoll and Guthrie (1997) believed that any increased lung cancer risk associated with silica may be a consequence of the inflammation and increased epithelial cell proliferation associated with the development of silicosis. However, these authors completed a further study and determined that there were other key factors in silica-induced alveolar epithelial cell mutagenesis in addition to the inflammatory response (Johnston et al., 2000). Additional proposed mechanisms involved in silica-induced carcinogenesis include direct DNA damage, inhibition of p53, loss of cell cycle regulation, stimulation of growth factors, and production of oncogenes (Castranova, 2004; Fubini et al., 2004; Shi et al., 1989, 1998). Thus, it appears that lung cancer could arise from either inflammatory reactions responsible for silicosis or from other mechanisms not involving fibrogenesis. OSHA preliminarily concludes that available animal and *in vitro* studies have not conclusively demonstrated that silicosis is a prerequisite for lung cancer in silica-exposed individuals.

A number of epidemiologic studies have also examined the relationship between silicosis and lung cancer (Checkoway and Franzblau, 2000; see also Section V.C.4). Checkoway and Franzblau (2000) concluded, and OSHA agrees, that the question of whether silicosis is required for elevated lung cancer risk in silica-exposed individuals is virtually unanswerable from currently available epidemiologic literature, and is unlikely to be addressable in future epidemiologic studies.

OSHA has examined evidence on the comparative toxicity of the silica polymorphs (quartz, cristobalite, and tridymite). A number of animal studies appear to suggest that cristobalite and tridymite are more toxic to the lung than quartz and more tumorigenic (e.g., King et al., 1953; Wagner et al., 1980). However, in contrast to these findings, several authors have reviewed the studies done in this area and concluded that cristobalite and tridymite are not more toxic than quartz (e.g., Bolsaitis and Wallace, 1996; Guthrie and Heaney, 1995). Furthermore, a difference in toxicity between cristobalite and quartz has not been observed in epidemiologic studies (tridymite has not been studied) (NIOSH, 2002). In an analysis of exposure-response for lung cancer, Steenland et al. (2001a) found similar exposure-response trends between cristobalite-exposed workers and other cohorts exposed to quartz.

A number of studies have compared the toxicity of freshly fractured versus aged silica. Although animal studies have demonstrated that freshly fractured silica is more toxic than aged silica, aged silica still retains significant toxicity (Porter et al., 2002; Shoemaker et al., 1995; Vallyathan et al., 1995). Studies of workers exposed to freshly fractured silica have demonstrated that these workers exhibit the same cellular effects as seen in animals exposed to freshly fractured silica (Castranova et al., 1998; Goodman et al., 1992). There have been no studies, however, comparing workers exposed to freshly fractured silica to those exposed to aged silica. Animal studies also suggest that pulmonary reactions of rats to short-duration exposure to freshly fractured silica mimic those seen in acute silicosis in humans (Vallyathan et al., 1995).

Surface impurities, particularly metals, have been shown to alter silica toxicity. Iron, depending on its state and quantity, has been shown to either increase or decrease toxicity. Aluminum has been shown to decrease toxicity (Castranova et al., 1997; Donaldson and Borm, 1998; Fubini, 1998). Silica coated with aluminosilicate clay exhibits lower toxicity possibly due to reduced bioavailability of the silica particle surface (Donaldson and Borm, 1998; Fubini, 1998). This may be due to aluminum ions left on the silica surface by the clay (Bruch et al., 2004; Cakmak et al., 2004; Fubini et al., 2004). Aluminum and other metal ions are thought to modify silanol groups on the silica surface, thus decreasing the membranolytic and cytotoxic potency and resulting in enhanced particle clearance from the lung before damage can take place (Fubini, 1998). An epidemiologic study found that the risk of silicosis was less in pottery workers than in tin and tungsten miners (Chen et al., 2005; Harrison et al., 2005), possibly reflecting that pottery workers were exposed to silica particles having less biologically available, non-clay-occluded surface area than was the case for miners. The authors concluded that clay occlusion of silica particles can be a factor in reducing disease risk.

Although it is evident that a number of factors can act to mediate the toxicological potency of crystalline silica, it is not clear how such considerations should be taken into account to evaluate lung cancer and silicosis risks to exposed workers. After evaluating many *in vitro* studies that had been conducted to investigate the surface characteristics of crystalline silica particles and their influence on fibrogenic activity, NIOSH (2002) concluded that further research is needed to associate specific surface characteristics that can affect toxicity with specific occupational exposure situations and consequent health risks to workers. According to NIOSH (2002), such exposures may include work processes that produce freshly fractured silica surfaces or that involve quartz contaminated with trace elements such as iron. NIOSH called for further *in vitro* and *in vivo* studies of the toxicity and pathogenicity of alpha quartz compared with its polymorphs, quartz contaminated with trace elements, and further research on the association of surface properties with specific work practices and health effects.

In discussing the "considerable" heterogeneity shown across the 10 studies used in the pooled lung cancer risk analysis, Steenland et al. (2001a) pointed to hypotheses that physical differences in silica exposure (e.g., freshness of particle cleavage) between cohorts may be a partial explanation of observed differences in exposure-response

coefficients derived from those cohort studies. However, the authors did not have specific information on whether or how these factors might have actually influenced the observed differences. Similarly, in the pooled analysis and risk assessments for silicosis mortality conducted by Mannetje et al. (2002b), differences in biological activity of different types of silica dust could not be specifically taken into account. Mannetje et al. (2002b) determined that the exposure-response relationship between silicosis and log-transformed cumulative exposure to crystalline silica was comparable between studies and no significant heterogeneity was found. The authors therefore concluded that their findings were relevant for different circumstances of occupational exposure to crystalline silica. Both the Steenland et al. (2001a) and Mannetje et al. (2002b) studies are discussed in detail in Section II, Preliminary Quantitative Risk Assessment.

OSHA preliminarily concludes that there is considerable evidence to support the hypothesis that surface activity of crystalline silica particles plays an important role in producing disease, and that several environmental influences can modify surface activity to either enhance or diminish the toxicity of silica. However, OSHA believes that the available information is insufficient to determine how these influences may affect disease risk to workers in any particular workplace setting.

I.G. *Overall Conclusions.*

Silicosis is a disabling, non-reversible, and progressive lung disease caused by inhaling dust containing crystalline silica. In its later stages, it is associated with significant loss of lung capacity and gas exchange function, and increased airflow obstruction. The person with silicosis experiences dyspnea (difficulty breathing), perhaps while attempting to complete the most simple activities of daily living. On average, those with silicosis have a life span approximately 11 years shorter than those without silicosis (NIOSH, 2008c; NORMS database).

Silicosis can be detected using chest radiography and computed tomography, though both techniques are relatively insensitive and will not detect the presence of silicosis in a large proportion of affected individuals, particularly in its early stages. Although many cases of silicosis may be missed using these imaging techniques, those cases that are identified are very likely to be not only true, but well-established silicosis cases. However, several recent studies and reviews have suggested that a newer type of computed tomography known as high resolution computed tomography may be superior to chest x-ray in the early detection of silicosis and the identification of progressive massive fibrosis (Blum et al., 2008; Sun et al., 2008; Lopes et al., 2008).

Progression of silicosis is typically defined in terms of increasing profusion of fibrotic tissue, which appears as opacities on x-ray; however decrements in lung function, as measured by spirometry or PFT, also characterize the progression of the disease. Lung function deterioration has been documented to occur more rapidly in workers exposed to crystalline silica, especially those with silicosis, than is expected from the normal aging process.

OSHA reviewed studies that evaluated the course of progression, as observed on x-ray and as measured by spirometry, and was particularly interested in studies that attempted to correlate x-ray progression with functional decrements over time. No studies were found that were designed to elicit information on the temporal relationship (i.e., which occurred first) between x-ray progression and changes in pulmonary function. Two studies attempted to evaluate progression by comparing both chest x-rays and PFTs for the same workers for at least two distinct points in time (Cowie, 1998; Ng and Chan, 1992;). Ng and Chan (1992) found statistically significant lung function decrements that exceeded the expected values for those men with chest x-rays consistent with ILO categories 2 and 3. In the literature and medical texts, silicosis graded on the ILO scale as Category 3 (3/2, 3/3, 3/+), due to either the size or the extent of opacities viewed on x-ray or due to the presence of complications such as pulmonary massive fibrosis (PMF) or tuberculosis (TB), has been widely associated with significant pulmonary impairment. For ILO Category 2, the extent of pulmonary impairment has been less definitive.

For the earlier stages of silicosis (0/1 or 1/0 to 1/1), the literature reported, in general, that associated impairment may be relatively mild, and few studies included examination and testing of workers whose silicosis was categorized as less than ILO Category 2. One exception, however, was Cowie (1998), who reported that lung function deteriorated across all categories and that the deterioration increased in proportion to the degree of silicosis. Other studies have reported finding measurable decrements in pulmonary function that exceed those related to age, with no radiographic evidence of silicosis, and have raised the question of whether functional decrements precede the detection of silicosis on chest x-rays.

Based on the evidence in these studies, OSHA preliminarily concludes that there is a positive association between pulmonary function decrements and radiographic silicosis graded at least category 2 (i.e., for categories 2 and 3) on the ILO scale. For ILO category 1, OSHA believes that the evidence is insufficient to make a preliminary finding that pulmonary function decrements can occur among those with early radiologic evidence of silicosis (ILO Category 1), or even absent such evidence. While a few investigators found evidence of reduced lung function prior to radiological initiation of silicosis (ILO category 0/1 or 1/0), OSHA preliminarily determines that those decrements have not been substantial or reported consistently enough for a finding of an association between lung function decrements and a radiograph consistent with ILO category 0/1 or 1/0. It is important to note that this finding is based on insufficient evidence found in the research, and not sufficient evidence of a lack of an association.

Silicosis is known to be a progressive disease, both with and without further exposure to crystalline silica (Hessel et al., 1988; Ng et al., 1987a; Ogawa et al., 2003; Yang et al., 2006). Progression rates, i.e., the increase in the number of sub-categories on the ILO profusion scale exhibited by persons with silicosis, have been the subject of several studies. OSHA is particularly interested in studies that attempted to quantify progression in workers exposed to levels of silica near OSHA's current PEL (0.1 mg/m^3). Unfortunately, few studies have included reliable measurements of historical exposures, and when reconstructions of past exposures were attempted, they are generally

considerably higher than the current PEL. One study (Ng et al., 1987a), reported mean respirable silica exposure of 0.48 mg/m^3 for the workers identified as "simple silicotics," and found that 45% of the 53 patients progressed at least one sub-category on the ILO system over a mean of 7.2 years. In the cohort of South African miners followed longitudinally by Cowie (1998), silicosis progressed an average of one subcategory of nodule profusion during the 4.5 years. Unfortunately, no exposure data were provided.

Based on its review of the literature, OSHA preliminarily concludes that the exposure variables that are positively related to the progression of silicosis (i.e., those for which higher exposure correlates with higher risk) are average concentration of crystalline silica (Hughes et al., 1982; Ng et al., 1987a), cumulative respirable quartz (or silica) exposure, and duration of exposure (usually determined by duration of employment or length of service in a particular job). These are the same exposure factors that have been shown to play a role in the initiation of silicosis. Once silicosis has been detected, the likelihood of progression continues, even in the absence of additional exposure to silica (Hessel et al., 1988; Miller et al., 1998; Ogawa, et al., 2003; Yang et al., 2006), although those with silicosis exposed after onset of disease are more likely to progress than those who are not further exposed (Hessel et al., 1988).

Some authors have suggested that the decline in pulmonary function observed in occupational cohorts exposed to crystalline silica may not be directly due to the silica-related fibrosis, but may be due to an alternate process that occurs prior to the development of silicosis, for example, mixed dust fibrosis. Though this may account for some of the inconsistency in the findings in the studies that attempted to measure and correlate x-ray findings and PFT measures, differences in study design, exposure misclassification, and errors in exposure measurements, x-ray findings, and PFT measurements could also account for the observed inconsistencies.

Nonmalignant respiratory diseases (NMRD) other than silicosis have been linked to silica exposure, which may also explain some of the inconsistencies in findings attempting to correlate lung function with early radiographic evidence of silicosis. Based on the findings of studies of the relationship of silica exposure to morbidity from emphysema, bronchitis, and lung function impairment (as measured by spirometry), and mortality from NMRD (other than silicosis), OSHA preliminarily concludes that an exposure-response relationship exists for exposure to respirable crystalline silica and the risk of these conditions and that these conditions can occur in the absence of silicosis. However, except for NMRD mortality, data are insufficient for quantitative risk assessment. For emphysema, silica exposure may not increase risk among non-smokers. For all conditions, the effect of smoking may be additive (except for NMRD mortality, e.g., see Hnizdo, 1990) or synergistic.

OSHA conducted an independent review of the epidemiological literature on exposure to respirable crystalline silica and lung cancer, covering more than 30 occupational groups in over a dozen industrial sectors. In addition, OSHA reviewed a pooled case-control study, a large national death certificate study, two cancer registry studies, and six meta-analyses. Based on this review, OSHA preliminarily concludes that

the human data summarized in this section provides ample evidence that exposure to respirable crystalline silica increases the risk of lung cancer among exposed workers.

The strongest evidence for the carcinogenicity of respirable crystalline silica comes from the worldwide cohort and case-control studies reporting excess lung cancer mortality among workers exposed to silica dust as quartz in various industrial sectors, including granite/stone quarrying and processing, industrial sand, pottery and ceramic, and coal mining industries, as well as to cristobalite in diatomaceous earth and refractory brick industries. In addition, several studies of metal ore mining cohorts have found excess lung cancer risks to be associated with exposure to respirable crystalline silica, although exposures to other co-carcinogens were also present, complicating interpretation of the findings. The 10-cohort pooled case-control analysis by Steenland et al. (2001a) confirms these findings. A more recent, clinic-based pooled case-control analysis of seven European countries by Cassidy et al. (2007) as well as two national death certificate registry studies (by Pukkala et al., 2005 in Finland and by Calvert et al., 2003 in the United States) support the findings of the cohort and case-control analysis.

Among studies conducted on cohorts in three industry sectors (foundry, silicon carbide, and construction), OSHA found that silica exposures were profoundly confounded by the presence of exposures to other carcinogens. However, with respect to the construction industry, Cassidy et al. (2007) reported finding a statistically significant elevated odds ratio of 1.27 for lung cancer. This study was a very large multi-national European case-control study, which had detailed analysis of exposure to silica and many other occupational exposures, as well as smoking histories obtained principally from interviews of cases and controls.

OSHA reviewed the literature regarding concomitant exposure to crystalline silica and tobacco smoke. Given the findings of investigators who have accounted for the impact of smoking, OSHA believes that there is sufficient evidence to identify respirable crystalline silica as an independent risk factor for lung cancer mortality. This finding is also supported by animal studies demonstrating that exposure to silica alone can cause lung cancer (e.g., Muhle et al., 1995).

In general, studies of workers with silicosis, as well as meta-analyses that include these studies, have shown that silicotics have higher lung cancer risk than non-silicotics or mixed cohorts. Three meta-analyses attempted to look at the association of increasing ILO radiographic categories of silicosis with increasing lung cancer mortality; two showed no association with increasing lung cancer mortality, while Lacasse et al. (2005) demonstrated a positive dose-response for lung cancer with increasing ILO radiographic category. Animal and *in vitro* studies have demonstrated that the early steps in the proposed mechanistic pathways that lead to silicosis and lung cancer seem to share some common features. This has led some of these researchers to suggest that silicosis is a prerequisite to lung cancer in silica-exposed individuals. However, other studies have suggested alternative mechanisms such as direct DNA damage, inhibition of p53, loss of cell cycle regulation, stimulation of growth factors, and production of oncogenes. After reviewing all available evidence, OSHA preliminarily concludes that epidemiologic,

animal, and *in vitro* studies do not convincingly show that silicosis (as defined by chest x-ray findings) is a necessary precursor to lung cancer induction in silica-exposed individuals.

Respirable crystalline silica exposure has also been investigated as a potential risk factor for cancer at other sites including cancer of the larynx and nasopharynx and cancers of the digestive system including the esophagus or stomach. Although many of these studies suggest an association between exposure to crystalline silica and an excess risk of cancer mortality, most are too limited in terms of size, study design, or potential confounding to be conclusive. Other than for lung cancer, cancer mortality studies demonstrating a dose-response relationship are quite limited. In 2002, NIOSH concluded that, exclusive of the lung, an association has not been established between silica exposure and excess mortality from cancer at other sites. At this point in time, OSHA concurs with this finding.

Epidemiologic studies have demonstrated an association between exposure to crystalline silica and increased risk of renal and autoimmune disease. Studies have found statistically significant associations between occupational exposure to silica dust and chronic renal disease, sub-clinical renal changes, end-stage renal disease morbidity, chronic renal disease mortality, and Wegener's granulomatosis. A strong exposure-response association for renal disease mortality and silica exposure has also been demonstrated (Steenland et al., 2002a). A number of epidemiologic studies have found an association between silica exposure and increased risk of systemic autoimmune diseases, such as scleroderma, rheumatoid arthritis; and systemic lupus erythematosus. There are no quantitative exposure-response data with regard to autoimmune diseases.

OSHA preliminarily concludes that there is substantial evidence that silica exposure increases the risks of renal and autoimmune disease. The positive and monotonic exposure-response trends demonstrated for silica exposure and renal disease risk more strongly suggest a causal link. OSHA preliminarily concludes that the underlying data are sufficient to provide estimates of risk for renal disease. OSHA also preliminarily concludes that at the present time insufficient evidence exists for a quantitative estimate of risk of systemic autoimmune diseases associated with occupational exposure to silica.

A number of physical factors appear to influence the toxicity of silica. Freshly fractured silica has been shown to be more toxic than aged. Aluminum, by itself or as part of an aluminosilicate clay coating, appears to decrease toxicity. Iron can decrease or increase toxicity, depending on its valence state and amount. However, OSHA preliminarily concludes that available information on these factors is not specific enough at this time to predict how risks might vary among exposed employees in different industry sectors. OSHA also preliminarily concludes, based on epidemiologic and experimental evidence, that the crystalline silica polymorphs quartz, cristobalite, and tridymite have similar toxicity and carcinogenic potency.

II. Preliminary Quantitative Risk Assessment.

II.A. *Introduction*.

The Occupational Safety and Health Act (OSH Act or Act) and some landmark court cases have led OSHA to rely on quantitative risk assessment, where possible, to support the risk determinations required to set a permissible exposure limit (PEL) for a toxic substance in standards under the OSH Act. Section 6(b)(5) of the Act states that: "The Secretary [of Labor], in promulgating standards dealing with toxic materials or harmful physical agents under this subsection, shall set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard dealt with by such standard for the period of his working life" (29 U.S.C. 655).

In a further interpretation of the risk requirements for OSHA standard setting, the United States Supreme Court in the 1980 "Benzene" decision, (Industrial Union Department, AFL-CIO v. American Petroleum Institute, 448 U.S. 607, 639 (1980)), ruled that the OSH Act requires that, prior to the issuance of a new standard, a determination must be made that there is a significant risk of material impairment of health at the existing PEL and that issuance of a new standard will significantly reduce or eliminate that risk. The Court stated that "before he can promulgate any permanent health or safety standard, the Secretary is required to make a threshold finding that a place of employment is unsafe in the sense that significant risks are present and can be eliminated or lessened by a change in practices" (448 U.S. 642). While the Court indicated that the use of quantitative risk analysis was an appropriate means to establish significant risk, it made clear that "OSHA is not required to support its finding that a significant risk exists with anything approaching scientific certainty" (448 U.S. 656).

A determining factor in the decision to perform a quantitative risk assessment is the availability of suitable data for such an assessment. In the case of crystalline silica, there has been extensive research on its health effects and several quantitative risk assessments have been published in the peer-reviewed scientific literature that describe the risk to exposed workers of lung cancer mortality, silicosis and non-malignant respiratory disease mortality, renal disease mortality, and silicosis morbidity. These assessments were based on several studies of occupational cohorts in a variety of industry sectors, the underlying studies of which are described in the Health Effects section of this preamble.

Quantitative risk assessments for lung cancer and silicosis mortality were published after 1997, when the International Agency for Research on Cancer (IARC) determined that there was sufficient evidence to regard crystalline silica as a human carcinogen (IARC, 1997). This finding was based on several studies of worker cohorts demonstrating associations between exposure to crystalline silica and an increased risk of lung cancer. Although IARC judged the overall evidence as being sufficient to support this conclusion, IARC also noted that some studies of crystalline silica-exposed workers did not demonstrate an excess risk of lung cancer and that exposure-response trends were

not always consistent among studies that were able to describe such trends. These findings led Steenland et al. (2001a) and Mannetje et al. (2002b) to conduct comprehensive exposure-response analyses of the risk of lung cancer and silicosis mortality associated with exposure to crystalline silica. These studies, referred to as the IARC multi-center studies of lung cancer and silicosis mortality, relied on all available cohort data from previously published epidemiological studies for which there were adequate quantitative data on worker exposures to crystalline silica to derive pooled estimates of disease risk. In addition, OSHA identified four single-cohort studies of lung cancer mortality that it judged suitable for quantitative risk assessment; two of these cohorts (Attfield and Costello, 2004; Rice et al., 2001) were included among the 10 used in the IARC multi-center study and studies of two other cohorts appeared later (Hughes et al., 2001; Miller and MacCalman, 2009). For non-malignant respiratory disease mortality, in addition to the silicosis mortality study by Mannetje et al. (2002b), Park et al. (2002) conducted an exposure-response analysis of non-malignant respiratory disease mortality (including silicosis and other chronic obstructive pulmonary diseases) among diatomaceous earth workers. Exposure-response analyses for silicosis morbidity have been published in several single-cohort studies (Chen et al., 2005; Hnizdo and Sluis-Cremer, 1993; Steenland and Brown, 1995b; Miller et al., 1998; Buchanan et al., 2003).

In addition to these published studies, OSHA's contractor, Toxichemica, Inc., commissioned Drs. Kyle Steenland and Scott Bartell of Emory University to perform an uncertainty analysis to examine the effect on lung cancer and silicosis mortality risk estimates of uncertainties that exist in the exposure assessments underlying the two IARC multi-center analyses (Toxichemica, Inc., 2004). In the sections below, OSHA describes the published risk assessments for lung cancer mortality, silicosis mortality, and silicosis morbidity and the results of the uncertainty analysis. This is followed by discussions of the appropriateness of using cumulative exposure as the exposure metric in the risk assessments, factors that have been reported to attenuate or enhance the toxicological potency of crystalline silica, and OSHA's overall preliminary conclusions.

In quantitative risk assessments presented in past rulemakings, OSHA typically has estimated lifetime risks associated with exposure to the current permissible exposure limit (PEL) and the proposed exposure limit(s) over a full working life (i.e., 45 years). In the case of respirable silica, OSHA's PELs for general industry, shipyard employment, and construction are variable entities since the PELs are expressed as formulas that impose a limit on exposure to respirable dust, with the limit decreasing with increasing crystalline silica content. OSHA's current general industry PEL for respirable quartz is expressed both in terms of a particle count formula and a gravimetric concentration formula, while the current construction and shipyard employment PELs for respirable quartz are only expressed in terms of a particle count formula. OSHA's current gravimetric formula PEL for quartz in general industry is

$$10 \text{ mg/m}^3/(\%\text{quartz} + 2),$$

expressed as the 8-hour time-weighted average (TWA) concentration of respirable dust. As an example, if a respirable dust sample contained 18 percent quartz, the PEL would be 0.5 mg/m^3 (or 10/(18+2)) of respirable dust, which would be equivalent to a respirable

quartz concentration of 0.09 mg/m^3 (0.5 mg/m^3 X 18%). For quartz concentrations exceeding 5 percent, the PEL expressed as the concentration of respirable quartz exceeds 0.07 mg/m^3 and approaches 0.1 mg/m^3 as the quartz content increases. For the purposes of the risk assessment, the general industry PEL formula is considered approximately equal to 0.1 mg/m^3 respirable quartz. OSHA's general industry PEL for cristobalite and tridymite is half that of the PEL for quartz (i.e., approximately 0.05 mg/m^3).

OSHA's construction and shipyard PELs are based on particle count according to the formula

$$250 \text{ mppcf}/(\%\text{quartz} + 5),$$

where mppcf is million particles per cubic foot. The relationship between the particle-count PEL and gravimetric PEL will vary with the density of the particles and particle size distribution of airborne dust generated during an operation and thus is not expected to be constant across all construction and shipyard operations. However, a number of investigators have used concurrent particle count and mass dust sampling data from a variety of industrial settings to develop conversion factors that can be used to estimate mass-based exposures from particle count exposure measurements; these factors have been reported to range from 0.07 to 0.2 mg/m^3 respirable dust per mppcf, with most estimates clustering around 0.1 mg/m^3 per mppcf (Ayer et al., 1968; Ayer et al. 1973; Jacobson and Tomb, 1967; Sheehy and McJilton, 1987; Steenland et al., 2001a; Sutton and Reno, 1968). As described in Table I-1 of the health effects review, investigators have used similar values as a basis for estimating exposures of cohorts in epidemiological studies, although Rando et al. (2001) used higher conversion factors in their study of U.S. industrial sand workers (ranging from 0.206 to .364). Applying a conversion factor of 0.1 mg/m^3 respirable dust per mppcf to OSHA's construction and shipyard PELs for quartz, and assuming a quartz content of 5, 10, 50 or 100 percent in respirable dust, yields equivalent gravimetric PELs of 0.125, 0.167, 0.227, and 0.238 mg/m^3 of respirable quartz. Using a higher conversion factor of 0.2 mg/m^3 respirable dust per mppcf yields equivalent gravimetric PELs of 0.250, 0.333, 0.455, and 0.476 mg/m^3 respirable quartz for 5, 10, 50, and 100 percent quartz content of respirable dust, respectively. Thus, for the purpose of evaluating health risks associated with exposure to the current construction and shipyard industry PEL, OSHA assumes that the equivalent gravimetric PEL for respirable quartz would lie in the range of 0.25 to 0.5 mg/m^3.

OSHA is proposing a PEL of 0.05 mg/m^3 measured as respirable crystalline silica (i.e., quartz, cristobalite, and tridymite) for general industry, construction, and shipyards; this is equal to the NIOSH Recommended Exposure Limit (REL). To capture the range of exposures represented by OSHA's current and proposed PELs, this section provides estimates of mortality and morbidity risks corresponding to 45 years of exposure to 0.05, 0.1, 0.25, and 0.5 mg/m^3 respirable silica (i.e., cumulative exposures of 2.25, 4.5, 11.25, and 22.5 mg/m^3-years). In addition, OSHA is proposing an action level of 0.025 mg/m^3 for respirable crystalline silica; consequently, the preliminary risk assessment presents risk estimates associated with 45 years of exposure to the action level, which corresponds to a cumulative exposure of 1.125 mg/m^3-years.

Throughout this assessment, reference is made to a variety of model forms and different treatments of the exposure metric within the models. For clarity, OSHA uses the following terms in describing the models used most often by various investigators:

- A "linear model" is one where relative risk is linearly related to exposure, i.e., has the form $RR = 1 + \beta x$, where RR is relative risk, x is the measure of exposure, and β is the parameter to be estimated;

- A "log-linear" model is one where the log of relative risk is linearly related to exposure, i.e., $\log RR = \beta x$, or alternatively, $RR = \exp(\beta x)$; and

- "Log cumulative exposure" or "log-transformed cumulative exposure" means that the model uses the log of cumulative exposure plus 1 as the exposure metric (1 is added to avoid taking the log of zero). Typically, cumulative exposure is expressed in units of mg/m^3-years, and log-transformed cumulative exposure in mg/m^3-days.

Both linear and log-linear models may make use of cumulative exposure (i.e., untransformed cumulative exposure) or log-transformed cumulative exposure. Other model forms will be defined as they occur throughout the document.

II.B. *Lung Cancer Risk Estimates.*

Based on its review of studies presented in Section I, OSHA identified a number of published studies that analyzed exposure-response relationships for crystalline silica and lung cancer and provided estimates of risk associated with exposure to the PEL. These include the quantitative analysis by Steenland et al. (2001a) of worker cohort data pooled from ten studies; a dose-response analysis by Rice et al. (2001) of a cohort of diatomaceous earth workers primarily exposed to cristobalite; an analysis by Attfield and Costello (2004) of U.S. granite workers; a risk assessment by Kuempel et al. (2001), who employed a kinetic lung model, derived from rat studies, to describe the relationship between quartz lung burden and cancer risk based on the diatomaceous earth worker and granite worker cohort mortality data; a study of North American industrial sand workers (Hughes et al., 2001; McDonald et al., 2001; McDonald et al., 2005); and a study of British coalminers (Miller et al., 2007; Miller and MacCalman, 2009). Each of these studies are described below, along with the estimates of silica-related lung cancer risk derived from them by OSHA and, where available, by the investigators themselves.

To estimate lifetime risks at the exposure levels of interest to OSHA (0.025, 0.05, 0.1, 0.25, and 0.5 mg/m^3 respirable crystalline silica), the Agency implemented each of the risk models in a life table analysis that accounted for competing causes of death due to background causes and cumulating risk through age 85. For these analyses, OSHA used lung cancer and all-cause mortality rates to account for background lung cancer and competing risks (U.S. 2006 data for all males, obtained from cause-specific death rate tables published by the National Center for Health Statistics (2009)). Like the risk estimates reported by the authors of some of the original studies, OSHA calculated these risk estimates assuming occupational exposure from age 20 to age 65. In calculating

each risk estimate, OSHA used the same lag period selected by the original investigators. The life table method used by OSHA appears in an Appendix to this preliminary quantitative risk assessment. For all analyses, OSHA used the life table method to estimate excess risk, i.e., $P_x - P_0$, where P_x is the lifetime probability of dying from lung cancer given exposure to respirable silica and P_0 is the background lifetime probability given no exposure.

II.B.1. Steenland et al. (2001a) Pooled Cohort Analysis.

The lung cancer analysis conducted by Steenland et al. (2001a) as part of the IARC multi-centric study consisted of a pooled exposure-response analysis and risk assessment based on raw data obtained for ten cohorts of silica-exposed workers (65,980 workers, 1,072 lung cancer deaths). The ten cohort studies were selected from 13 that were identified at the time as containing exposure information sufficient to develop a quantitative exposure assessment. Three cohort studies were excluded for reasons of data unavailability or incompatibility. In addition, studies of coal workers and foundry workers were not considered because (1) studies of coal workers were not included in the IARC evaluation of silica carcinogenicity, and (2) because of the likely confounding of foundry worker studies due to potential exposure to carcinogenic polycyclic aromatic hydrocarbons. The cohorts in the pooled analysis included U.S. gold miners (Steenland and Brown, 1995a), U.S. diatomaceous earth workers (Checkoway et al., 1997), Australian gold miners (de Klerk and Musk, 1998), Finnish granite workers (Koskela et al., 1994), U.S. industrial sand employees (Steenland et al., 2001b), Vermont granite workers (Costello and Graham, 1988), South African gold miners (Hnizdo and Sluis-Cremer, 1991; Hnizdo et al., 1997), and Chinese pottery workers, tin miners, and tungsten miners (Chen et al., 1992).

The exposure assessments developed for the pooled analysis are described by Mannetje et al. (2002a). The exposure information available from each of the 10 cohort studies varied and included dust measurements representing particle counts, mass of total dust, and respirable dust mass. Measurement methods also changed over time for each of the cohort studies investigated, generally with impinger sampling performed in earlier decades and gravimetric sampling performed later. Exposure data based on analysis for respirable crystalline silica by x-ray diffraction (the current method of choice) were available only from the study of U.S. industrial sand workers. In order to develop cumulative exposure estimates for all cohort members and pool the cohort data, all exposure information was converted to units of mg/m^3 respirable crystalline silica by generating cohort-specific conversion factors based on the silica content of the dust to which workers were exposed and, in some instances, results of side-by-side comparison sampling. Within each cohort, available job- or process-specific information on the silica composition or nature of the dust was used to reconstruct silica exposures of cohort members. Most of the studies did not have exposure measurement data prior to the 1950s; exposures occurring prior to that time were estimated either by assuming such exposures were the same as the earliest recorded for the cohort, or by modeling that accounted for documented changes in dust control measures.

To evaluate the reasonableness of the exposure assessment for the lung cancer pooled study, Mannetje et al. (2002a) investigated the relationship between silicosis mortality and cumulative exposure by performing a nested case-control analysis for silicosis or unspecified pneumoconiosis using conditional logistic regression. Since exposure to crystalline silica is the sole cause of silicosis, a finding that cumulative exposure was unrelated to silicosis mortality risk would suggest that serious misclassification of the exposures assigned to cohort members had taken place. Cases and controls were matched for race, sex, age (within 5 years) and study; 100 controls were matched to each case. Each cohort was stratified into quartiles by cumulative exposure, and standardized rate ratios (SRR) were calculated using the lowest-exposure quartile as the baseline. Odds ratios (OR) were also calculated for the pooled data set overall, which was stratified into quintiles based on cumulative exposure. For the pooled data set, the relationship between odds ratio for silicosis mortality and cumulative exposure were as follows:

--4.45 mg/m^3-years, OR = 3.1 (95% CI, 2.5-4.0);

--9.08 mg/m^3-years, OR = 4.6 (95% CI, 3.6-5.9);

--16.26 mg/m^3-years, OR = 4.5 (95% CI, 3.5-5.8); and

--42.33 mg/m^3-years, OR = 4.8 (95% CI, 3.7-6.2).

In addition, in seven of the cohorts, there was a statistically significant trend between silicosis mortality (SRR) and cumulative exposure. For two of the cohorts (U.S. granite workers and U.S. gold miners), the trend test was not statistically significant ($p = 0.10$). An analysis could not be performed on the South African gold miner cohort because silicosis was never coded as an underlying cause of death, apparently due to coding practices in that country. Based on this analysis, Mannetje et al. (2002a) concluded that the exposure-response relationship for the pooled data set was "positive and reasonably monotonic" (that is, the response was reasonably consistently increasing with exposure) and indicated that the exposure assessments yielded reasonable estimates of cumulative exposures. In addition, despite some large differences in the range of cumulative exposures between cohorts, a clear exposure-related trend was evident in seven of the cohorts. Furthermore, in their pooled analysis of silicosis mortality for six of the cohorts, Mannetje et al. (2002b) found a clear and consistent positive response with increasing decile of cumulative exposure, although there is an anomaly in the 9^{th} decile (the pooled silicosis mortality study by Mannetje et al (2002b) is discussed in detail below in section II.C.1). Overall, these data support a monotonic exposure-response for silicosis. Thus, although some exposure misclassification almost certainly exists in the pooled data set, the authors concluded that exposure estimates did not appear to have been sufficiently misclassified so as to obscure an exposure-response relationship.

As part of an uncertainty analysis conducted for OSHA, Drs. Steenland and Bartell examined the quality of the original data set and analysis to identify and correct any data entry, programming, or reporting errors (Toxichemica, Inc., 2004). This quality assurance process revealed a small number of errors in exposure calculation for the

originally reported results, primarily resulting from rounding of job class exposures when converting the original data file for use with a different statistical program. Although the corrections affected some of the exposure-response models for individual cohorts (see discussion of results below), Steenland and Bartell (Toxichemica, Inc., 2004) reported that models based on the pooled dataset were not impacted by the correction of these errors.

For the pooled lung cancer mortality analysis, Steenland et al. (2001a) conducted a nested case-control analysis via Cox regression, in which there were 100 controls chosen for each case randomly selected from among cohort members who survived past the age at which the case died, and matched on age (the time variable in Cox regression), study, race/ethnicity, sex, and date of birth within 5 years (which, in effect, matched on calendar time given the matching on age). Exposures were truncated for controls when they attained the age at which their index case died. The principal exposure metrics of interest were cumulative exposure, the log of cumulative exposure plus 1, and average exposure. After testing models based on unlagged exposure and exposure lags of 5, 10, 15, and 20 years to account for disease latency, the authors selected an exposure lag of 15 years for most analyses. Exposure-response models included only a term for exposure since other variables of interest were matched between cases and controls.

Categorical analysis of the pooled data set showed that the risk of lung cancer increased in a monotonic fashion using categories of cumulative exposure (quintiles based on the cases' exposures), with odds ratios of 1.0, 1.0, 1.3, 1.5, and 1.6. Findings for categorical analyses using average exposure were similar (odds ratios 1.0, 1.4, 1.6, 1.6, 1.7). Duration of exposure alone did not show a monotonic relationship with lung cancer in categorical analysis (odds ratios 1.0, 1.3, 1.8, 1.4, 1.2). Using alternative continuous exposure variables in a log-linear relative risk model (log RR = βx, where x represents the exposure variable and β the coefficient to be estimated), Steenland et al. (2001a) found that the use of either 1) cumulative exposure with a 15-year lag, 2) the log of cumulative exposure with a 15-year lag, or 3) average exposure resulted in positive statistically significant ($p \leq 0.05$) exposure-response coefficients.

Steenland et al. (2001a) also employed a spline function using the log of cumulative exposure (15-year lag), which is largely unconstrained and allows any cubic function to be fit between two adjacent exposure points, or knots. Five knots were selected across the exposure range of the pooled data set. Because of its increased flexibility, the spline model provided a statistically significantly improved fit over the log-linear model; however, the resulting model was not monotonic over the entire range of exposure, particularly in the region corresponding to 45-year exposures below about 0.002 mg/m^3 (less than 3 log mg/m^3-days) and between 0.1 and 0.25 mg/m^3 (less than 7 to 8 log mg/m^3-days). OSHA believes that the lack of a consistently monotonic exposure-response curve from the spline model lessens its credibility since there is no reason to believe that the biological response to increasing silica exposure should not be monotonic throughout the observed range of exposure.

The models that provided the best fit to the data were those that used cumulative exposure and log-transformed cumulative exposure. Steenland et al. (2001a) reported

roughly similar fits for all log-linear relative risk models based on cumulative or log-cumulative exposure, with model likelihoods ranging from 17.3 (1 d.f., unlagged cumulative exposure) to 21.4 (1 d.f., 15-year lagged cumulative exposure) and log-transformed cumulative exposure models in between (model likelihoods of 18.8, 1 d.f., 15-year lagged and 19.2, 1 d.f., unlagged) (Steenland, 2001a). The average exposure metric was clearly inferior to the cumulative and log-cumulative metrics, with a model likelihood of 4.4 (1 d.f.). Table II-1 summarizes the exposure-response coefficients determined from each of the ten cohorts as well as a weighted average coefficient for the pooled analysis, based on using the log-linear model with cumulative exposure and the log of cumulative exposure (15-year lag, taken from Steenland et al., 2001a). Table II-1 also presents coefficients calculated after Dr. Steenland examined the quality of the original data set to identify and correct any data entry, programming, or reporting errors (Toxichemica, Inc., 2004). Although the corrections affected some of the regression coefficients for individual cohorts (e.g., the Finnish granite workers' cohort 15-year lagged log-cumulative exposure coefficient changed from 0.049 (se = 0.07) to -0.015 (se = 0.063)), Steenland reported that the pooled coefficients are virtually unchanged. The coefficient for 15-year lagged log cumulative exposure was 0.062 (se 0.015) in the original analysis and 0.060 (se 0.015) in the revised analysis

There was significant heterogeneity among studies (cohorts) using either cumulative exposure or average exposure. The authors suggested a number of possible reasons for such heterogeneity, including errors in measurement of high exposures (which tends to have strong influence on the exposure-response curve when untransformed exposure measures are used), the differential toxicity of silica depending on the crystalline polymorph, the presence of coatings or trace minerals that alter the reactivity of the crystal surfaces, and the age of the fractured surfaces. (See section I.F for a discussion of factors that may modify the toxicity of crystalline silica). Models that used the log transform of cumulative exposure showed no statistically significant heterogeneity among cohorts ($p = 0.36$), possibly because they are less influenced by very high exposures than models using untransformed cumulative exposure. For this reason, as well as the good fit of the model using log-cumulative exposure, Steenland et al. (2001a) conducted much of their analysis and calculated their risk estimates using log-transformed cumulative exposure.

Among the 10 cohort studies included in the pooled data set, the South African gold miner study provided the largest exposure-response coefficient regardless of the exposure metric used. Steenland et al. (2001a) found that excluding this cohort from the data set and re-fitting the model using log-cumulative exposure yielded almost no change in the exposure-response coefficient for the pooled data set ($\beta = 0.062$, se = 0.015 with the South African data vs. $\beta = 0.060$, se = 0.015 without) (Steenland et al., 2001a). Furthermore, exclusion of the three Chinese studies from the pooled data set, where there was potential confounding by exposures to radon, arsenic, and polycyclic hydrocarbons, resulted in a small but statistically significant increase in the exposure-response coefficient ($\beta = 0.075$, se 0.025, $p = 0.003$). Based on these analyses, there is no evidence to indicate that data from any particular cohort unduly influenced the results of the pooled analysis.

Table II-1. Descriptive data and log-linear exposure-response coefficients for 10 studies and for pooled data, using 15-year lagged log cumulative exposure

Study	Median respirable crystalline silica exposure (mg/m^3)[a]	Median cumulative silica exposure (mg/m^3-years)	Number of lung cancer deaths[b,c]	Original exposure-response coefficient (SE)[d,e]	Revised exposure-response coefficient (SE)[d,f]
US Diatomaceous earth (Checkoway et al., 1997)	0.18	1.05	77	0.089 (0.054)	0.086 (0.054)
S Africa gold (Hnizdo and Sluis-Cremer, 1991; Hnizdo et al., 1997)	0.19	4.23	77	0.666 (0.336)	0.582 (0.329)
US gold (Steenland and Brown, 1995a)	0.05	0.23	156	-0.039 (0.078)	-0.041 (0.078)
Australian gold (de Klerk and Musk, 1998)	0.43	11.37	135	0.194 (0.115)	0.172 (0.111)
US granite (Costello and Graham, 1988)	0.05	0.71	124	0.112 (0.050)	0.118 (0.048)
Finnish granite (Koskela et al., 1994)	0.59	4.63	38	0.049 (0.070)	-0.015 (0.063)
US industrial sand (Steenland et al., 2001b)	0.04	0.13	85	0.031 (0.057)	0.045 (0.057)
Ch. Tungsten (Chen et al., 1992)	0.32	8.56	174	0.030 (0.026)	0.039 (0.027)
Ch. Pottery (Chen et al., 1992)	0.22	6.07	81	0.076 (0.036)	0.086 (0.039)
Ch. Tin (Chen et al., 1992)	0.19	5.27	119	0.078 (0.034)	0.054 (0.033)
Pooled			1066	0.062 (0.015)	0.060 (0.015)

Footnotes for Table II-1

[a] From Mannetje et al. (2002b)

[b] Lung cancer deaths among exposed workers; about 32% of the lung cancer deaths among Chinese tungsten, pottery, and tin workers occurred among non-exposed workers.

[c] 6 lung cancer deaths were excluded due to problems with their demographic data or work history.

[d] Units are log odds per log(mg/m^3-days).

[e] Reported in Steenland et al. (2001a).

[f] Coefficient reflects corrections to data used in Steenland et al. (2001a); see Toxichemica, Inc. (2004).

Source: Toxichemica, Inc. (2004)

Steenland et al. (2001a) estimated excess lifetime risk of lung cancer based on rate ratios from the spline and log-linear models (15-year lagged log-cumulative exposure for both), using NIOSH data on U.S. males in the early 1990s in a life table formula to account for background lung cancer and competing mortality (Gail, 1975). Results from the log-linear model indicated that 45 years of exposure at 0.1 mg/m^3 would result in a lifetime risk (through age 75) of 28 excess lung cancer deaths per 1,000 workers (95% CI, 13-46) (Steenland et al., 2001a), with U.S.-specific results and confidence intervals reported in Toxichemica, Inc. (2004). The spline model yielded a somewhat lower risk estimate of 17 per 1,000 (95% CI, 2-36) due to a shallower rise in risk at low cumulative exposures compared to the log-linear model (Steenland et al., 2001a), with U.S.-specific results and confidence intervals reported in Toxichemica, Inc. (2004).

Steenland and Deddens (2002) conducted further analyses of the data to determine whether there was any empirical evidence of a threshold (e.g., a level of exposure below which there is no excess risk of lung cancer). Threshold models using average exposure or untransformed cumulative exposure did not show any statistically significant improvement in fit over models without a threshold. They found that a threshold model based on the log of cumulative dose (15-year lag) fit better than a no threshold model, with the best threshold at 4.8 log mg/m^3-days (representing an average exposure of 0.01 mg/m^3 over a 45-year working lifetime). This suggests that, among the studies evaluated by Steenland et al. (2001a) in the pooled analysis, there is no empirical evidence of a threshold for lung cancer in the exposure range represented by the current and proposed PELs (i.e., at 0.05 mg/m^3 or higher).

During the external peer review, OSHA received comments questioning the appropriateness of relying on non-linear models and log transformation of exposure over the more preferred linear model for estimating cancer risks. In response, OSHA asked Drs. Steenland and Bartell to conduct additional analyses with linear relative risk models on the pooled data set; this approach favors the use of linear models over reducing heterogeneity between cohorts (Steenland, personal communication, 2010). For this analysis, the following models were fit to the pooled data set:

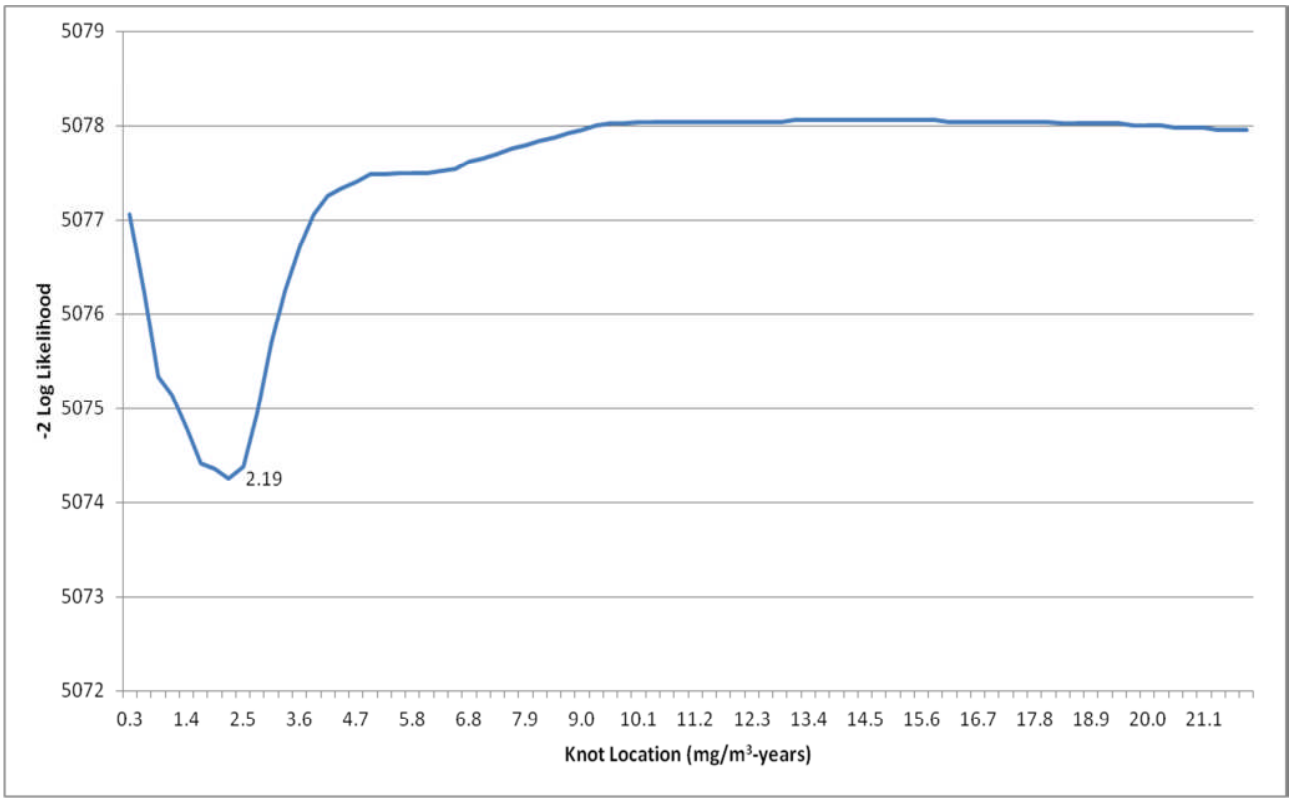
- Linear relative risk ($RR = 1 + \beta x$) with cumulative exposure in mg/m^3-years;
- Log-linear ($RR = \exp(\beta x)$) with cumulative exposure in mg/m^3-years;
- A 2-piece linear spline model with cumulative exposure in mg/m^3-years; and
- A linear relative risk model with log cumulative exposure (mg/m^3-days + 1).

The 2-piece spline model is a 2-parameter model and has the form:

- $RR = 1 + \beta_1 x$ for $x \leq X_{knot}$, and
- $RR = 1 + \beta_1 x + \beta_2(x-X_{knot})$ for $x > X_{knot}$

where X_{knot}, which defines the inflection point, is selected based on maximizing the likelihood (see Figure II-1). For cumulative exposure with a 15-year lag, the knot is 2.19 mg/m^3-years.

Figure II-1. Plot of Model Likelihood vs. Knot Location for the Linear 2-Piece Spline Model



As was done in the original analysis by Steenland, et al. (2001a), a case-control design was used, matching each case with 100 controls. Models were fit via SAS using the statistical methods proposed by Langholz and Richardson (2009), which maximizes the Cox partial likelihood used in conditional logistic regression, while allowing various functional forms to model relative risk.

Figure II-2 shows the results for the models incorporating a 15-year exposure lag, and compares the models to a categorical analysis that shows the observed relative risk by quintile of cumulative exposure. The results for models without an exposure lag were similar, fitting only slightly worse than those with the lag. The linear relative risk models using cumulative exposure (lagged or unlagged) fit somewhat worse than did the log-linear model with log cumulative exposure that was used in the original analysis; this difference was not statistically significant. However, the linear relative risk models using cumulative exposure fail to capture the initial steeper slope of the exposure-response curve, as is evident from the categorical analysis (Figure II-2). The shape of the exposure-response curve is better captured using either the linear model with log-transformed cumulative exposure, or with the 2-piece linear spline.

The linear model with log cumulative exposure and the linear spline model yielded lifetime risk estimates (to age 85) that were comparable to those reported by Steenland et al. (2001a) from the log linear model using log cumulative exposure; the estimates reported by Steenland and

Bartell were 38 and 27 deaths, respectively, per 1,000 workers exposed for 45 years to 0.1 mg/m^3 respirable crystalline silica (Steenland, personal communication, 2010). In contrast, the lifetime risk estimated from the linear model using cumulative exposure was almost an order of magnitude lower (4 deaths per 1,000 workers). Since the 2-piece linear spline model and linear relative risk model with log cumulative exposure best reflect the shape of the underlying exposure-response curve observed for the pooled cohort data set, OSHA believes that these models are more appropriate than the linear model with untransformed cumulative exposure for estimating lung cancer risk.

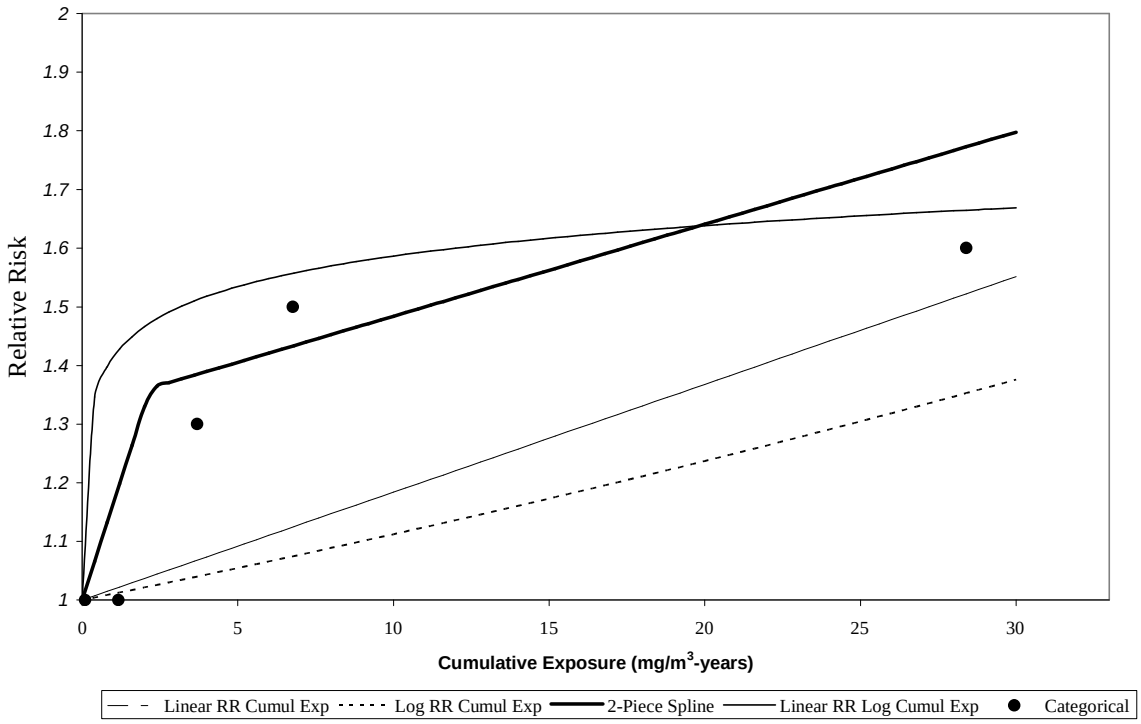
Therefore, OSHA is basing its lung cancer risk estimates from the pooled cohort on the log-linear model with log cumulative exposure (i.e., the original model used by Steenland et al., 2001a, with corrections to the data set as described by Toxichemica, Inc., 2004), as well as on the linear model with log cumulative exposure and the 2-piece linear spline model. For the models using log cumulative exposure, OSHA assumed 250 days of exposure per year (since the unit for exposure in these cases is mg/m^3-days). Based on these models, OSHA estimates the excess lifetime lung cancer risk resulting from 45 years of exposure to the current general industry PEL (0.1 mg/m^3) to range from 22 to 29 deaths per 1,000 workers, and, for exposure to the current construction/shipyard PEL (0.25 – 0.5 mg/m^3), to range from 27 to 38 deaths per 1,000 workers. For the proposed PEL of 0.05 mg/m^3, OSHA estimates the excess lung cancer risk ranges from 18 to 26 deaths per 1,000 and, for the proposed action level of 0.025 mg/m^3, to range from 9 to 23 deaths per 1,000.

In addition to the analyses conducted by Steenland (2010), OSHA also used the individual exposure coefficients for the 10 cohort studies used in the pooled analysis to estimate the range of risks reflected by the individual studies. The exposure coefficients used were reported in Table 3 of Steenland et al. (2001a) and are the coefficients for untransformed cumulative exposure with a 15-year lag. At the current general industry PEL, the range of risks derived from the 10 studies is 0.83-69 deaths per 1,000, and for exposure to the current construction/shipyard PEL, the range is 2.1-687 deaths per 1,000. For exposure at the proposed PEL over a working lifetime, the range is from 0.41 to 28 deaths per 1,000. The low end of the range is derived from the Chinese pottery cohort and the upper end of the range by the South African gold miner cohort. These ranges, which span more than two orders of magnitude, reflect the heterogeneity that was addressed originally in Steenland et al. (2001a) by relying on the log transformed cumulative exposure metric.

II.B.2. Rice et al. (2001) Analysis of Diatomaceous Earth Workers.

Rice et al. (2001) applied a variety of exposure-response models to the same California diatomaceous earth cohort data originally reported on by Checkoway et al. (1993, 1996, 1997) and included in the pooled analysis conducted by Steenland et al. (2001a) described above. The cohort consisted of 2,342 white males employed for at least one year between 1942 and 1987 in a California diatomaceous earth mining and processing plant. The cohort was followed until 1994, and included 77 lung cancer deaths.

Figure II-2. Plot and Parameters of Relative Risk Models Fit to the Pooled Cohort Data Originally Analyzed by Steenland et al. (2001a)



Model	Dose Metric	Parameters	SE	-2*Log-Likelihood
Linear Relative Risk	Cumulative Exposure (mg/m^3-years)	β= 0.018388	SE = 0.0056557	9641.37
Log Relative Risk	Cumulative Exposure (mg/m^3-years)	β = 0.010638	SE = 0.002063	9642.61
2-Piece Spline	Cumulative Exposure Knot=2.19 mg/m^3-years	β_1 = 0.16498 β_2 = -0.149285	SE_1=0.065335 SE_2=0.0657	9634.58
Linear Relative Risk	Log Cumulative Exposure (mg/m^3-days)	β = 0.074950	SE = 0.024121	9646.49
Categorical Analysis	Cumulative Exposure (mg/m^3-years)	N/A	N/A	N/A

Rice et al. (2001) relied on the dust exposure assessment developed by Seixas et al. (1997) from company records of over 6000 samples collected from 1948 to 1988; cristobalite was the predominate form of crystalline silica to which the cohort was exposed. Each worker in the cohort was assigned a cumulative silica dust exposure based on this exposure assessment and employment records; the mean cumulative exposure for the cohort was 7.31 mg/m^3-years for respirable dust and 2.16 mg/m^3-years for respirable crystalline silica dust. The mean concentration of respirable crystalline silica over the employment period of the cohort was 0.29 mg/m^3. Rice et al. (2001) considered lag periods of 0, 2, 5, 8, 10, 12, and 15 years in the development of cumulative exposure estimates, selecting 10 years for the risk analysis based on model fit (statistics not reported).

The authors developed Poisson regression models to estimate the relationship between silica exposure and lung cancer mortality rate, including both relative rate ($\lambda = \lambda_0 \times f(E)$) and additive excess rate ($\lambda = \lambda_0 + f(E)$) models, where λ is the predicted lung cancer incidence, f(E) is a function of cumulative silica exposure in mg/m^3-years, and λ_0 is the background incidence. The following model forms were evaluated:

- Log-linear: $RR = \exp(\beta_1 E)$;
- Log square root: $RR = \exp(\beta_1 E^{0.5})$;
- Log quadratic: $RR = \exp(\beta_1 E + \beta_2 E^2)$;
- Power: $RR = (1+E)^{\beta}_1$;
- Linear relative rate: $RR = 1 + \beta_1 E$;
- Shape(α): $RR = 1 + \beta_1 E^{\alpha}$, and;
- Additive excess rate: $AER = \beta_1 E$,

where β_1, β_2, and α are parameters to be estimated, E is cumulative exposure, RR is relative rate, and AER is additive excess rate. Background lung cancer mortality incidences were determined both internally from the cohort, stratifying on three levels of time since first observation (< 10, 10-19, and $\geq$ 20 years), calendar time, age, and ethnicity (Hispanic vs. non-Hispanic), and externally, based on U.S. mortality rates from 1940 to 1994, adjusted for age and calendar time. Rice et al. (2001) examined a variety of exposure groupings, including 5, 10, 20, and 50 exposure levels, selecting 50 levels for the main analysis based on model fit (statistics not reported). The authors also fit Cox's proportional hazards models using the log linear, log square root, log quadratic, and power model forms described above, stratifying as in the Poisson models on time since first observation, calendar time, and ethnicity.

Rice et al. (2001) reported that exposure to crystalline silica was a significant predictor of lung cancer mortality for nearly all of the models employed, with the linear relative risk model providing the best fit to the data in the Poisson regression analysis. Results from Cox's proportional hazards models were similar to the Poisson regression when 50 exposure categories were used in the latter, supporting Rice et al.'s (2001) use of that exposure categorization scheme.

The use of external cancer mortality rates to estimate background lung cancer incidence yielded slope estimates that were similar to, but substantially more precise than, those based on internally standardized models

Rice et al. (2001) estimated excess lung cancer risk based on the log linear, log square root, power, and linear relative rate models with 10-year lagged cumulative exposure and using 1992 U.S. mortality data to adjust for competing mortality. Based on the linear relative rate model with external standardization, the authors predicted an excess risk of lung cancer by age 85, for a mixed-gender population, of 29 per 1,000 workers after 45 years of exposure at 0.1 mg/m^3 respirable crystalline silica (95% CI, 8-68, calculated as part of the Toxichemica, Inc., 2004 analysis based on information provided in Rice et al., 2001). Excess risk estimates for male workers were 36-37 per 1,000 (no CI reported). Note that the same exposure-response coefficients were used by Rice et al. (2001) to estimate risk for all demographic groups; however, the higher background lung cancer rates found among men than in the general population result in higher excess risk estimates using a relative risk model. At an exposure level of 0.05 mg/m^3 (equal to the proposed PEL and NIOSH REL), Rice et al. (2001) estimated a lifetime excess risk of 15 per 1,000 for the total U.S. population, or 19 per 1,000 for male workers (95% CI 5-46 reported for white males). Excess risk estimates based on models other than the linear relative rate model were reported to be, in general, higher than those based on the linear relative rate model. Sources of uncertainty in the risk estimates based on the Rice et al. (2001) study include possible error in exposure estimates and confounding of the exposure-response analysis due to smoking and occupational co-exposures such as asbestos. These issues are addressed in the discussion on uncertainty presented later in this section.

II.B.3. Attfield and Costello (2004) Analysis of Granite Workers.

Attfield and Costello (2004) analyzed the same U.S. granite cohort originally studied by Costello and Graham (1988) and Davis et al. (1983) and included in the Steenland et al. (2001a) pooled analysis, consisting of 5414 male granite workers who were employed in the Vermont granite industry between 1950 and 1982 and who had received at least one chest x-ray from the surveillance program of the Vermont Department of Industrial Hygiene. Attfield and Costello (2004) extended follow-up from 1982 to 1994, increasing the number of lung cancer deaths from 124 in the original Costello and Graham (1988) study and the pooled analysis to 201. Workers' cumulative exposures were estimated by Davis et al. (1983) based on historical exposure data collected in six environmental surveys conducted between 1924 and 1977 and work history information collected at the time that each worker was X-rayed, including start and stop year for each job worked in the industry. Attfield and Costello (2004) did not update work histories beyond the original 1982 follow-up.

Categorical analyses were performed using seven exposure groups, allocating approximately equal numbers of deaths from all causes into each. Poisson regression models were evaluated using unlagged exposure vs. a 15-year lag, untransformed vs. log transformed cumulative exposure, and internal vs. external adjustment of baseline lung cancer rates. Attfield and Costello (2004) evaluated the exposure-response both with and without the highest exposure group, based on their belief that this group is marked by a stronger healthy worker effect than the rest of the cohort. In addition, the authors believed that lung cancer may have been underreported as a cause of death among the workers in the highest exposure group, most of whom worked for 20

years or more prior to institution of exposure controls, during a time when tuberculosis and silicosis were the primary health concerns among granite workers.

The results of the categorical analysis showed a generally increasing trend of lung cancer rate ratios with increasing cumulative exposure. However, the rate ratio for the highest exposure group in the analysis (cumulative exposures of 6.0 mg/m^3-years or higher) was substantially lower than those for other exposure groups; for example, the lung cancer rate ratios for the categorical analysis using 15-year lagged cumulative exposures were 1.00; 1.24; 2.14; 1.93; 1.68; 2.60; 1.90; and 1.18. The highest exposure category appeared to have a strong effect on the overall exposure response relationship observed in models using untransformed exposure metrics, which yielded relatively weak, non-statistically significant exposure coefficients when the highest exposure group was included in the analysis, and highly significant ($p < 0.005$) exposure coefficients when the highest group was excluded. A significant exposure-response relationship ($p < 0.01$) was observed in all models using a log transformation on exposure, which tends to decrease the influence of very high exposures on the model.

Attfield and Costello (2004) reported that the best-fitting model was based on a 15-year lag, use of untransformed cumulative exposure, and omission of the highest exposure group. Based on this model, and using 1992 NIOSH data on white U.S. males in a life table formula to account for background lung cancer and competing mortality (Gail, 1975), they estimated a lifetime lung cancer mortality risk (through age 85) of 64 deaths per 1,000 workers (95% CI, 22/1000, 123/1000) exposed for 45 years to 0.1 mg/m^3 respirable quartz. At an exposure of 0.05 mg/m^3, the estimated lifetime risk was 27 deaths per 1,000 (95% CI, 10/1000, 48/1000). The authors argued that it was appropriate to base their risk estimates on a model that was fitted without the highest exposure group for several reasons. They believed the underlying exposure data for the high-exposure group was weaker than for the others, and that there was a greater likelihood that competing causes of death and misdiagnoses of causes of death attenuated the lung cancer death rate. Second, all of the remaining groups comprised 85 percent of the deaths in the cohort and showed a strong linear increase in lung cancer mortality with increasing exposure. Third, Attfield and Costello (2004) believed that the exposure-response relationship seen in the lower exposure groups was more relevant given that the exposures of these groups were within the range of current occupational standards. Finally, the authors stated that risk estimates derived from the model after excluding the highest exposure group were more consistent with other published risk estimates than was the case for estimates derived from the model using all exposure groups. In a letter responding to criticism of these reasons for excluding the high-exposure group (Graham, 2004), Attfield (2004) pointed out that attenuation of an observed response at high exposures was often seen in epidemiological studies, and referred to Stayner et al. (2003), who described several reasons that explain such observations, including survivor effects, a limit on the relative risk that can be achieved for diseases with a high background rate (e.g. lung cancer), and misclassification of exposure.

Graham et al. (2004) reported on the mortality experience of this cohort, extending the follow-up period by two years, through 1996. The relationship between lung cancer mortality and exposure to quartz dust was examined by comparing mortality rates of granite shed workers hired before 1940 to those of workers hired after 1940 when dust control measures were introduced. Prior to 1940, estimated respirable quartz levels in the sheds averaged 0.2 mg/m^3, with workers operating pneumatic chisels exposed to 0.6 mg/m^3. After 1940, implementation of dust controls

resulted in a gradual decline in exposures over several years until exposures were reduced by 80 to 90 percent by the 1950s. There were statistically significant increases in lung cancer mortality among shed workers hired before and up to 1940 (SMR = 1.48) and among shed workers hired after 1940 (SMR = 1.24); however, the difference in lung cancer mortality between these two groups was not statistically significant. In addition, Graham et al. (2004) reported that smoking histories were available for 80 percent of workers who died of lung cancer and that all of these workers smoked. They also noted that radiographic evidence of silicosis was evident in 27 percent of workers hired before 1940 compared to 5.7 percent of those hired after 1940, and that all but one of the post-1940 workers with radiographic evidence of silicosis were hired between 1940 and 1955 when dust levels were being reduced. Graham et al. (2004) concluded that dust control measures were shown to be effective in reducing lung disease and mortality among granite workers and that their analysis did not support a causal relationship between exposure to quartz and lung cancer.

However, OSHA believes that the finding by Attfield and Costello (2004) of a positive exposure-response relationship for lung cancer among granite workers is more convincing than are the results from the Graham et al. (2004) study. In particular, OSHA believes it likely that some of the workers hired after 1940 continued to be exposed to dust levels that, although somewhat lower than before 1940, were still appreciably higher than those that resulted after dust controls had been fully implemented after 1950. For example, Attfield and Costello (2004) summarized respirable quartz levels for several granite shed jobs and reported that, for cutter/marker/surfacer jobs, respirable quartz exposures averaged 0.37 mg/m^3 prior to 1940, 0.22 mg/m^3 between 1940 and 1950, and 0.07 mg/m^3 after 1950. Similarly, crane operators, which included shed derrickmen, were exposed to average quartz levels of 0.14 mg/m^3 before 1940, 0.09 mg/m^3 between 1940 and 1950, and 0.03 mg/m^3 after 1950. OSHA notes that about one-fourth of the lung cancer deaths among post-1940 hires were associated with 40 or more years of latency, indicating that these workers were, for the most part, hired between 1940 and 1950. Given these considerations, OSHA believes that the finding by Attfield and Costello (2004) of a positive exposure-response relationship among granite workers, which was based on a quantitative assessment of the exposure of each cohort member, provides evidence of a causal relationship between exposure to crystalline silica and lung cancer, and that it is reasonable to estimate lung cancer risk from their analysis.

II.B.4. Kuempel et al. (2001) Assessment Based on a Lung Dosimetry Model.

Kuempel et al. (2001) used kinetic lung models for both rat and human to relate lung burden of crystalline silica to cancer risk based on studies of diatomaceous earth workers (Rice et al., 2001) and U.S. granite workers (Attfield and Costello, 2001). The models were also used to estimate a threshold lung burden of quartz above which macrophage-mediated particle clearance begins to decline and neutrophilic inflammation begins to increase. The rat model used is a compartmentalized model that was modified from a coal dust model to account for the uptake of silica particles by alveolar macrophages (AM) and, once a critical silica burden within the macrophages is reached, the initiation of the inflammatory response and subsequent impairment of particle clearance (Tran et al., 2001). Parameters of the model, which included the critical AM burden of silica particles and kinetics of neutrophil and alveolar macrophage recruitment, were estimated by fitting the model to NIOSH data obtained by exposing rats to MIN-U-SIL 5 for up to 84 days and measuring various indicators of inflammation. From the model estimate of critical AM silica burden, Kuempel et al. (2001) estimated the mean critical total quartz burden in the rat

lung and lymph nodes (M_{crit}) to be 0.39 mg/g lung; this represented the threshold for quartz-induced pulmonary inflammation and reduced particle clearance.

Kuempel et al. (2001) then used a previously developed human model describing respirable particle clearance and retention in coal miners to estimate the external exposure of respirable quartz necessary to accumulate a critical quartz burden in the lung. The human model was developed from data describing dust lung burdens in U.S. coal miners and modified to describe quartz clearance and retention based on quartz lung burden data from U.K. coal miners. The model predicted a quartz burden of about 1.7 times greater than the mean burden reported from autopsy data from U.S. coal workers, but the predicted value was within the confidence interval reported from the autopsy study. From this model, Kuempel et al. (2001) estimated that a 45-year exposure to 0.36 mg/m^3 respirable quartz was necessary to accumulate a total quartz burden (lung and lymph node) equal to the mean M_{crit} value of 0.39 mg/g. Since the critical quartz burden is a mean value derived from the model, the authors also reported that a 45-year exposure to 0.005 mg/m^3 respirable quartz would result in a lung quartz burden equal to the 95% lower confidence limit on M_{crit}.

The rat and human models were then used to estimate lung cancer risk as a function of lung burden in both rats and humans. Kuempel et al. (2001) found that the rat model yielded reasonably close predictions of long-term lung burden when compared to lung burden data from a 2-year quartz inhalation study in rats (Bellmann et al., 1991; Muhle et al., 1991; Muhle et al., 1995); overall, lung burden values predicted from the rat model were somewhat lower than those seen in chronically exposed rats, with the predicted burden after 2 years of exposure being 86 percent of the values reported from the chronic rat study (Muhle et al., 1991; Muhle et al., 1995). Using a linear multistage model, Kuempel et al. (2001) then used the rat lung model to predict excess lung cancer risks in rats at lung burdens equal to M_{crit}, and the quartz lung burden in humans associated with 45 years of exposure to 0.05 or 0.1 mg/m^3 respirable quartz.

Finally, Kuempel et al. (2001) used the dose coefficients from the previously discussed diatomaceous earth (Rice et al., 2001) and U.S. granite worker (Attfield and Costello, 2001) studies (linear relative risk models with cumulative exposure lagged 10 and 15 years, respectively) to estimate human lung cancer risk associated with 45 years of occupational exposure to respirable quartz at 0.036 mg/m^3, 0.05 mg/m^3 and 0.1 mg/m^3. Lifetime risk from each of these exposure levels, adjusted for competing mortality, was estimated through age 75 using a life table method and 1992 U.S. vital statistics for age-specific rates for lung cancer and competing causes of death.

The excess lung cancer risk predicted at the critical quartz dose using the relative rate coefficients from the diatomaceous earth and granite cohort studies were 8.7 deaths per 1,000 workers (95% upper confidence limit (UCL) of 18 per 1,000) and 9.7 per 1,000 (95% UCL of 15 per 1,000), respectively (lower confidence limits not reported). The predicted lung cancer risks for workers exposed to 0.1 mg/m^3 for 45 years were 24 per 1,000 (95% UCL of 50 per 1,000) from the diatomaceous earth study and 27 per 1,000 (95% UCL of 42 per 1,000) from the granite worker study. For exposure to 0.05 mg/m^3, predicted lung cancer risks were 12 per 1,000 (95% UCL of 26) and 13 per 1,000 (95% UCL of 21) for the diatomaceous earth and granite worker cohorts, respectively. The risk estimates based on the Muhle et al. (1991, 1995) 2-year rat study were about 3-fold higher for male rats, with a predicted excess risk at the critical dose of 28 per 1,000 (upper 95% confidence limit of 65 per 1,000). Kuempel et al. (2001) identified a number of

factors that may have contributed to the observed difference between the risk estimates based on epidemiological cohort studies and those based on animal data, including: (1) the risk estimates derived from animal data were based on a single chronic study that investigated several types of quartz using a single dose; (2) extrapolating from animals to humans involved an assumption that the critical mass of quartz in the lung is the same in rats and humans, on a mg/g lung basis; (3) use of mass as the dose metric assumes that the particle surface area, which may be a better predictor of risk than particle mass, was the same in rats and humans; and (4) potential misclassification of exposures in the human studies and possible confounding by smoking introduced uncertainties in the human data. Nevertheless, Kuempel et al. (2001) concluded that the estimates of excess cancer risk to rats and humans exposed to quartz are reasonably similar.

The work by Kuempel et al. (2001) suggests that lung burden may be a reasonable exposure metric for predicting lung cancer risk. Toxichemica, Inc. (2004) investigated whether use of the dosimetry model would substantially affect the results of the pooled lung cancer data analysis initially conducted by Steenland et al. (2001a). They replicated the lung dosimetry model using Kuempel et al.'s (2001) reported median fit parameter values, and compared the relationship between log cumulative exposure and 15-year lagged lung burden at the age of death in case subjects selected for the pooled case-control analysis. Although the two were found to be highly correlated ($r = 0.99$), Toxichemica, Inc. (2004) reported finding some differences between the two measures of exposure, particularly in individuals with sporadic exposures such as many workers in the Australia cohort. Fitting the conditional logistic regression model with a 15-year exposure lag, Toxichemica, Inc. (2004) found that log silica lung burden and log cumulative exposure were similarly good predictors of lung cancer risk in the pooled analysis (similar log-likelihoods of –4843.96 and –4843.996, respectively).

In summary, the Kuempel et al. (2001) study is a rat-based toxicokinetic/ toxicodynamic modeling effort to predict human lung cancer risk based on lung burden concentrations necessary to cause the precursor events that can lead to adverse physiological effects in the lung. These adverse physiological effects can then lead to lung fibrosis and an indirect genotoxic cause of lung cancer. The hypothesized first step, or earliest expected response, in these disease processes is chronic lung inflammation, which the authors consider as a disease limiting step. Since the threshold effect level of lung burden associated with this inflammation (M_{crit}), based on the authors' rat-to-human lung model conversion, is the equivalent of exposure to 0.036 mg/m^3 for 45 years, exposures below this level would presumably not lead to an excess lung cancer risk (based on an indirect genotoxic mechanism), at least in the "average individual." If at least some of the silica-related lung cancer risk is from a direct genotoxic mechanism, then this threshold value doesn't hold. Since silicosis also is inflammation mediated, this exposure could also be considered to be an average threshold level for that disease as well.

OSHA believes that the Kuempel et al. (2001) analysis is a credible attempt to quantitatively describe the retention and accumulation of quartz in the lung, and to relate the external exposure and its associated lung burden to the inflammatory process. However, for the purpose of quantitatively evaluating lung cancer risk in exposed workers, OSHA has chosen to rely on the epidemiology studies themselves and the exposure metrics used in those studies. The use by Kuempel et al. (2001) of the cumulative exposure coefficients from the two epidemiology studies to estimate lung cancer risk as a function of lung quartz burden involved converting cumulative exposure metrics to equivalent lung burdens after the epidemiology exposure-response

analysis has already been done; in other words, the analysis did not involve estimating lung burdens for individual cohort members (based on their exposure histories) in order to evaluate dose-response based on lung burden and mortality experience of the cohort. Therefore, OSHA believes that the dose-response analysis performed by Kuempel et al., adds little new information about the dose-response relationships seen in these studies beyond that provided by the epidemiological studies themselves. Although a risk assessment based on the estimated or measured lung burden in humans whose mortality experience is known might provide an improved basis for risk assessment, the Kuempel et al. (2001) analysis does not provide that kind of information.

II.B.5. Hughes et al. (2001) Analysis of Industrial Sand Workers.

McDonald et al. (2001), Hughes et al. (2001), and McDonald et al. (2005) followed up on a cohort study of North American industrial sand workers that overlapped with the industrial sand cohort (18 plants, 4,626 workers) studied by Steenland and Sanderson (2001). The McDonald et al. (2001) follow-up cohort included 2,670 men employed before 1980 for three years or more in one of nine North American (8 U.S. and 1 Canadian) sand-producing plants, including 1 large associated office complex. Information on cause of death was obtained, from 1960 through 1994, for 99 percent of the deceased workers for a total 1,025 deaths representing 38 percent of the cohort. A nested case-control analysis based on 90 lung cancer deaths from this cohort was also conducted by Hughes et al. (2001). A later update, through 2000, of both the cohort and nested case-control studies by McDonald et al. (2005), eliminated the Canadian plant, following 2,452 men from the 8 U.S. plants. For the lung cancer case-control part of the study, the update included 105 lung cancer deaths. Both the initial and update case control studies used up to two controls per case. Both of these case-control analyses relied on an analysis of exposure information published by Rando et al. (2001). Additional details on these studies are given in the Health Effects literature review (section I.B).

The cohort study by McDonald et al. (2001) showed a statistically significantly elevated SMR for trachea/lung/bronchus cancer (83 deaths, SMR = 150, $p = 0.001$, based on U.S. rates) for deaths occurring 20 or more years from hire. The SMR for trachea/lung/bronchus cancer declined slightly when regional cancer mortality rates were used (SMR = 139, $p = 0.001$). SMRs for trachea/lung/bronchus cancer, using U.S. rates, increased with increasing time since hire (SMRs: 87, 127 and 162 for <20, 20-30 and $\geq$ 30 years, respectively), but not with duration of employment. There was no consistent correlation between duration of employment and lung cancer risk in this cohort. SMRs for NMRD and tuberculosis were statistically elevated for deaths occurring 20 years or more from hire (SMR = 178 (97 deaths) and 393 (8 deaths) for <20 and $\geq$ 30 years, respectively; $p < 0.01$). McDonald et al. (2001) also noted a statistically significant elevation in chronic renal disease (SMR = 212; 16 deaths; $p < 0.002$).

Although the cohort studies provided evidence of increased risk from lung cancer, the nested case-control studies, Hughes et al. (2001) and McDonald et al. (2005), allowed for individual job, exposure, and smoking histories to be taken into account, allowing for good exposure-response analysis for lung cancer. The method of determining exposure and developing a job exposure matrix was reported by Sanderson et al. (2000). Smoking data were collected from medical records supplemented by information from next of kin or living subjects for over 90 percent of cases and controls. These case-control studies were analyzed by conditional logistic

regression to evaluate the relationships between lung cancer mortality and cumulative exposure, average exposure, duration, and peak exposure, all adjusted for smoking histories. Statistically significant positive exposure-response trends for lung cancer were found for both cumulative exposure (lagged 15 years) and average exposure concentration, but not for duration of employment, after controlling for smoking. A monotonic increase was seen for both lagged and unlagged cumulative exposure when the four upper exposure categories were collapsed into two. With exposure lagged 15 years and after adjusting for smoking, increasing quartiles of cumulative silica exposure were associated with lung cancer mortality odds ratios of 1.00, 0.84, 2.02 and 2.07 (p-value for trend = 0.04). There was no indication of an interaction effect of smoking and cumulative silica exposure (Hughes et al., 2001).

OSHA considers this Hughes et al (2001) study and analysis to be of high enough quality to provide risk estimates for excess lung cancer for silica exposure to industrial sand workers. Using the median exposure levels of 0, 0.758, 2.229 and 6.183 mg-years/m^3, respectively, for each of the four categories described above, and using the model: ln OR = $\alpha + \beta$ x Cumulative Exposure, the coefficient for the exposure estimate was $\beta = 0.13$ per (mg/m^3-years), with a standard error of $\beta = 0.074$ (calculated from the trend test p-value in the same paper). In this model with background lung cancer risks of about 5 percent, the OR provides a suitable estimate of the relative risk. Using this slope estimate from Hughes et al. (2001), OSHA has used the life table program (see Appendix) to estimate excess lifetime lung cancer risks for these workers at concentrations from 0.025 to 0.5 mg/m^3 for 45 years. At the proposed action level, the proposed PEL, and the current general industry PEL, excess risk estimates from this study are 7, 15, and 34 deaths per 1,000 workers, respectively. For exposure at the higher construction/shipyard PEL, the estimated risk ranges from 120 to 387 deaths per 1,000. The estimates at the lower exposure levels of 0.025, 0.05 and 0.10 mg/m^3 levels very closely approximate those of the other studies for which OSHA has estimated excess risk. Some divergence in the risk estimates seen at the higher exposure levels is related to the risk models used.

The McDonald et al. (2005) update of the Hughes et al. (2001) study, extended the observation period by six years, from 1995 to 2000. In the original cohort study, there were 990 deaths among a cohort of industrial sand workers employed in nine plants. The update was limited to workers in eight U.S. plants, eliminating the Canadian plant. An additional 231 deaths were identified, for a total of 1,205 deaths (49 percent of the cohort). Vital status and cause of death was obtained and determined for 99 percent of the cohort. Exposure estimation and case-control selection and analysis were similar to the original study. Differences in smoking were analyzed by conditional multiple regression and exposure categories were the same as in the original study.

The findings of the follow-up study confirmed the findings of the original Hughes et al. (2001) analysis. SMRs for all causes of death, based on U.S. male death rates, for workers who died 20 or more years after hire were elevated in the follow-up (SMR = 142; $p < 001$) as compared to the initial study (SMR = 118; $p < 0.001$). Elevated SMRs were also identified for lung cancer (SMR = 147, $p = 0.001$, 102 deaths) for workers who died 20 or more years after hire. These values were not significantly different than the initial study. Also, as was observed in the original study, the follow-up study found that the risk of lung cancer was related to average silica concentration but not to the length of employment. Smoking was independently and strongly related to silicosis and lung cancer.

For the updated nested case control analysis McDonald et al. (2005) found that, with exposure lagged 15 years and after adjusting for smoking, increasing quartiles of cumulative silica exposure were associated lung cancer odds ratios (deaths) of 1.00 (13), 0.94 (17), 2.24 (38), and 2.66 (37) (p-value for trend = 0.006). These OR's were very similar to the original study. The slope of this exposure-response from the update appeared to be slightly greater than the slope given by Hughes et al. (2001), but could not be calculated with assurance, because, unlike Hughes et al. (2001), the medians of the exposure categories were not provided in the update. Because of the missing information in the McDonald et al. (2005) update, and because of otherwise very similar results in the two papers, OSHA has chosen to base its lifetime excess lung cancer risk estimate for these industrial sand workers on the Hughes et al. (2001) case-control study.

II.B.6. Miller and MacCalman (2009) Analysis of British Coal Workers.

Miller et al. (2007) and Miller and MacCalman (2009) conducted a follow-up study of cohort mortality, begun in 1970. Their previous report on mortality presented a follow-up analysis on 18,166 coalminers from 10 British coalmines followed through the end of 1992 (Miller et al., 1997). The two recent reports analyzed the mortality experience of 17,800 of these miners (18,166 minus 346 men whose vital status could not be determined), and extended the analysis through the end of 2005. By that time, there were 516,431 person years of observation, an average of 29 years per miner, with 10,698 deaths from all causes. Causes of deaths of interest included pneumoconiosis, other non-malignant respiratory diseases (NMRD), lung cancer, stomach cancer, and tuberculosis. The authors noted that no additional exposure measurements were included in the updated analysis, since all the mines had closed by the mid 1980's. However, some of these men might have had additional exposure at other mines or facilities, not reported in this study. (One of these coalmines has already been discussed in section I.B.3.a, above for the relationship of silica exposure and silicosis progression and morbidity among 547 miners exposed to high levels of quartz during the early to mid 1970's.)

For this cohort mortality study there were analyses using both external and internal controls. The external controls used British administrative regional age-, time-, and cause-specific mortality rates from which to calculate SMR's. The internal controls from the mines used Cox's proportional hazards regression methods, which allowed for each individual miner's age and smoking status, as well as the individual's detailed dust and quartz time-dependent exposure measurements. Cox regression analyses were done in stages, with the initial analyses used to establish what factors were required for baseline adjustment.

For the analysis using external mortality rates, the all-cause mortality SMR from 1959 through 2005 was 100.9 (95% C.I., 99.0-102.8), based on all 10,698 deaths. However, these SMRs were not uniform over time. For the period from 1990-2005, the SMR was 109.6 (95% CI 106.5-112.8), while the ratios for previous periods were less than 100. This pattern of increasing SMRs in the recent past was also seen for cause-specific deaths from chronic bronchitis, SMR = 330.0 (95% CI 268.1-406.2); tuberculosis, SMR = 193.4 (95% CI 86.9-430.5); cardiovascular disease, SMR = 106.6 (95% CI 102.0-111.5); all cancers, SMR = 107.1 (95% CI 101.3-113.2); and lung cancer, SMR = 115.7 (95% CI 104.8-127.7). The SMR for NMRD was 142.1 (95% CI 132.9-152.0) in this recent period, and remained highly statistically significant. In their previous analysis on mortality from lung cancer, reflecting follow-up through 1995, Miller et al. (1997), had not found any increase in lung cancer mortality risk.

Three of the strengths of this study are the availability of detailed time-exposure measurements of both quartz and total mine dust, detailed individual work histories, and individual smoking histories. All these data were used in the internal analyses using Cox regression methods. Using these analyses, Miller and MacCalman (2009) estimated relative risks for a lifetime exposure of 5 gram-hours/m^3 (ghm^{-3}) to respirable quartz (equivalent to approximately 0.055 mg/m^3 for 45 years, assuming 2,000 hours per year of exposure) and/or 100 ghm^{-3} total dust. They presented (see their Table 4) estimated relative risks for various causes of death - pneumoconiosis, COPD, ischemic heart disease, lung cancer, and stomach cancer - based on models with either single (dust or quartz) exposures or to simultaneous exposures to both, either with or without 15-year lag periods. Generally, the risk estimates were slightly greater using a 15-year lag period. For the models using only quartz exposures with a 15-year lag, only pneumoconiosis, RR = 1.21 (95% CI 1.12-1.31); COPD, RR = 1.11 (95% CI 1.05-1.16); and lung cancer, RR = 1.07 (95% CI 1.01-1.13) showed statistically significant increased risks.

For lung cancer, analyses based on these Cox regression methods provide strong evidence that, for these coal miners, quartz exposures were associated with increased lung cancer risk, but simultaneous exposures to coal dust were not associated with increased lung cancer risk. The relative risk estimate for lung cancer deaths using coal dust with a 15-year lag in the single exposure model was 1.03 (95% CI 0.96 to 1.10). In the model using both quartz and coal mine dust exposures, the relative risk based on coal dust decreased to 0.91, while that for quartz exposure remained statistically significant, increasing to a RR = 1.14 (95% CI 1.04 to 1.25).

The RRs in the Miller and MacCalman (2009) report can be used to estimate excess lung cancer risk for OSHA's purposes, using the same life table analyses as was done for the other studies above. Based on the relative risk of 1.14 (95% C.I. 1.04-1.25) for a cumulative exposure of 5 ghm^{-3}, the regression slope is recalculated as $\beta = 0.0524$ per mg/m^3-years and used in the life table program (see Appendix). Similarly, the 95-percent confidence interval on slope is 0.0157 – 0.08926. From this study, the lifetime (to age 85) risk estimates for 45 years of exposure to 0.05 mg/m^3 and 0.100 mg/m^3 crystalline silica are 6 and 13 excess lung cancer deaths per 1,000 workers, respectively. These lung cancer risk estimates are less by about 2- to 4-fold than those estimated from the other cohort studies described above. However, three factors might explain these differences. First, these estimates are adjusted for individual smoking histories so any smoking-related lung cancer risk (or smoking – silica interaction) that might possibly be attributed to silica exposure in the other studies will not be reflected in the risk estimates derived from the study of these coalminers. Second, these coalminers had significantly increased risks of death from other lung diseases, which could tend to decrease the lung-cancer-susceptible population. Of note, for example, are the higher increased SMRs for NMRD during the years 1959-2005 for this cohort (see Table 2, Miller and MacCalman, 2009). Third, the difference in risk seen in these coalminers could be the result of differences in the toxicity of quartz present in the coal mines as compared to the work environments of the other cohorts. One Scottish mine (Miller et al., 1998) in this 10-mine study had been cited as having presented "unusually high exposures to [freshly fractured] quartz." However, this was also described as an atypical exposure among miners working in the 10 mines. Miller and MacCalman (2009) stated that increased quartz-related lung cancer risk in their cohort was not confined to that Scottish mine alone. They also stated that "the general nature of some quartz exposures in later years … may have been different from earlier periods when coal extraction was largely manual …."

All of these factors in this British coalminer cohort mortality analysis could combine to yield lung cancer risk estimates on the lower side of all the lung cancer risk estimates. However, OSHA believes that these coalminer-derived estimates are quite credible because of the quality of several study factors relating to both study design and conduct. In terms of design, the cohort was based on union rolls with very good participation rates and good reporting. The study group was also over 17,000 with an average of nearly 30 years of follow-up, and about 60 percent of the cohort had died. Just as important was the high quality and detail of the exposure measurements, both of total dust and quartz. However, one exposure factor that may have biased the estimates upward was the lack of exposure information available for the cohort after the mines closed in the mid 1980's. Since the lung cancer death ratio was higher during this last study period, 1990 – 2005, this period of time contributed to the increased lung cancer risk. It is possible that any quartz exposure experienced by the cohort after the mines had closed could have accelerated either death or tumor growth. Not accounting for this exposure, if there were any, would bias the risk estimates upwards. Although the 15-year lag period for quartz exposure used in the analyses provided slightly higher risk estimates than use of no lag period, the better fit seen with the lag may have been artificial, since there appear to have been no exposures during the recent period when risks were seen to have increased.

II.B.7. Summary of OSHA's Estimates of Lung Cancer Mortality Risk.

Table II-2 summarizes the excess risk estimates based on each of the lung cancer risk assessments discussed in this section. OSHA's estimates of lifetime lung cancer risk associated with 45 years of exposure to crystalline silica at 0.1 mg/m^3 (approximately the current general industry PEL) range from 13 to 60 deaths per 1,000 workers. For exposure to the proposed PEL of 0.05 mg/m^3, the lifetime risk estimates calculated by OSHA are in the range of 6 to 26 deaths per 1,000. For a 45-year exposure at he proposed action level of 0.025 mg/m^3, OSHA estimates the risk to range from 3 to 23 deaths per 1,000 workers. The results from these assessments are reasonably consistent despite the use of data from different cohorts and the reliance on different analytical techniques for evaluating dose-response relationships. Furthermore, OSHA notes that in this range of exposure there is statistical consistency between the risk estimates, as evidenced by the considerable overlap in the 95-percent confidence intervals of the risk estimates presented in Table II-2.

Estimating lung cancer risks over the range of cumulative exposures of interest to OSHA required some degree of extrapolation above the range of exposures experienced by most of the workers included in the occupational studies. Exposure to 0.25 or 0.5 mg/m^3 (the range approximating the current construction/shipyard PEL) over 45 years represents cumulative exposures of 11.25 and 22.5 mg/m^3-years, respectively. This range of cumulative exposure is well above the median cumulative exposure for the diatomaceous earth cohort, the U.S. granite cohort, and each of the other cohorts included in the pooled risk analysis, the highest being 11.37 mg/m^3-years for the Australian gold miner cohort. In addition, third quartile cumulative exposures were within or above this range for only three cohorts (Australian gold miners, Chinese tungsten miners, and Finnish granite workers, see Table II of Mannetje et al., 2002a), although for 7 of the 10 cohorts, the maximum cumulative exposure of cohort members exceeded this range. As such, a 45-year occupational exposure to 0.25 or 0.5 mg/m^3 respirable silica reflects cumulative exposures of the minority of workers who were the most highly exposed among the cohorts included in the

Table II-2. Estimates of Lifetime[a] Lung Cancer Mortality Risk Resulting from 45-Years of Exposure to Crystalline Silica (Deaths per 1,000 Workers (95% Confidence Interval))

Cohort	Model	Exposure Lag (years)	Model Parameters (Standard Error)	Exposure Level (mg/m^3)				
				0.025	0.05	0.10	0.25	0.50
Ten pooled cohorts (see Table II-1)	Log-linear[b]	15	$\beta = 0.60$ (0.015)	22 (11-36)	26 (12-41)	29 (13-48)	34 (15-56)	38 (17-63)
	Linear[b]	15	$\beta = 0.074950$ (0.024121)	23 (9-38)	26 (10-43)	29 (11-47)	33 (12-53)	36 (14-58)
	Linear Spline[c,d]	15	$\beta_1 = 0.16498$ (0.0653) and $\beta_2 = -0.1493$ (0.0657)	9 (2-16)	18 (4-31)	22 (6-38)	27 (12-43)	36 (20-51)
Range from 10 cohorts	Log-linear[c]	15	Various	0.21 – 13	0.41 – 28	0.83 – 69	2.1 – 298	4.2 - 687
Diatomaceous earth workers	Linear[c]	10	$\beta = 0.1441$[e]	9 (2-21)	17 (5-41)	34 (10-79)	81 (24-180)	152 (46-312)
U.S.Granite workers	Log-linear[c]	15	$\beta = 0.19$[e]	11 (4-18)	25 (9-42)	60 (19-111)	250 (59-502)	653 (167-760)
North American industrial sand workers	Log-linear[c]	15	$\beta = 0.13$ (0.074)[f]	7 (0-16)	15 (0-37)	34 (0-93)	120 (0-425)	387 (0-750)
British coal miners	Log-linear[c]	15	B = 0.0524 (0.0188)	3 (1-5)	6 (2-11)	13 (4-23)	37 (9-75)	95 (20-224)

Footnotes for Table II-2

[a] Risk to age 85 and based on 2006 background mortality rates for all males (see Appendix for life table method).

[b] Model with log cumulative exposure (mg/m^3-days + 1).

[c] Model with cumulative exposure (mg/m^3-years).

[d] 95% confidence interval calculated as follows (where CE = cumulative exposure in mg/m^3-years and SE is standard error of the parameter estimate):

For $CE \leq 2.19$: $1 + [(\beta_1 \pm (1.96 * SE_1)) * CE]$

For $CE > 2.19$: $1 + [(\beta_1 * CE) + (\beta_2 * (CE-2.19))] \pm 1.96 * SQRT[(CE^2 * SE_1^2) + ((CE-2.19)^2 * SE_2^2) + (2*CE*(CE-3.29)*-0.00429)]$

[e] Standard error not reported, upper and lower confidence limit on beta estimated from confidence interval of risk estimate reported in original article.

[f] Standard error of the coefficient was estimated from the p-value for trend.

pooled analysis and thus represents cumulative exposures that lie above the observed range of exposures experienced by most of the workers included in the pooled cohort study.

Thus, estimates of lung cancer risk at higher exposures approximating the current construction/shipyard PEL (0.25 and 0.5 mg/m^3) are more uncertain. The estimates calculated by OSHA based on four individual cohort studies range from 37 to 250 deaths per 1,000 at 0.25 mg/m^3, and range from 95 to 653 deaths per 1,000 at 0.5 mg/m^3. Estimates based on the model from the pooled analysis yielded estimates approximately 1.3- to 18-fold lower (27 to 34 deaths per 1,000 at 0.25 mg/m^3 and 36-38 deaths per 1,000 at 0.5 mg/m^3). This difference reflects the shape of the underlying exposure-response model, which flattens out at higher exposures. It is unclear whether the flattening out of the exposure-response curve fit by Steenland et al. (2001a) captures some feature of the actual exposure-response (e.g., a decline in slope at high exposures due to saturation or an increase in competing non-cancer risks associated with exposure to silica), or whether attenuation of the observed exposure-response slope reflects methodological limitations (such as the presence of a survivor effect, or exposure misclassification). All of these were suggested by Steenland et al. (2001a) as reasons why attenuation of the observed exposure-response curve is often observed in epidemiological studies. OSHA notes that, in contrast, such attenuation of the exposure-response curve was not seen in three of the four individual cohort studies evaluated in the risk assessment (Rice et al., 2001; Hughes et al., 2001; Miller and MacCalman et al., 2009), and, in the fourth study used by OSHA (Attfield and Costello, 2004), the exposure-response trend was linear except for a decline in the lung cancer rate seen only for the highest exposure group. This group had cumulative exposures of 6 mg/m^3-years or more with an average of about 10 mg/m^3-years, which corresponds to 45 years of exposure to 0.22 mg/m^3. In contrast, no decline in lung cancer mortality rate was evident among diatomaceous earth workers with similarly high exposures (13 mg/m^3-years or higher), based on a categorical analysis of the cohort (see Figure 1 in Rice et al., 2001). In the industrial sand and coal miner studies, cumulative exposures of the more highly exposed workers were comparable to the granite and diatomaceous earth studies, with the 75th-percentile exposure of industrial sand workers being about 5 mg/m^3-years (Hughes et al., 2001) and the upper quartile of cumulative exposure for the coal miners reported to be about 9 ghm^{-3} (4.5 mg/m^3-years), with a maximum exposure of 42 ghm^{-3} (21 mg/m^3-years) (Miller and MacCalman, 2009). There was no evidence of a decline in lung cancer mortality among the more highly exposed workers in these two cohorts based on information presented in the reports.

It should also be noted that, although the log transformation of cumulative exposure reduced the heterogeneity observed by Steenland et al. among the 10 cohorts used in the pooled analysis, there was no statistically significant difference in fit between the models using log-transformed cumulative exposure vs. untransformed lagged cumulative exposure. OSHA believes that use of log-transformed cumulative exposure provides a highly credible basis for deriving a central tendency estimate of risk from the 10 cohorts used for the analysis, but these estimates of risk may understate the risk presented to workers in some industry sectors, based on risk estimates derived from the single-cohort studies.

The cohort studies included in the pooled analysis relied in part on particle count data and the use of conversion factors to estimate exposures of workers to mass respirable quartz. A few studies were able to include at least some respirable mass sampling data. OSHA believes that uncertainty in the exposure assessments that underlie each of the 10 studies included in the pooled analysis is likely to represent one of the most important sources of uncertainty in the risk estimates. To evaluate the potential impact of uncertainties in the underlying exposure assessments on estimates of the risk, OSHA's contractor, Toxichemica, Inc. (2004), commissioned Drs. Kyle Steenland and Scott Bartell of Emory University to conduct an uncertainty analysis using the raw data from the pooled cancer risk assessment. The findings from their uncertainty analysis and other sources of uncertainty in OSHA's risk estimates, such as selection bias and confounding by smoking and occupational co-exposures, are presented in section II-D following the discussion of silicosis and non-malignant respiratory disease mortality risk below.

II.C. Silicosis and Non-Malignant Respiratory Disease Mortality Risk Estimates.

There are two published quantitative risk assessment studies of silicosis and non-malignant respiratory disease (NMRD) mortality; a pooled analysis of silicosis mortality by Mannetje et al. (2002b) of data from six epidemiological studies, and an exposure-response analysis of NMRD mortality among diatomaceous earth workers (Park et al., 2002). These studies are summarized below, with detailed discussion and analysis of uncertainty in the studies and associated risk estimates.

II.C.1. Mannetje et al. (2002b) Pooled Analysis.

The pooled analysis conducted by Mannetje et al. (2002b) was based on six of the ten cohorts that were part of the IARC multi-centric exposure-response study of lung cancer (Steenland et al., 2001a) discussed in section II.B.1 above, including U.S. diatomaceous earth (DE) workers (Checkoway et al., 1997); Finnish granite workers studied by Koskela et al. (1994); U.S. granite workers assessed by Costello and Graham (1988); U.S. industrial sand workers examined by Steenland et al. (2001b); U.S. gold miners studied by Steenland and Brown (1995b); and Australian gold miners assessed by de Klerk and Musk (1998). These six cohorts contained 18,634 subjects and 170 silicosis deaths, where Mannetje et al. (2002b) defined silicosis mortality as death from silicosis (ICD-9 502, n = 150) or from unspecified pneumoconiosis (ICD-9 505, n = 20). The authors believed this definition to be conservative in that some cases of death from silicosis in the cohorts were probably miscategorized as other causes (e.g., tuberculosis or chronic obstructive pulmonary disease without mention of pneumoconiosis). Information on these cohorts is provided in Table II-3, including size, time period studied, overall number of deaths and number of deaths identified as silicosis for the pooled analysis. Four cohorts were not included in the silicosis mortality study; the three Chinese studies did not use the International Classification of Diseases (ICD) to code cause of death and, in the South African gold miner study, silicosis was not generally recognized as an underlying cause of death in South Africa and thus did not appear on death certificates.

Table II-3. Summary of Cohort Data Used in the Pooled Analysis for Silicosis Mortality

Author	Cohort	Size of cohort	Time period of study	Number of deaths	Number of silicosis deaths
Checkoway et al., 1997	U.S. diatomaceous earth	2,342	1942-1994	749	15 ("other" NMRD[a], including silicosis)
Koskela et al., 1994	Finnish granite	1,026	1940-1993	418	14
Costello and Graham, 1988	U.S. granite	5,408	1950-1982	1,762	43
Steenland et al., 2001b	U.S. industrial sand	4,027	1974-1996	860	15
Steenland and Brown, 1995b	U.S. gold miners	3,348	1940-1996	1925	39
de Klerk and Musk, 1998	Australian surface and underground gold miners	2,213	1961-1993	1,351	44

Footnotes for Table II-3

[a] Non-malignant respiratory disease

Source: Adapted from Mannetje et al., 2002b

The exposure assessment used in the pooled silicosis mortality study is the same as that used in the lung cancer study and is summarized in section II.B.1 (Mannetje et al., 2002a). As also discussed in Section II.B.1, an analysis later conducted by Dr. Kyle

Steenland for OSHA corrected a small number of errors primarily related to rounding in exposure calculations for the originally reported results. Correction of these errors did not significantly impact the results of the exposure-response analysis (Toxichemica, Inc., 2004).

Silicosis mortality was evaluated using standard life table analysis. Poisson regression, using ten categories of cumulative exposure and adjusting for age, calendar time, and cohort, was conducted to derive silicosis mortality rate ratios using the lowest exposure group (0-1 mg/m^3-year) as the referent group. More detailed exploration of the exposure-response curve using a variety of exposure metrics, including cumulative exposure, duration of exposure, average exposure (calculated as cumulative exposure/duration), and the log transformations of these variables, was conducted via nested case-control analyses (conditional logistic regression). Each case was matched to 100 controls selected from among those who had survived to at least the age of the case, with additional matching on cohort, race, sex, and date of birth within five years. The authors explored lags of 0, 5, 10, 15, and 20 years, noting that there is no a priori reason to apply an exposure lag, as silicosis can develop within a short period after exposure, but that a lag could potentially improve the model as there is often a considerable delay in the development of silicosis following exposure. In addition to the parametric conditional logistic regression models, the authors ran some analyses using a cubic spline model with knots at 5%, 25%, 50%, 75%, and 95% of the distribution of exposure. Models with cohort-exposure interaction terms were fit to assess heterogeneity between cohorts.

The categorical analysis found a nearly monotonic increase in silicosis rates with cumulative exposure, from 4.7 per 100,000 person-years in the lowest exposure category (0-0.99 mg/m^3-years) to 299 per 100,000 person-years in the highest exposure category (>28 mg/m^3-years). Nested case-control analyses showed a significant association between silicosis mortality and cumulative exposure, average exposure, and duration of exposure. The best fitting conditional logistic regression model used log-transformed cumulative exposure with no exposure lag, with a model χ^2 of 73.2 vs. χ^2 values ranging from 19.9 to 30.9 for average exposure, duration of exposure, and untransformed cumulative exposure (1 d.f.). No significant heterogeneity was found between individual cohorts for the model based on log-cumulative exposure. The cubic-spline model did not improve upon the model fit for the parametric logistic regression model using the log of cumulative exposure.

Mannetje et al. (2002b) developed estimates of silicosis mortality risk through age 65 for two levels of exposure (0.05 and 0.1 mg/m3 crystalline silica), assuming a working lifetime of occupational exposure from age 20 to 65. Risk estimates were calculated based on the silicosis mortality rate ratios derived from the categorical analysis described above using the standard formula:

$$\text{Risk} = 1 - \exp(-\sum \text{time} * \text{rate})$$

Here, the time period over which workers' exposures and risk are calculated (age 20 to 65) is divided into one-year intervals, and the mortality rate used to calculate risk in any given interval depends on the worker's cumulative exposure at that time; the equation is:

$$\text{Risk} = 1 - \exp\left(- \sum_{i=20}^{65} time_i \cdot rate_i \right)$$

where $time_i$ is equal to 1 for every age i, and $rate_i$ is the age-, calendar time-, and cohort-adjusted silicosis mortality rate associated with the level of cumulative exposure acquired at age i, as presented in Table 2 of Mannetje et al., 2002b). Absolute risks rather than excess risks were calculated since there is no background rate of silicosis in the exposed population. Mannetje et al. (2002b) estimated the lifetime risk of death from silicosis, assuming 45 years of exposure to 0.1 mg/m^3 to be 13 deaths per 1,000 workers; at an exposure of 0.05 mg/m^3, the estimated lifetime risk was 6 per 1,000 (confidence intervals not reported).

To estimate the risk of silicosis mortality at the current and proposed PELs, OSHA used the model described by Mannetje et al. (2002b) but used rate ratios that were estimated from a nested case-control design implemented as part of a sensitivity analysis conducted by Toxichemica, Inc. (2004), rather than the Poisson regression originally conducted by Mannetje et al. (2002b). The case-control design was selected because it was expected to better control for age; in addition, the rate ratios derived from the case-control study were derived from a Monte Carlo analysis to reflect exposure measurement uncertainty (see section II.D below). (The adjusted rate ratios appear in Table 7 of Toxichemica, Inc. (2004) and in Table II-8 of this report). The rate ratio for each interval of cumulative exposure was multiplied by the annual silicosis rate assumed to be associated with the lowest exposure interval, 4.7 per 100,000 for exposures of 0-0.99 mg/m^3-years, to estimate the silicosis rate for each interval of exposure. The lifetime silicosis mortality risk is the sum of the silicosis rate for each year of life through age 85 and assuming exposure from age 20 to 65. From this analysis, OSHA estimates the silicosis mortality risk for exposure to the current general industry and proposed PEL to be 11 (95% CI 5-37) and 7 (95% CI 3-21) deaths per 1,000 workers. For exposure to 0.25 and 0.5 mg/m^3, the range approximating the current construction/shipyard PEL, OSHA estimates the risk to range from 17 (95% CI 5-66) to 22 (95% CI 6-85) deaths per 1,000.

II.C.2. Park et al. (2002) Study of Diatomaceous Earth Workers.

Park et al. (2002) analyzed the California diatomaceous earth cohort data originally studied by Checkoway et al. (1997), consisting of 2,570 diatomaceous earth workers employed for 12 months or more from 1942 to 1994, to quantify the relationship between exposure to cristobalite and mortality from chronic lung disease other than cancer (LDOC). Diseases in this category included pneumoconiosis (which included silicosis), chronic bronchitis, and emphysema, but excluded pneumonia and other infectious diseases. The investigators selected LDOC as the health endpoint for three reasons. First, increased mortality from LDOC had been documented among crystalline silica-exposed workers in several industry sectors, including gold mining, pottery, granite, and foundry industries (see Section I.D. of the Health Effects literature review for a discussion). In addition, they pointed to the likelihood that silicosis as a cause of death is often misclassified as emphysema or chronic bronchitis. Finally, the number of deaths

from the diatomaceous earth worker cohort that were attributed to silicosis was too small (10) for analysis. Industrial hygiene data for the cohort were available from the employer for total dust, silica (mostly cristobalite), and asbestos. Smoking information was available for about 50 percent of the cohort and for 22 of the 67 LDOC deaths available for analysis, permitting Park et al. (2002) to at least partially adjust for smoking.

Park et al. (2002) used the exposure assessment previously reported by Seixas et al. (1997) and used by Rice et al. (2001) to estimate cumulative crystalline silica exposures for each worker in the cohort based on detailed work history files, as discussed in Section I.C.2.r. of Health Effects. The mean silica concentration for the cohort overall was 0.29 mg/m^3 over the period of employment (Seixas et al., 1997). The total respirable dust concentration in the diatomaceous earth plant was 3.55 mg/m^3 before 1949, and declined by more than 10-fold after 1973. The concentration of crystalline silica in the dust ranged from 1 to 25 percent depending on location within the establishment; it was lowest at the mine and greatest in the plant where the raw ore was calcined into final product. The mean cumulative exposure values for total respirable dust and respirable crystalline silica were 7.31 and 2.16 mg/m^3-year, respectively. Similar cumulative exposure estimates were made for asbestos.

Using both Poisson regression models and Cox's proportional hazards models, they fit the same series of relative rate exposure-response models that were evaluated by Rice et al. (2001) for lung cancer (i.e., log-linear, log-square root, log-quadratic, linear relative rate, a power function, and a shape function). In general form, the relative rate model was:

$$\text{Rate} = \exp(a_0) \times f(E),$$

where $\exp(a_0)$ is the background rate and E is the cumulative exposure to silica. Park et al. (2002) also employed an additive excess rate model of the form:

$$\text{Rate} = \exp(a_0) + \exp(aE).$$

Relative or excess rates were modeled using internal controls and adjusting for age, calendar time, ethnicity (Hispanic versus white), and time since first entry into the cohort. In addition, relative rate models were evaluated using age- and calendar time-adjusted external standardization to U.S population mortality rates for 1940 to 1994.

There were no LDOC deaths recorded among workers having cumulative exposures above 32 mg/m^3-years, causing the response to level off or decline in the highest exposure range. The authors believed the most likely explanation for this observation (which was also observed in their analysis of silicosis morbidity in this cohort, see section II.F.2 below) was some form of survivor selection, possibly smokers or others with compromised respiratory function leaving work involving extremely high dust concentrations. Alternative explanations suggested by the investigators included a greater depletion of susceptible populations in high dust areas, a higher degree of misclassification of exposures in the earlier years where exposure data were lacking (and when exposures were presumably the highest), and the nature of relative risk models for

which both background disease rates and cumulative exposures increase with age. Therefore, Park et al. (2002) performed exposure-response analyses that restricted the dataset to observations where cumulative exposures were below 10 mg/m^3-years, a level more than four times higher than that resulting from 45 years of exposure to the current PEL for cristobalite (which is about 0.05 mg/m^3), as well as analyses using the full dataset.

Model fit was assessed by evaluating the decrease in deviance resulting from addition of the exposure term, and cubic spline models were used to test for smooth departures from each of the model forms described. Park et al. (2002) found that both lagged and unlagged models fit well, but that unlagged models provided a better fit. In addition, they believed that unlagged models were biologically plausible in that recent exposure could contribute to LDOC mortality. The Cox's proportional hazards models yielded results that were similar to those from the Poisson analysis; consequently, only the results from the Poisson analysis were reported. In general, the use of external adjustment for age and calendar time yielded considerably improved fit over models using internal adjustment. The additive excess rate model also proved to be clearly inferior compared to the relative rate models. Use of cumulative exposure as the exposure metric consistently provided better fits to the data than did intensity of exposure (cumulative exposure divided by duration of exposure), with one exception: when the highest-exposure cohort members were included in the analysis, the log linear model produced a significantly improved fit with exposure intensity as the exposure metric, but a poor fit with cumulative dose as the metric.

Among the models based on the restricted dataset (excluding observations with cumulative exposures $\geq$ 10 mg/m^3-years) the best-fitting model with a single exposure term was the linear relative rate model using external adjustment. Most of the other single-term models using external adjustment fit almost as well. Of the models with more than one exposure term, the shape model provided no improvement in fit compared with the linear relative rate model; the log-quadratic model fit slightly better than the linear relative rate model, but Park et al. (2002) did not consider the gain in fit sufficient to justify an additional exposure term in the model.

Based on its superior fit to the cohort data, Park et al. (2002) selected the linear relative rate model with external adjustment and use of cumulative exposure as the basis for estimating LDOC mortality risks among exposed workers. Competing mortality was accounted for using U.S. background death rates published by the National Center for Health Statistics (1996). The authors estimated the excess lifetime risk for white men exposed to mainly respirable cristobalite dust for 45 years at 0.05 mg/m^3 to be 54 deaths per 1000 workers (95% CI 17, 150) using the restricted dataset, and 50 deaths per 1000 using the full dataset (confidence interval not reported). For exposure to 0.1 mg/m^3, they estimated 100 deaths per 1000 using the restricted dataset, and 86 deaths per 1000 using the full dataset (confidence intervals not reported).

Park et al.'s (2002) estimates, which are about 8 to 9 times higher than those calculated for the pooled analysis of silicosis mortality (Mannetje et al., 2002b), are not directly comparable to the Mannetje et al. risk estimates since the mortality endpoint for

the Park et al. (2002) analysis is death from all non-cancer lung diseases, including pneumoconiosis, emphysema, and chronic bronchitis, whereas the pooled analysis by Mannetje et al. (2002b) included only deaths coded as silicosis or other pneumoconiosis. Less than 25% of the LDOC deaths in the Park et al. (2002) analysis were coded as silicosis or other pneumoconiosis (15 of 67). As noted by Park et al. (2002), it is likely that silicosis as a cause of death is often misclassified as emphysema or chronic bronchitis; thus, Mannetje et al.'s selection of deaths may tend to underestimate the true risk of silicosis mortality, and Park et al.'s (2002) analysis would more fairly capture the total respiratory mortality risk from all non-malignant causes, including silicosis and chronic obstructive pulmonary disease. Another difference between the analyses is the use by Park et al. (2002) of untransformed cumulative exposure in a linear model compared to the log-transformed cumulative exposure metric used by Mannetje et al. (2002b), which causes the exposure-response to flatten out in the higher exposure ranges. It is also possible that some of the difference between Mannetje et al.'s and Park et al.'s risk estimates reflects factors specific to the nature of exposure among diatomaceous earth workers (e.g., exposure to cristobalite vs. quartz). However, neither the cancer risk assessments nor assessments of silicosis morbidity (discussed in sections II.B and II.F, respectively) support the hypothesis that cristobalite is more hazardous than quartz.

Based on the available risk assessments for silicosis mortality, OSHA believes that the estimates from the pooled study represent the most conservative estimates of mortality risk (i.e., unlikely to overstate risks) from silicosis given that the estimates reflect only those deaths where silicosis was specifically identified on death certificates, and is therefore most likely an underestimate of the true silicosis mortality risk. In contrast, the risk estimates provided by Park et al. (2002) for the diatomaceous earth cohort would capture some of this misclassification and include risks from other lung diseases (emphysema, chronic bronchitis) that have been associated with exposure to crystalline silica. Therefore, OSHA believes that the Park et al. study provides a better basis for estimating the silica-related risk of NMRD mortality, including that from silicosis. Based on Park et al.'s linear relative rate model ($RR = 1 + \beta x$, $\beta = 0.5469$ (no standard error reported) and x = cumulative exposure), OSHA used a life table analysis (see Appendix to this section) to estimate the lifetime excess NMRD mortality through age 85. For this analysis, OSHA used all-cause and cause-specific background mortality rates for for all males (National Center for Health Statistics, 2009). Background rates for NMRD mortality were based on rates for ICD-10 codes J40-J47 (chronic lower respiratory disease) and J60-J66 (pneumoconioses and chemical effects), which OSHA believes correspond closely to the ICD-9 disease classes (ICD 490-519) used by the original investigators; according to CDC (2001), background rates for chronic lower respiratory diseases were increased by less than 5 percent as a result of the re-classification to ICD-10. From the life table analysis, OSHA estimates that the excess NMRD risk due to exposure to the current general industry and the proposed PEL for 45 years are 83 and 43 deaths per 1,000, respectively. For exposure at the the current construction/shipyard PEL, OSHA estimates that the excess NMRD risk ranges from 188 to 321 deaths per 1,000.

II.D. *Uncertainty in Lung Cancer and Silicosis Mortality Risk Estimates.*

The risk estimates for lung cancer and silicosis presented in the previous sections are inherently uncertain, as they depend on a variety of assumptions and inputs. In this section, sources of uncertainty in OSHA's risk assessment are identified and evaluated, and potentially significant sources of uncertainty are quantitatively analyzed where it is reasonable to do so given the significance of the uncertainty and the availability of methods and data for use in a quantitative uncertainty analysis. This treatment of uncertainty contributes to the development of reasonable risk estimates, provides for informed decision-making, and is consistent with the Department of Labor's Information Quality Guidelines.

Uncertainty that results from estimating risk from these studies is reflected in the confidence limits for the risk estimates presented in Table II-2 and in the earlier discussions of this section. These confidence limits depend on the study design, the study sample sizes, the number of deaths, and the goodness of fit of the models to the data. They do not explicitly reflect other important sources of uncertainty. Sources of non-random or "systematic" error that frequently affect epidemiological risk assessments include confounding, selection bias, and measurement error. These types of error can sometimes create bias in a risk assessment, leading to risk estimates that are substantially higher or lower than the true risk. As discussed below, OSHA does not have reason to believe that either selection bias or confounding has a substantial impact on the risk estimates for lung cancer or silicosis mortality. It is more difficult to assess the importance of exposure measurement error, but the quantitative analyses conducted by Steenalnd and Bartell for Toxichemica, Inc. (2004) to explore uncertainty due to measurement error do not suggest that such errors have a substantial impact on the previously presented risk estimates.

II.D.1. Selection Bias.

Selection bias is error due to systematic differences in risk-related characteristics between individuals who participate in a study and those who do not. The pooled risk analyses for lung cancer and silicosis mortality are unlikely to have substantial selection bias because all potentially eligible workers were typically included in the cohorts, and because follow-up was generally quite complete. Furthermore, virtually all known cohort studies for which quantitative exposure data were available at the time were included in the Steenland et al. (2001a) pooled analysis for lung cancer. For the pooled analysis of silicosis mortality, Mannetje et al. (2002b) included six of these same studies for which ICD coding was available on death certificates; ICD coding was not available from the three Chinese cohorts and the South African miner cohort. OSHA does not believe that exclusion of these four cohorts was likely to contribute to any significant selection bias in the silicosis mortality study since there is no evidence that indicates that the characteristics of the excluded cohorts would be substantially different from the others. With respect to the South African cohort, Mannetje et al. (2002b) reported that, although silicosis was not typically coded as a cause of death in that country, the cohort did exhibit an exposure-related increase in mortality from related causes of death, such as tuberculosis and chronic obstructive pulmonary disease. Furthermore, exclusion of either

the South African cohort or the three Chinese cohorts did not appreciably change the resulting coefficient or fit of the log-linear model in the pooled lung cancer analysis (Steenland et al., 2001a).

II.D.2. Confounding.

Confounding occurs when the estimated effect of exposure on disease risk is distorted due to an extraneous factor associated with both the exposure and the disease. Cigarette smoking can act as a positive confounder in studies of occupational disease when smoking rates are higher among the working-class study participants than in the larger populations whose lung cancer rates often serve as the point of comparison or "reference rates"; in this case, the observation that lung cancer is related to exposure would be spurious since the observed effect could just as easily be attributed to smoking. Positive confounding by smoking in lung cancer studies becomes less likely when (1) comparison populations are drawn internally using subjects from the same work environment as the exposed population because it is less likely that smoking histories will be substantially different between controls and study subjects; (2) analyses are performed to look for an exposure-response gradient, since smoking history would have to be positively correlated with exposure to contribute to the observed exposure-response gradient, again an unlikely outcome; and (3) data on smoking history are available to permit including a smoking term in a quantitative exposure-response analysis. Smoking can also act to bias a weak exposure-response trend towards the null when baseline cancer risks are elevated due to smoking; this is not considered confounding per se, but modifies the magnitude of the exposure-related effect relative to the baseline risk such that the exposure-related effect becomes more difficult to detect (Axelson, 1989). Smoking can act as a true negative confounder in cases where the referent population has a greater proportion of smokers than does the exposed population.

Occupational co-exposures are another potential confounder, since workers may be exposed to a variety of carcinogenic or toxic agents other than the exposure of interest. Among the cohorts discussed here, radon and asbestos were potential occupational confounders for the lung cancer risk analysis.

The Steenland et al. (2001a) pooled analysis compared lung cancer rates in workers with higher exposures to workers with lower exposures rather than to the general population, and, for this reason, is unlikely to be much affected by confounding due to smoking. Furthermore, complete or partial smoking data were collected and considered in the original exposure-response analyses for four of the ten cohorts in the pooled analysis, with little or no effect on exposure-response coefficients (Steenland et al., 2001a). Another potential source of confounding in the pooled lung cancer analysis is radon exposure of the mining cohorts included. Serious confounding from radon exposure seems unlikely in that, according to Steenland et al. (2001a), the mining cohorts demonstrated exposure-response relationships of a magnitude similar to those for non-mining cohorts. In addition, removal of the South African mining cohort, which showed the highest exposure-response and where radon exposure was most likely to confound the results, did not have any appreciable effect on the magnitude of exposure-response for the remainder of the pooled cohort.

Two studies relied on by OSHA to estimate excess lung cancer risks had individual smoking status data and could thus include an adjustment for smoking in the regression models (Hughes et al., 2001; Miller and MacCalman 2009). In both cases, the exposure-response trend remained statistically significant and the risk estimates derived from the exposure-response coefficients reflect estimates adjusted for smoking.

Because of the lack of smoking data on the cohort (69.4% of the lung cancer deaths had unknown smoking habits), Rice et al. (2001) did not formally evaluate potential confounding of the exposure-response from smoking. However, they referred to the original analysis of the cohort in which Checkoway et al. (1997) employed an indirect method to evaluate the impact of smoking. This approach entailed estimating smoking-related lung cancer rates for the highest cumulative exposure group and for the reference group, based on available data on smoking prevalence and a conservative estimate of smoking-related relative risk. Using this method, Checkoway et al. (1997) predicted a lung cancer mortality rate ratio of 1.67 for the high-exposure group, which was smaller than the observed rate of 2.15. In addition, the smoking prevalences of the two highest exposure groups were comparable (0.86 vs. 0.83) but there was a substantial difference in observed lung cancer rate ratios (1.26 vs. 2.15), again indicating that smoking was an unlikely confounder and that the observed increases in risk were associated with exposure to crystalline silica. Rice et al. (2001) also argued that smoking was not likely to be a serious confounder because the prevalence of smoking was unrelated to cumulative exposure to crystalline silica in the cohort. In addition, internal adjustment models that compare the mortality experience of exposed and non-exposed workers in the same cohort reduce the likelihood that results are confounded by smoking. In Rice et al.'s (2001) analysis, the use of internally standardized models yielded slope estimates that were similar to those based on external mortality rates.

As described in the Health Effects section, Gibbs (1998) argued that the results of the diatomaceous earth study were confounded by concurrent exposure to asbestos, in particular among workers employed prior to 1930. In examining the influence of potential asbestos exposure on the mortality experience of the cohort, Checkoway et al. (1993) found that the risk ratio for the highest silica exposure group after excluding these workers from the cohort (RR = 1.73) was almost identical to the risk ratio of the high-exposure group after excluding workers hired prior to 1930 (RR = 1.74). In addition, Checkoway et al.'s (1996) reanalysis of the original cohort study (Checkoway et al., 1993) examined those members of the cohort for whom there was quantitative information on asbestos exposure, based on a mixture of historical exposure monitoring data, production records, and recorded quantities of asbestos included in mixed products of the plant. Cohort members' cumulative exposures to asbestos were calculated from these estimates using the same methods as for the silica exposure assessment. The authors found an increasing trend in lung cancer mortality with exposure to crystalline silica after controlling for asbestos exposure, and found only minor changes in relative risk estimates after adjusting for asbestos exposure. Finally, Checkoway et al. (1998) reported that the prevalence of pleural plaques among workers hired before 1930 (4.2%) was similar to that of workers hired after 1930 (4.9%) when asbestos was presumably no longer used in the process. From these findings, Checkoway et al. (1998) concluded that asbestos was not likely to significantly confound the exposure-response relationship

observed between lung cancer mortality and exposure to crystalline silica in diatomaceous earth workers. Rice et al. (2001) also utilized Checkway et al.'s (1997) data to test for confounding by asbestos in their Poisson and Cox's proportaional hazards models; finding no evidence of confounding, they did not include asbestos exposure as a variable in the final models presented in their 2001 paper.

According to Mannetje et al. (2002b), it was not possible to adjust for smoking in the pooled silicosis mortality analysis. Park et al. (2002) used what smoking data were available for the cohort to adjust for smoking in their Poisson analyses of LDOC mortality among diatomaceous earth workers. They reported that analyses that did not control for smoking yielded slightly smaller risk estimates than did analyses that partially controlled for smoking, suggesting that estimates of silicosis mortality risk based on this cohort are not likely to be exaggerated due to cohort members' smoking habits. However, as discussed by Rice et al. (2001) in their analysis of this cohort for lung cancer, their ability to control for smoking in this cohort is constrained by the limited smoking data, which was available for only 50% of the overall cohort and 33% of the workers who died of LDOC. As in the Rice et al. (2001) study, Park et al. (2002) performed internally standardized analyses, which tend to be less susceptible to confounding by smoking as they compare groups of workers in the cohort rather than comparing workers with an unexposed population (which sometimes have lower smoking rates than worker populations). The authors reported that internally standardized models yielded only slightly lower exposure-response coefficients than externally adjusted models (exact values not presented). Park et al. (2002) used externally standardized models to produce excess risk estimates because they appeared to provide a considerably better fit to the data than the internally standardized models. Finally, Park et al. (2002) also cited the original Checkoway et al. (1997) study, which presented analyses indicating that confounding by smoking was not likely to account for the observed relationship between cumulative exposure to crystalline silica and LDOC mortality.

II.D.3. Exposure Measurement Error.

The lung cancer and silicosis risk estimates discussed in previous sections may be affected by one or more sources of error in silica exposure measurements. First, individual workers' exposures were assigned based on exposure measurements for a sample of workers in the same job (defined by facility, task, and work areas to the extent permitted by the available data), or based on estimated exposure levels for specific jobs in the past when no measurements were available, via a job-exposure matrix (JEM) (Mannetje et al., 2002a). The observed or assigned job-specific mean exposure from the matrix is assumed to equal the true mean exposure level for workers in a specific job, but assignment of individual workers' exposure levels using the mean level for specific jobs necessarily results in an assigned exposure level different from the true exposure for each individual. Second, error results from the conversion of historically available dust measurements, typically particle count concentrations, to gravimetric respirable silica measurements. The conversion factors used in the exposure assessment may not have accounted for all of the differences in silica content of the dust at different worksites or in different jobs within a worksite.

Errors resulting from the assignment of job-specific mean exposures to individuals results in a type of error known as a Berkson error, in which the true exposure level in a job is assumed to vary randomly around the assigned, or "observed" exposure level for the job (Snedecor and Cochran, 1989). That is:

$$\text{Exposure}_{\text{true}} = \text{Exposure}_{\text{observed}} + \varepsilon.$$

In this instance, measurement error is independent of the observed exposure and is positively correlated with the true exposure level. This is in contrast to the classical error model, where the error is independent of the true exposure and the observed exposure varies randomly around the true value. When, as is the case for the pooled cohort analysis, the exposure metric is a log transformed measure, the Berkson model becomes:

$$\text{Log Exposure}_{\text{true}} = \text{Log Exposure}_{\text{observed}} + \varepsilon$$

which is a multiplicative error model in which both the mean and variance of the true exposure is correlated with the observed exposure.

Berkson error can result in overestimation or underestimation of exposure-related disease risk in log-linear models with dichotomous disease outcomes, such as the dose-response models presented earlier (Armstrong, 1988, 1990; Deddens and Hornung, 1994; Prentice, 1982). Bias has been shown to occur when 1) the disease is rare, 2) the true exposure levels are distributed log-normally, and 3) the variance in the measurement error increases with exposure level, all common conditions in occupational epidemiology (Deddens and Hornung, 1994). For this reason, OSHA believed it important to assess these errors and their potential effects on the lung cancer and silicosis risk estimates. To accomplish this, OSHA's contractor, Toxichemica, Inc., conducted an uncertainty analysis using the raw data from the IARC multi-centric study to address the separate and joint effects of errors resulting from exposure metric conversion and from assignment of exposure values to individual members of the cohort. In addition, the analysis evaluated the effect of a systematic bias in the exposure estimates. The methods and results are summarized below and reported in detail in Toxichemica, Inc. (2004).

II.D.3.a. Lung cancer uncertainty analysis.

Monte Carlo analysis of error in the assignment of individual exposure values

A common approach to quantitatively assess uncertainty in a model is to test its sensitivity to error in the values that were assigned to the model's various inputs. In the simplest type of sensitivity analysis, the analyst isolates a single model input and calculates the model results for a range of values the selected input might have, while holding all other inputs constant. Toxichemica, Inc.'s (2004) approach to account for error caused by the assignment of mean exposures to individual workers is similar, except that the input they test is the matrix of job-specific exposure estimates used to calculate individual workers' cumulative exposures used in the exposure-response analysis previously described. Given the substantial difficulties of defining and testing a "range" of possible values for an exposure matrix of this size, Toxichemica, Inc. randomly sampled new values for workers' job-specific exposure levels from a distribution that

they believed characterizes the variability in exposures of individual workers in each job. The sampled exposure values were then used to repeat the risk analysis. The extent to which altering the exposure values leads to changes in the results suggests how sensitive the previously presented risk estimates may be to Berkson error in the exposure estimates.

For each worker in the 10 cohorts included in the Steenland et al. (2001a) pooled analysis, a possible value for every exposure concentration for every job worked was sampled from a distribution of values constructed specifically for that worker and job. To construct the estimated exposure distributions for each worker-job combination, Toxichemica, Inc. (2004) assumed that the mean exposure value reported for each job in the original analysis represents the mean μ of an underlying log normal distribution of exposures experienced by workers in that job. The standard deviation σ of the distribution was estimated based on respirable quartz measurements collected from one of the industrial sand plants that was studied by Steenland et al. (2001b). A total of 37 observations were available, each representing a job-specific mean based on at least 10 respirable quartz measurements. From these exposure measurement data, Toxichemica, Inc. assigned the distribution a standard deviation of $\sigma = 0.8 * \mu$. This relationship was then used to derive the mean (μ_{lni}) and standard deviation (σ_{lni}) of the distribution of the log of exposure values, which was assumed to be normally distributed. μ_{lni} and σ_{lni} were then used as parameters of a normal distribution to generate random values of log mean exposure, which represented possible true mean exposure values for a given job and a given worker. The sampled mean exposure values were then used to calculate a new estimate of each worker's cumulative exposure(s). When an entire set of cumulative exposure values was assembled for all workers based on these randomly sampled values, the set was used in a conditional logistic regression to fit a new exposure-response model. Toxichemica, Inc. fit a set of ten new exposure-response models based on ten of these exposure simulations. The mean of the resulting exposure-response coefficients for each cohort and the standard deviation for the coefficients appear in Table II-4.

Toxichemica, Inc. (2004) reported that the presence of Berkson error in the exposure estimates adds additional uncertainty to the fitted model coefficients, as indicated by the standard deviations across 10 iterations. Among the individual cohorts, most of the mean regression coefficients resulting from the simulation analysis were similar to the coefficients from the exposure-response analyses reported in Steenland et al. (2001) and Toxichemica, Inc. (2004) (following correction for minor data entry and rounding errors), except for the mean of the simulation coefficients based on the South Africa gold cohort (0.26), which was lower than the previously calculated exposure coefficient (0.582). The simulations also resulted in somewhat lower coefficients for Australia gold (0.156 vs. 0.172), U.S. granite (0.106 vs. 0.118), and China tungsten (0.033 vs. 0.039) cohorts. The mean of the coefficients for the pooled analysis after simulating random error in job-specific exposure assignments was very close to the previously calculated coefficient (0.058 vs. 0.060; standard error not reported). Based on the mean coefficient values after adjusting for Berkson error in the exposure estimates, Toxichemica, Inc. (2004) concluded that this error source probably did not appreciably change the estimated exposure-response coefficient for the pooled data set.

Table II-4. Conditional logistic regression coefficient for silica and lung cancer, 10 simulations adjusting for Berkson error in job-specific exposures for each worker, due to assignment of job-specific mean to each worker

Study	Unadjusted coefficient (std error)[a]	Mean Adjusted Coefficient[b]	Standard Deviation of Adjusted Coefficient[c]
US Diatomaceous earth (Checkoway et al., 1997)	0.086 (0.054)	0.086	0.014
S Africa gold (Hnizdo and Sluis-Cremer, 1991; Hnizdo et al., 1997)	0.582 (0.329)	0.260	0.147
US gold (Steenland and Brown, 1995a)	-0.041 (0.078)	-0.037	0.021
Australian gold (de Klerk and Musk, 1998)	0.172 (0.111)	0.156	0.038
US granite (Costello and Graham, 1988)	0.118 (0.048)	0.106	0.011
Finnish granite (Koskela et al., 1994)	-0.015 (0.063)	-0.013	0.012
US industrial sand (Steenland et al., 2001b)	0.045 (0.057)	0.047	0.010
Ch. Tungsten (Chen et al., 1992)	0.039 (0.027)	0.033	0.003
Ch. Pottery (Chen et al., 1992)	0.086 (0.039)	0.086	0.005
Ch. Tin (Chen et al., 1992)	0.054 (0.033)	0.059	0.005

Footnotes for Table II-4

[a] Coefficients without adjustment for Berkson error , using corrected data, single run

[b] Mean of coefficients from 10 simulated data sets adjusting for Berkson error

[c] Standard deviation of coefficients from 10 simulated data sets reflects only measurement error

Note: Coefficients are log odds per log (mg/m^3-days) lagged 15 years

Source: Toxichemica, Inc. (2004)

Monte Carlo analysis of error in estimating exposures to silica from historical dust concentration data

A second source of Berkson error in the pooled lung cancer and silicosis mortality studies is the conversion of historical dust samples to equivalent measures of gravimetric respirable crystalline silica. These adjustments involved converting particle count measurements, total dust measurements, and respirable dust measurements to measures of respirable crystalline silica based on available data on the silica content of dust present in

different work areas of the workplaces from which the cohorts were drawn. Uncertainties exist in both the estimates of silica content and in the conversion factors used, which were based in some cases on side-by-side comparison sampling but were estimated in other cases absent such sampling. To consider this source of uncertainty, Toxichemica, Inc. (2004) used a procedure similar to that used to assess uncertainties in individual exposure value assignments. Toxichemica, Inc. assumed that, for each job in the dataset, a specific conversion factor existed that related workers' exposure measurements to gravimetric respirable silica exposures, and that this conversion factor comes from a normal distribution with a standard deviation $\sigma = ½$ its mean μ. This relationship was derived from data reported by Kreiss and Zhen (1996), who found that silica content among 80 samples taken from one region of a Colorado mine averaged 19 percent with a standard deviation of 11 percent. For the sensitivity analysis, Toxichemica, Inc. sampled a new conversion factor for each job from the appropriate distribution, then used the complete set of sampled conversion factors to re-run the risk analysis. Since the estimated silica exposure level for a particular job is a simple product of the job's dust exposure d and a scalar conversion factor, this amounts to selecting a new exposure level for each job from a normal distribution with mean μ equal to the job's reported silica exposure level and standard error $\sigma = ½ \mu$. To avoid extreme outliers, Toxichemica, Inc. constrained the sampling such that each generated exposure level was between 10% and 190% of the original value.

Toxichemica, Inc. (2004) generated ten sets of sampled exposure levels for each individual in the cohort, using each set to fit a study-specific coefficient and a pooled coefficient, holding the original exposures fixed in all other cohorts. The mean of the 10 study-specific coefficients, the standard deviation of the 10 study-specific coefficients, and the mean pooled coefficient are presented for each cohort in Table II-5. The results are similar to the coefficients originally derived from each cohort; the only coefficient much affected by the procedure was that for the South African cohort, with an average value of 0.350 across ten runs compared to the original value of 0.582 (pooled coefficients not reported for this analysis).

Monte Carlo analysis incorporating both types of measurement error

To explore the potential effects of both kinds of random uncertainty described above, Toxichemica, Inc. (2004) used the distributions representing the error in job-specific exposure assignment and the error in converting exposure metrics to generate 50 new exposure simulations for each cohort. A study-specific coefficient and a pooled coefficient were fit for each new simulation, with the assumption that the two sources of uncertainty are independent. The distribution describing error in converting to gravimetric exposure measures was used first to generate randomly sampled job-specific exposure levels, which represented a new estimate of the mean exposure for each job. Randomly sampled exposure levels for each individual in each cohort were then generated using the distribution representing error in individual exposure assignments using the sampled mean job exposure values.

Table II-5. Study-specific coefficients for log cumulative exposure in relation to lung cancer, after adjusting for measurement error in job-specific silica dust fractions within each cohort. Last column is a sensitivity analysis based on 10 simulations for each cohort adjusting for Berkson error in job-specific silica dust fractions in that cohort while holding exposures constant for all other cohorts.

Study	Unadjusted coefficient (std error)[a]	Mean Adjusted Coefficient[b]	Standard Deviation of Adjusted Coefficient[c]
US Diatomaceous earth (Checkoway et al., 1997)	0.086 (0.054)	0.086	0.011
S Africa gold (Hnizdo and Sluis-Cremer, 1991; Hnizdo et al., 1997)	0.582 (0.329)	0.350	0.170
US gold (Steenland and Brown, 1995a)	-0.041 (0.078)	-0.050	0.017
Australian gold (de Klerk and Musk, 1998)	0.172 (0.111)	0.157	0.030
US granite (Costello and Graham, 1988)	0.118 (0.048)	0.104	0.013
Finnish granite (Koskela et al., 1994)	-0.015 (0.063)	-0.016	0.010
US industrial sand (Steenland et al., 2001b)	0.045 (0.057)	0.041	0.007
Ch. Tungsten (Chen et al., 1992)	0.039 (0.027)	0.034	0.004
Ch. Pottery (Chen et al., 1992)	0.086 (0.039)	0.086	0.006
Ch. Tin (Chen et al., 1992)	0.054 (0.033)	0.058	0.005

Footnotes for Table 11-5

[a] Coefficient estimate without adjustment for Berkson error (single run)

[b] Mean of study-specific coefficients from 10 simulated data sets adjusting for Berkson error due to use of a single conversion factor to convert dust to silica for all jobs in a cohort

[c] Standard deviation of study-specific coefficients from 10 simulated data sets adjusting for Berkson error due to use of a single conversion factor to convert dust to silica for all jobs in a cohort.

Source: Toxichemica, Inc. (2004)

The mean coefficients for these 50 simulations, and their observed standard deviations, are shown in Table II-6 for the model using log cumulative dose (15-year lag). Again, the only cohort for which the mean of the exposure coefficients derived from the 50 simulations differed substantially from the previously calculated exposure coefficient was the South African cohort (simulation mean of 0.181 vs. original coefficient of 0.582). The mean exposure coefficient for the diatomaceous earth cohort was almost identical to the previously calculated coefficient (0.086 vs. 0.088, respectively) and that from the U.S. granite cohort was slightly lower (0.102 vs. 0.118). For the pooled analysis, the mean coefficient estimate from the simulations is 0.057, just

slightly lower than the previous estimate of 0.060. Although simulating exposure mis-measurement contributed additional uncertainty to the coefficient estimate (standard deviation of 0.004 across 50 iterations), the average standard error for the 50 simulated coefficients is only slightly smaller than the standard error of the original coefficient (0.014 versus 0.015). Adding the variance from the standard error due to sampling (0.014^2), and the Monte Carlo variance (0.004^2) results in a new variance estimate that incorporates both sampling uncertainty and measurement error uncertainty; the square root of that estimate is about 0.015, equivalent to the original standard error estimate for the pooled analysis. Based on the results of this uncertainty analysis, OSHA does not have reason to believe that random error in the underlying exposure estimates in the Steenland et al. (2001a) pooled cohort study of lung cancer is likely to have substantially influenced the original findings, although a few individual cohorts (particularly the South African and Australian gold miner cohorts) appeared to be sensitive to measurement errors.

Sensitivity analyses of biased conversion factors

Toxichemica Inc.'s (2004) consideration of the uncertainty in conversion factors in the discussion above assumed that the estimated conversion factors were unbiased. However, it is also possible that conversion factors may have been systematically under-estimated or over-estimated for a given cohort, if the "true" mean conversion factor was lower or higher than the estimated mean conversion factor used. For example, with respect to the South African gold miner cohort, Gibbs and Du Toit (2002) have argued that the assumption by Hnizdo et al. (1997) of a 30-percent silica content of the dust was in error, and that a value of 54 percent should have been used instead. Such an error would have resulted in about a 2-fold underestimate of the exposure of the cohort with a resulting 2-fold overestimate of disease risk. This issue is further discussed in OSHA's review of the Hnizdo and Sluis-Cremer (1993) study of silicosis morbidity among South African miners (see section II.F.2.c below). In addition, as pointed out in the Toxichemica, Inc. (2004) report, the exposure-response coefficients for lung cancer for the South African gold miner cohort are the highest among the ten cohorts in the Steenland et al. (2001a) pooled analysis, which could be a reflection of under-estimation of exposure due to under-estimation of the conversion factor. There is also a higher exposure-response seen for silicosis morbidity in the South African cohort compared to other studies (see section II.F.2.c below). Whether this is due to biased underestimation of exposure in the South African miner study, a reflection of an unusually high biological activity of freshly cleaved quartz particles (Hnizdo, personal communication, see Toxichemica, Inc., 2004), or a combination of these factors is not known. OSHA is unaware of any general criticism that the conversion factors used to estimate exposures of the other cohorts analyzed by Steenland et al. (2001a) resulted in a systematic bias; nevertheless, it remains possible that some conversion factors may have been similarly over or under-estimated, resulting in systematic over or under-estimation of exposure, with the resulting systematic under or over-estimation of the exposure coefficient for a given study.

Table II-6. Conditional logistic regression coefficient for silica and lung cancer, 50 simulations adjusting for Berkson error in both job-specific exposures for each worker and job-specific silica dust fractions (single conversion factor)

Study	Unadjusted coefficient (std error)[a]	Mean Adjusted Coefficient[b]	Standard Deviation of Adjusted Coefficient[c]
US Diatomaceous earth (Checkoway et al., 1997)	0.086 (0.054)	0.088	0.014
S Africa gold (Hnizdo and Sluis-Cremer, 1991; Hnizdo et al., 1997)	0.582 (0.329)	0.181	0.150
US gold (Steenland and Brown, 1995a)	-0.041 (0.078)	-0.042	0.026
Australian gold (de Klerk and Musk, 1998)	0.172 (0.111)	0.137	0.031
US granite (Costello and Graham, 1988)	0.118 (0.048)	0.102	0.014
Finnish granite (Koskela et al., 1994)	-0.015 (0.063)	-0.015	0.017
US industrial sand (Steenland et al., 2001b)	0.045 (0.057)	0.045	0.013
Ch. Tungsten (Chen et al., 1992)	0.039 (0.027)	0.034	0.005
Ch. Pottery (Chen et al., 1992)	0.086 (0.039)	0.085	0.006
Ch. Tin (Chen et al., 1992)	0.054 (0.033)	0.060	0.007
Pooled	0.060 (0.015)	0.057 (0.014)	0.004

Footnotes for Table II-6

[a] Coefficients without adjustment for Berkson error, using corrected data (based on a single run); for pooled data, number in parentheses is standard error of coefficient (reflects random error)

[b] Mean of coefficients from 50 simulated data sets adjusting for Berkson error; for pooled data, number in parentheses is average standard error of coefficient over 50 runs (reflects random error)

[c] Standard deviation of coefficients from 50 simulated data sets adjusting for Berkson error, reflects only measurement error

Source: Toxichemica, Inc. (2004)

Absent a priori reasons to suspect bias in a specific direction (with the possible exception of the South African cohort), Toxichemica, Inc. (2004) considered possible biases in either direction by assuming that exposure was under-estimated by 100% (i.e., the true exposure was twice the estimated) or over-estimated by 100% (i.e., the true exposure was half the estimated) for any given cohort in the original pooled dataset. This type of sensitivity analysis considered the possible influence of consistently biased

exposure estimation across an entire cohort by generating 20 new simulations of exposure estimates for each of the workers in the pooled case-control data set. This exercise was done without considering the two Berkson sources of uncertainty discussed above.

For the conditional logistic regression model using log cumulative exposure with a 15-year lag, doubling or halving the exposure for a specific study resulted in virtually no change in the exposure-response coefficient for that study or for the pooled analysis overall. According to Toxichemica, Inc., (2004) the use of the log transformation (i.e., either the log-linear model with log cumulative exposure or the spline model using log cumulative exposure) ensures that any constant multiplicative bias in exposure has virtually no effect on conditional logistic regression coefficients, and would have no effect at all using a pure log transformation (i.e., without adding 1 to allow for exposures at 0 mg/m^3-days). The maximum change in the pooled exposure-response coefficient using the log of cumulative exposure was a 1.7-percent increase when exposure is halved for Chinese tungsten miners. The maximum decrease in the coefficient for pooled analysis was a decline of only 1.3 percent when exposure is doubled in China tungsten miners.

II.D.3.b. Silicosis mortality.

Monte Carlo analyses incorporating two types of random measurement error

Following the procedures described above for the lung cancer analysis, Toxichemica, Inc. (2004) combined both sources of random measurement error (error due to assignment of a mean exposure for each job to each worker and error due to use of converting exposure measurements to a single metric) in a Monte Carlo analysis of the silicosis mortality data. Categorical analyses were done with a nested case control model (in contrast to the Poisson model used previously by Mannetje et al., 2002b), which can be expected to control more effectively for age in that it uses exact age matching rather than matching by age categories as was done in the Poisson analysis. This yielded categorical rate ratio results using the original data (prior to simulation of measurement error) which were approximately 20-25% lower than those reported by Mannetje et al. (2002b).

Table II-7 provides the original exposure coefficients (i.e., rate ratios for silicosis death per unit increase in log mg/m^3-day) reported by Mannetje et al. (2002b) for each cohort and the pooled data set, which were based on a nested case control study selecting 100 controls per case and using the best fitting exposure-response model (i.e., a conditional logistic regression model with the log of cumulative exposure and no exposure lag). Table II-7 also provides the mean coefficients resulting from 50 iterations (50 selections of 100 controls per case) after simulating both types of random measurement error. The mean of the simulation coefficients was lower than the previously calculated exposure-response coefficient for the pooled data set by about 25 percent (log 1.74/log 2.08=0.76), although the precision of the estimate was virtually unchanged. Table II-8 provides the results for the categorical analyses for the original pooled data set (single run), the corrected data set (after correcting minor coding errors

discovered in the original data set) (single run), and the corrected data with simulation of both types of random measurement error (50 runs).

Table II-7. Rate ratios for silicosis from cohort-specific and combined data, using conditional logistic regression with log cumulative exposure (nested case-control analysis, 100 controls per case) -- Original data (single run), corrected data (single run), corrected data were adjusted for two type of measurement error (average of 50 runs).

Cohort	Original data (95% CI.)[a]	Corrected data (95% CI)[b]	Corrected data with measurement error (95% observed interval)[c]
US diatomaceous earth	2.08 (1.23-3.53)	1.96 (1.20-3.19)	1.77 (1.12-2.79)
Finnish granite	2.76 (1.37-5.57)	2.73 (1.36-5.49)	2.63 (1.47-4.69)
US granite	1.76 (1.30-5.57)	1.74 (1.30-2.33)	1.97 (1.15-3.40)
US industrial sand	1.63 (1.03-2.57)	1.66 (1.03-2.67)	1.50 (1.12-2.01)
US gold miners	3.57 (1.90-6.69)	3.84 (2.03-7.27)	2.04 (1.17-3.55)
Australian gold miners	2.31 (1.34-3.97)	2.33 (1.35-4.02)	1.56 (1.00-2.44)
Combined	2.08 (1.71-2.53)	2.07 (1.71-2.51)	1.74 (1.45-2.08)

Footnotes for Table 11-7

[a] Rate ratio for one unit increase in log mg/m^3-day, no lag, model controls for age, date of birth within five years, and includes an indicator variable for cohort (six cohorts); taken from Table 3 of Mannetje et al. (2002b)

[b] Based on a single run (single selection of 100 controls); multiple runs with re-selection of 100 controls per case showed very little change in these coefficients

[c] Average coefficient across 50 selection of controls incorporating two sources of Berkson error, with the errors generated anew with each control selection The 95% observed interval is based on a standard error, which was the square root of the sum of two variances. The average variance of coefficient in 50 runs (random or sampling error) was 0.006 for the pooled data, and the observed variance of the coefficient across the 50 runs (measurement error+variance in control selection), was 0.0022 for the pooled data.

Source: Toxichemica, Inc. (2004)

The categorical analysis simulating the two types of random measurement error (third column, Table II-8) does not result in much change in the rate ratios for the first four categories above the referent, but causes an approximate 20- to 25-percent reduction in the log of the rate ratios for the uppermost five categories. Furthermore, the confidence intervals for the rate ratios across all exposure categories after simulating random measurement error are considerably wider than those from the original analysis. For the first three categories above the referent, where the point estimates are scarcely altered by simulating measurement error, the ratio of the upper to lower confidence limit is approximately 11, while the ratio from the original result not simulating measurement error is approximately 4-5. The silicosis mortality dataset thus appears to be more sensitive to possible error in exposure measurement than the lung cancer dataset, for which the mean of the simulation coefficients was virtually identical to the original. According to the Toxichemica, Inc. (2004) report, the reason for this greater sensitivity is not known. It is possible that the smaller size of the silicosis mortality data set (170 silicosis cases among 18,000 cohort members vs. 1,066 lung cancer cases among 66,000 cohort members) rendered it more sensitive to changes in underlying exposure data.

Table II-8. Rate ratios for silicosis by cumulative exposure category derived from categorical analysis of the combined data set and using corrected data incorporating two sources of measurement error.

Exposure Category	Original data (95% CI.)[a]	Corrected data, Unadjusted for measurement error (95% observed interval)[a]	Corrected data, adjusted for measurement error (95% observed interval)[b]
0-.99 mg/m^3-years	1.00	1.00	1.00
0.99-1.97	2.09 (1.05-4.19)	2.14 (1.07-4.27)	2.18 (0.64-7.38)
1.97-2.87	3.14 (1.51-6.53)	3.29 (1.59-6.79)	3.35 (1.00-11.27)
2.87-4.33	4.20 (1.95-9.02)	4.26 (1.98-9.19)	4.27 (1.26-14.55)
4.33-7.12	6.07 (2.72-13.55)	6.17 (2.73-13.98)	5.35 (1.48-19.39)
7.12-9.58	10.86 (4.69-25.34)	12.30 (5.34-28.36)	6.26 (1.48-26.53)
9.58-13.21	10.85 (4.60-25.13)	12.18 (5.17-28.69)	7.42 (1.80-30.65)
13.21-15.89	19.15 (7.97-46.02)	18.17 (7.46-44.25)	7.65 (1.47-39.74)
15.89-28.10	12.60 (5.12-30.97)	13.46 (5.52-32.85)	9.20 (2.44-34.77)
>28.10	29.56 (11.51-75.91)	27.66 (10.75-71.44)	12.83 (3.34-49.82)

Footnotes for Table 11-8

[a] Single run (single selection of controls), model adjusts for age, date of birth within 5 years, and includes an indicator variable for cohort (six cohorts included)

[b] Average across 50 runs (50 selection of controls). 95% observed confidence intervals derived using the standard deviation of the exposure coefficient (sd) across the 50 Monte Carlo estimates (measurement error) and the average standard error (se) of these estimates (sampling error), ie, 95% interval = average coefficient +/- $1.96*\sqrt{(sd^2 + se^2)}$

Source: Toxichemica, Inc. (2004)

Potential effects of random measurement errors on silicosis mortality risk estimates

Toxichemica, Inc. (2004) estimated the risk of death from silicosis to age 75, assuming 45 years of exposure to crystalline silica beginning at age 20, based on converting predicted silicosis mortality rates to risk (risk = 1-exp(-Σ(rate*time)), where time is divided into intervals of one year). Predicted rates were derived either from the categorical analysis of the corrected data after incorporating simulated measurement error (ten categories, Table II-8), or the conditional logistic regression model using the mean of the log cumulative exposure coefficients after incorporating simulated measurement error (Table II-7). The log cumulative exposure model and the spline both fit the data well and conformed to the categorical analysis (see Figure 5 of Toxichemica, Inc., 2004). In both cases, the referent rate was taken to be that of the low exposure group of the cohort under study (i.e., 4.7/100,000 for the group with 0 to 0.99 mg/m^3 years, based on 17 silicosis deaths). The risk of silicosis mortality to age 75 was calculated for exposure levels of 0.05 and 0.10 mg/m^3, resulting in cumulative exposures of 2.25 and 4.5 mg/m^3-years respectively. Two exposure categories in Table II-9 from the categorical model that reflect this range of exposure are 1.97-2.87 and 4.33-7.12 mg/m^3-years, which correspond to 45 years of exposure to 0.05 and 0.10 mg/m^3, respectively. The variance of the log rate for each category was estimated by adding the variance of the log of referent group rate (4.7/100,000) and the variance of the categorical log rate ratio taken from either the categorical model or the linear model using log cumulative exposure. The variance of the log of the referent group rate was derived via the delta method approximation assuming a Poisson distribution for the observed number of silicosis deaths (n = 17) in the referent group, resulting in an approximate variance of 1/17 or 0.06.

Table II-9 presents risk estimates for silicosis death by age 75 after a 45-year working lifetime exposed to various levels of crystalline silica, based on either the categorical model or the model with the log of cumulative exposure (no lag). Results of the categorical model were slightly higher than those for the log cumulative exposure. Estimated lifetime risks for age 65 are also presented for comparison with Mannetje et al. (2002b), who estimated a risk of silicosis death of 13 deaths per 1000 for exposure to 0.10 mg/m^3, and 6 per 1000 for exposure to 0.05 mg/m^3. After simulating random measurement error, Toxichemica, Inc. (2004) estimated corresponding risks of 7 (95% CI 2-23) and 4 (95% CI 2-12) per 1,000, respectively, based on the categorical model. According to Toxichemica, Inc., the decrease in estimated risk partly reflects the use of a nested case-control analysis here versus the Poisson regression originally performed by Mannetje et al. (2002b). The control over age, which is tighter in the nested case-control approach, is likely to be a factor that led to somewhat decreased rate ratios for the first three exposure categories above the referent in the current analysis compared to the analysis by Mannetje et al. (2002b). However, incorporation of uncertainty in the exposure estimates had the effect of further reducing estimates of silicosis rate ratios in the higher cumulative exposure categories.

To summarize, a quantitative examination of the potential effects of unbiased and biased exposure uncertainty suggested little effect on the pooled exposure coefficient

Table II-9. Silicosis mortality. Absolute risk estimates (in deaths per 1,000 workers) and 95% CI assuming a 45-year working lifetime, by model[a], by exposure level, and by age, taking into account measurement error

Exposure level	Age	Categorical model (95% CI)	Log-Linear model[b] (95% CI)
1.00 mg/m^3	75	0.026 (0.007-0.094)	0.023 (0.010-0.054)
0.75 mg/m^3	75	0.024 (0.006-0.087)	0.019 (0.009-0.045)
0.50 mg/m^3	75	0.019 (0.005-0.069)	0.016 (0.007-0.034)
0.25 mg/m^3	75	0.014 (0.004-0.053)	0.011 (0.006-0.021)
0.20 mg/m^3	75	0.013 (0.004-0.047)	0.010 (0.005-0.019)
0.15 mg/m^3	75	0.011 (0.003-0.040)	0.009 (0.005-0.016)
0.1 mg/m^3	75	0.009 (0.003-0.033)	0.006 (0.004-0.011)
0.1 mg/m^3	65	0.007 (0.002-0.023)	0.005 (0.003-0.008)
0.05 mg/m^3	75	0.006 (0.002-0.018)	0.004 (0.003-0.007)
0.05 mg/m^3	65	0.004 (0.002-0.012)	0.003 (0.002-0.005)

Foot notes for Table II-9.

[a] Both models use the lowest exposure group (<1.00 mg/m^3-year) from Mannetje et al. (2002b) as the referent category for rate ratios, which in turn are used to calculate estimated rates for higher exposures (i.e., multiplying the rate in lowest exposure group (0.000047/100,000) by the rate ratio)

[b] Uses 0.5 mg/m^3-years (the midpoint of lowest exposure category) as the exposure level for the referent group to calculate rate ratios (and hence rates) for higher exposure levels

Source: Toxichemica, Inc. (2004)

(and the variance around that estimate) for the lung cancer risk model. For the silicosis mortality risk model, consideration of exposure uncertainty had some effect on predicted silicosis mortality rates, particularly for higher exposure categories, and resulted in an overall decline in estimated risk from the pooled analysis. OSHA believes that it is difficult to fully assess the uncertainty associated with error in exposure estimates on the basis of Toxichemica, Inc.'s (2004) analysis, in part because the computational intensity of their analysis limited the number of runs that could be performed. It is also unclear whether the mean value of the exposure coefficients produced by this analysis may be regarded as adjusted for Berkson error and meaningfully compared with the original estimates. However, OSHA believes Toxichemica, Inc.'s analysis to be a reasonable approach to quantitative evaluation of the uncertainty associated with error in exposure estimates. Considering the information available to Toxichemica, Inc. and the limits on the number of simulations that could reasonably be performed, the Agency regards their analysis as best available treatment of exposure uncertainty and believes that their results, overall, do not suggest that Berkson error in the exposure assessment is likely to have introduced substantial error in risk estimates for lung cancer related to silica exposure.

II.E. Quantitative Assessment of Renal Disease Mortality.

OSHA believes that there is substantial epidemiological evidence that exposure to respirable crystalline silica increases the risk of renal disease morbidity and mortality (see

section I.E). OSHA also reviewed a pooled cohort exposure-response analysis by Steenland et al. (2002a) and believes that this study provides a suitable basis for quantitatively estimating renal disease risks because the findings are based on a large number of workers and sufficient exposure data were available to characterize exposures of these cohorts. The three cohorts included U.S. gold miners (Steenland and Brown, 1995a), U.S. industrial sand workers (Steenland et al., 2001b), and Vermont granite workers (Costello and Graham, 1998). These cohorts were chosen because data were available for both underlying cause mortality and multiple cause mortality; this was believed important because renal disease is often listed on death certificates without being identified as an underlying cause of death.

Details of the pooled analysis were provided in the health effects literature review (section II.E) and are summarized here. The combined cohort for the pooled analysis (Steenland et al., 2002a) consisted of 13,382 workers with exposure information available for 12,783 (95 percent). Exposure matrices for the three cohorts had been used in previous studies (Steenland and Brown, 1995; Attfield and Costello, 2001; Steenland et al., 2001b) that showed positive exposure-response trends for silicosis morbidity or mortality, thus tending to validate the underlying exposure and work history data. The mean duration of exposure, cumulative exposure, and concentration of respirable silica for the pooled cohort were 13.6 years, 1.2 mg/m^3-years, and 0.07 mg/m^3, respectively. SMRs (compared to the U.S. population) for renal disease (acute and chronic glomerulonephritis, nephrotic syndrome, acute and chronic renal failure, renal sclerosis, and nephritis/nephropathy) were statistically significantly elevated using multiple cause data (SMR 1.29, 95% CI 1.10-1.47, 193 deaths) and underlying cause data (SMR 1.41, 95% CI 1.05-1.85, 51 observed deaths).

Exposure-response trends were examined in a categorical analysis where renal disease mortality of the cohort divided by exposure quartile was compared to U.S. rates. This analysis included 95 percent of the cohort for which there were adequate data on work history and exposure to respirable quartz. In this analysis, highly statistically significant exposure-response trends for SMRs were observed for both multiple-cause ($p < .000001$) and underlying cause ($p = .0007$) mortality.

A nested case-control analysis was also performed which allowed for more detailed examination of exposure-response. This analysis included either 50 cases (underlying cause mortality) or 194 cases (multiple-cause mortality), each matched by race, sex, and age within 5 years to 100 controls from the cohort. With the lowest exposure quartile group serving as a referent, the case-control analysis showed monotonic trends in mortality with increasing cumulative exposure. Conditional regression models using log cumulative exposure fit the data better than cumulative exposure (with or without a 15-year lag), or average exposure. For multiple-cause mortality, the exposure-response trend was statistically significant for both cumulative exposure ($p = .004$) and log cumulative exposure ($p = .0002$), whereas for underlying cause mortality, the trend was statistically significant only for log cumulative exposure ($p = .03$). The exposure-response trend was homogeneous across the three cohorts and interaction terms did not improve model fit.

Based on the exposure-response coefficient for the model with the log of cumulative exposure, the authors estimated the lifetime excess risk of death (underlying cause) from renal disease by age 75 for an exposure of 0.10 mg/m^3 over a working lifetime (age 20 to 65) to be 1.8 percent (95% CI 0.8-9.7%) above a background risk of 0.3 percent. The authors concluded that their study added to the evidence that renal disease is associated with exposure to crystalline silica. Noting that statistically significantly increased odds ratios and SMRs were seen primarily for cumulative exposures of >0.5 mg/m^3-years, the authors pointed out that this would come from working for five years at an exposure level of 0.1 mg/m^3 or 10 years at 0.05 mg/m^3. OSHA believes that the findings of this pooled analysis are credible because the analysis involved a large number of workers from three cohorts for which there were substantial exposure and job history data that were previously used in analyses that found monotonic increases in silicosis morbidity or mortality with increasing exposure, thus indicating that the exposure and work history data were unlikely to have been seriously misclassified. Consequently, OSHA is including the pooled cohort analysis of renal disease mortality (underlying cause) in its preliminary risk assessment.

To estimate renal disease mortality risk from the pooled cohort analysis, OSHA implemented the same life table approach as was done for the assessments on lung cancer and non-malignant respiratory disease. However, for this life table analysis, OSHA used 1998 background all-cause and renal mortality rates for U.S. males, rather than the 2006 rates used for lung cancer and NMRD. The 1998 rates are based on the ICD-9 classification of diseases, which is the same as used by Steenland et al. (2002a) to ascertain the cause of death of workers in their study. However, U.S. cause-of-death data from 1999 to present are based on the ICD-10, in which there were significant changes in the classification system for renal diseases. According to CDC (2001), the change in the classification from ICD-9 to ICD-10 increased death rates for nephritis, nephritic syndrome, and nephrosis by 23 percent, in large part due to reclassifying end-stage renal disease (ESRD). The change from ICD-9 to ICD-10 did not materially affect background rates for those diseases grouped as lung cancer or NMRD. Consequently, OSHA is conducting its analysis of excess renal disease mortality associated with exposure to crystalline silica using background mortality rates for 1998. As before, lifetime risk estimates reflect excess risk through age 85.

To estimate renal mortality risks, OSHA used the log-linear model with log cumulative exposure that Steenland et al. (2002a) found provided the best fit to the pooled cohort data. The coefficient for this model is 0.269 (se = 0.120) (Steenland, personal communication, 2010).

Based on the life table analysis, OSHA estimates that exposure to the current and proposed general industry PEL over a working life would result in a lifetime excess renal disease risk of 39 (95% CI 2-200) and 32 (95% CI 1.7-147) deaths per 1,000, respectively. For exposure to the current construction/shipyard PEL, OSHA estimates the excess lifetime risk to range from 52 (95% CI 2.2-289) to 63 (95% CI 2.5-368) deaths per 1,000 workers.

II.F. Quantitative Assessment of Silicosis Morbidity Risk.

In this section, OSHA summarizes the principal cross-sectional and cohort studies that have quantitatively characterized relationships between exposure to crystalline silica and development of radiographic evidence of silicosis. These studies were identified from reviews by Finkelstein (2000), NIOSH (2002), Toxichemica, Inc. (2004); literature search; and contact with outside organizations. The studies reviewed in this section are summarized in Table II-10. Each of these studies relied on estimates of cumulative exposure to evaluate the relationship between exposure and silicosis prevalence in the worker populations examined. The health endpoint of interest in these studies is the appearance of opacities on chest roentgenograms indicative of pulmonary fibrosis.

The studies evaluated fall into three major types. Some are cross-sectional studies in which radiographs taken at a point in time were examined to ascertain cases (Kreiss and Zhen, 1996; Love et al., 1999; Ng and Chan, 1994; Rosenman et al., 1996; Churchyard et al., 2003, 2004); these radiographs may have been taken as part of a health survey conducted by the investigators or represent the most recent chest x-ray available for study subjects. Other studies were designed to examine radiographs over time in an effort to determine onset of disease. Some of these studies examined radiographs taken primarily from active, or current, workers (Hughes et al., 1998; Muir et al., 1989a, 1989b; Park et al., 2002), while others evaluated radiographs for both active and retired workers (Chen et al., 2001, 2005; Hnizdo and Sluis-Cremer, 1993; Miller et al., 1995, 1998; Buchannan et al., 2003; Steenland and Brown, 1995b).

In this section of the risk assessment, OSHA first describes the criteria used in these studies to identify silicosis cases. This is followed by a discussion of each of the studies identified by OSHA where estimates of silicosis morbidity risk could be estimated.

Table II-10. Summary of Silicosis Morbidity Studies

Authors	Industry	Number in study	Time period of study	Number of cases (ILO classification)
Rosenman et al. (1996)	Grey iron foundry	1,072	Current: as of 6/91, started < 1/1/86 Retired: started < 1/1/86, pension as of 7/2/91	28 (≥ 1/0 rounded opacities)
Ng and Chan (1994)	Hong Kong granite	338	Employed at least 1 yr between 1967 and 1985	(≥ 1/1 rounded or irregular opacities)
Kreiss and Zhen (1996)	Hardrock mining	100 + 34 community controls w/o occupational silica exposure	40 years old in 1986, chest radiograph then if not previous 2 yrs	32 (small opacities ≥ 1/0)
Churchyard et al. (2003, 2004)	South African miners	520	Current workers who participated in a medical exam over a 5-month period in 2000-2001	94 from one reader, 102 from another ((≥ 1/1 rounded or irregular opacities)
Love et al. (1999)	Structural brick workers in the U.K.	1,831	Exposure and medical surveys carried out in 1990-1991	25 (≥ 1/0 rounded and irreegular opacities) 67 (≥ 0/1 rounded and irregular opacities)
Muir et al. (1989a,1989b) and Verma et al. (1989)	Canadian gold and uranium miners	2,109	Started and worked ≥ 5 yrs between 1940 and 1959; followed to 1982 or end of exposure, whichever came first	32 (≥ 1/1 and small, rounded opacities)
Hughes et al. (1998)	U.S. Diatomaceous earth mining and processing	1,809	Employed at least 1 yr between 1942 and 1987, radiograph taken more than 1 month after hire	81 (small opacities ≥ 1/0 and /or large opacities)

Table II-10. Summary of Silicosis Morbidity Studies

Authors	Industry	Number in study	Time period of study	Number of cases (ILO classification)
Park et al. (2002)	U.S. Diatomaceous earth mining and processing	2,342	Employed for at least 1 yr between 1942-1994, followed from the later of date of 1yr employment or 1942 until earlier of 12/31/94 or date of death	70 (≥ 1/0 or large opacities)
Hnizdo and Sluis-Cremer (1993)	South African gold miners	2,235	Aged 45-54 at 1968-1971 medical exam; started working after 1938, worked ≥ 10 yrs., followed until 1991	313 (≥ 1/1 and rounded opacities)
Steenland and Brown (1995b)	U.S. underground gold miners	3,330	Employed ≥ 1 yr between 1940 and 1965; followed through 1990	170 total (≥ 1/1 [1976 radiographic survey] of "small opacities" or "large opacities"[1960 radiographic survey]); 128 by death certificate (any mention)
Miller et al. (1998)	Coal	547	Had worked during the 1970s, chest radiograph in 1990/91 compared to most recent one in 1970, 1974, or 1978	203 showed progression from earlier radiographs; 47 had profusion of median small opacities of ≥ 2/1
Buchanan et al. (2003)	Coal	371	Members of Miller et al. (1998) cohort who were between the ages of 50 and 74 at the time of follow-up in 1990/91	35 with profusion of opacities consistent with ILO 2/1+
Chen et al. (2001)	Chinese tin miners	3,010	Employed for at least 1 yr between 1/1/60 and 12/31/65, followed from first employment to end of 1994	1,015 (Chinese classification system stages I, II, or III)
Chen et al. (2005)	Tin and tungsten mining, pottery workers	4,028 tin miners 14,427 tungsten miners 4,547 pottery workers	Males who worked at least one year between 1960 and 1974. Follow-up at end of 1994	855 tin miners 2,816 tungsten miners 785 pottery workers (Chinese classification system stages

Table II-10. Summary of Silicosis Morbidity Studies

Authors	Industry	Number in study	Time period of study	Number of cases (ILO classification)
				I, II, or III)

II.F.1. Definition of Silicosis.

The International Labour Organization's (ILO) 1980 International Classification of Radiographs of the Pneumoconioses is now accepted as the standard against which chest radiographs are measured in epidemiologic studies, for medical surveillance, and for clinical evaluation. According to this standard, if radiographic findings are or may be consistent with pneumoconiosis, then the size, shape, and extent of profusion of opacities are characterized by comparing the radiograph to standard films. Classification by shape (rounded vs. irregular) and size involves identifying primary and secondary types of small opacities on the radiograph and classifying them into one of six size/shape categories. The extent of profusion is judged by recording the lung zone in which the small opacities are observed. The six zones correspond to the upper, middle, and lower thirds of the right and left lungs, respectively. Profusion is an assessment of the concentrations of opacities as compared with that on the standard radiographs and is graded on a 12-point scale of four major categories, each with three subcategories:

MAJOR CATEGORY:	SUBCATEGORY:		
Category 0	0/-	0/0	0/1
Category 1	1/0	1/1	1/2
Category 2	2/1	2/2	2/3
Category 3	3/1	3/2	3/+

Categories 1, 2 and 3 and their subcategories are intended to model a continuum of increasing concentration of opacities. Major category 0 is defined as no opacities or a concentration of opacities less than the lowest subcategory of category 1. For each subcategory, the top number indicates the major category that the profusion most closely resembles, and the bottom number indicates the major category that was given secondary consideration. For example, a radiograph that most closely resembles the category 1 standard, but in which consideration was given to category 0, would be classified 1/0: 1 being the primary profusion, and 0 the secondary profusion. Thus, the major categories and their respective subcategories constitute a continuum of increasing concentration of opacities.

Profusion is rated by considering profusion over all affected zones and comparing this integrated profusion with the standard radiographs. Where there is a marked difference in profusion between zones of three minor categories or more, the zone or zones with the lowest profusion are ignored. The ILO scheme also recognizes the importance of pleural changes, any pleural thickening or pleural calcification, and also any comments made by the radiograph reader.

Silicosis is initially characterized by small rounded opacities in the middle and upper lung zones. Normal radiographs are categorized as 0/-. Simple, or uncomplicated, silicosis may appear as category 1, 2, or 3 on x-ray. Complicated (or conglomerate)

silicosis is defined by the appearance of an opacity greater than 1 cm in diameter against a background of opacities of category 2 or 3.

Most of the studies described here defined a case of silicosis as one having a chest radiograph classified as ILO 1/0 or greater, or 1/1 or greater. One study of Scottish coal miners (Miller et al., 1995, 1998; Buchanan et al., 2003) assessed exposure-response relationships for cases having a radiograph classified as 2/1 or greater (Miller et al. (1995) also presented data for x-ray films classified 1/0 or greater). Another study (Steenland and Brown, 1995b) used death certificates as well as radiographs to define cases. A study of Chinese tin miners (Chen et al., 2001) used a Chinese classification system that closely corresponded to the ILO major categories, and defined a case as a Class I or greater degree of perfusion (i.e., about the same as ILO Major Category 1). Table II-10 includes the ILO category used by each study to define silicosis.

Many, but not all, of the studies relied on panels of physicians known as B-readers to classify radiographs according to the ILO system. B-readers are those who have been trained, tested, and certified by NIOSH in the classification of chest radiographs using the ILO system. All but one study (Hnizdo and Sluis-Cremer, 1993) used at least three readers to classify each radiograph.

Chest radiography is not the most sensitive tool used to diagnose or detect silicosis. In 1993, Hnizdo et al. reported the results of a study that compared autopsy and radiological findings of silicosis in a cohort of 557 white South African gold miners. The average period from last x-ray to autopsy was 2.7 years. Silicosis was not diagnosed radiographically for over 60 percent of the miners for whom pathological examination of lung tissue showed slight to marked silicosis. The study used 3 readers and defined a profusion score of 1/1 as positive for silicosis. Sensitivity values for radiography (compared to autopsy findings) from each of the three readers were 0.393, 0.371 and 0.236, with specificity values of 0.987, 0.965 and 0.978, respectively. This indicated that each of the three readers produced very few false positives, but a high percentage of false negatives. In addition, the likelihood of false negatives (negative by x-ray, but silicosis is actually present) increased with years of mining and average dust exposure of the miners.

The low sensitivity seen for radiographic evaluation suggests that risk estimates derived from radiographic evidence likely understate the true risk of developing fibrotic lesions as a result of exposure to crystalline silica.

II.F.2. Summary of Silicosis Morbidity Studies.

II.F.2.a. Cross-sectional studies.

In 1996, Rosenman et al. presented the findings of a cross-sectional study of 549 active production workers, 26 active salaried workers, and 497 retired workers from an iron foundry. All workers included in the cohort had been employed at least 5 years as of June 1991, and about half had worked for 20 years or more. Most of the cohort members (57.7 percent) were African-American. Employment history data was obtained from medical and personnel records, industrial hygiene files from management and the union,

and from personal interviews. The latest available chest radiograph was obtained from the plant or, if unavailable, an effort was made to locate one elsewhere. Radiographs were read independently by three B-readers and a diagnosis of silicosis was made if at least two readers classified a radiograph as 1/0 or greater.

Exposure estimates were based on industrial hygiene data including both mass respirable quartz monitoring and particle count data from the earlier years. Particle count measurements were converted to mass respirable silica based on information on average quartz content of bulk samples.

Chest films were available for nearly all active workers (96.5 percent) and most of the retirees (79.9 percent). For 120 workers, radiographs were either unavailable or judged unreadable. The proportion of active and retired workers who returned the questionnaire were 77 and 72 percent, respectively. Sixty workers were found to have pneumoconiosis of which 28 had silicosis and the remainder had radiologic findings that were more consistent with asbestos exposure. Prevalence of silicosis increased with years worked at the foundry, as well as with cumulative silica exposure. Those with 20 to 29 years of exposure had a silicosis prevalence of 6 percent, while those with over 30 years at the foundry had a 12% prevalence. A single subject had silicosis earlier than 20 years from first exposure.

The exposure-response relationship was examined using logistic regression with race, smoking consumption, silica exposure outside the foundry, and either exposure concentration or cumulative exposure used in the model. Based on the relationship between odds ratio for silicosis and cumulative exposure, Rosenman et al. (1996) estimated the risk of radiographic opacities to be 3 percent for a 40-year exposure to 0.1 mg/m^3 respirable quartz. The estimated risk for exposure to 0.05 mg/m^3 for 40 years was 2 percent. The investigator believed it possible that exposures for the cohort were overestimated since cumulative exposure was calculated up to the last day at work or the time of the radiograph, whichever was earlier. Since only the latest available radiograph was examined, it is possible that some of the cases developed the disease earlier and their cumulative exposure to time of onset would have thus been smaller than estimated. In addition, there was some respirator use in the plant (although sporadic) and respirator use was not factored in to develop exposure estimates. Finkelstein (2000) also remarked that exposure misclassification was possible since the study did not determine when silicosis first appeared in the affected workers.

Another cross-sectional prevalence study was that of Ng and Chan (1994) who studied 338 current and former male employees who had worked at least a year between 1967 and 1985 in two granite quarries in Hong Kong. The cohort consisted of 206 active workers (91 percent of those eligible) and 132 former workers (representing 61 percent of eligible survivors). Workers were interviewed and received chest x-rays. The most recent radiograph for each worker was classified by three readers and a case was defined as such when at least two readers classified a film as ILO 1/1 or greater for rounded or irregular opacities. Exposure estimates were based on particle count measurements (which were converted to mass respirable quartz) supplemented by gravimetric respirable quartz measurements made in 1982.

The prevalence of silicosis was significantly related to cumulative silica exposure. For the cohort overall, the prevalence of radiological opacities indicative of silicosis was 9.2 percent for a mean cumulative exposure of 2.81 mg/m^3-years, and 24.2 percent for an exposure of 7.04 mg/m^3-years. Prevalences were higher for cohort members aged 50 years or more; for average cumulative exposures of 3.1 and 7.1 mg/m^3-years, silicosis prevalences were 12.8 and 25 percent, respectively.

Exposure-response was modeled using logistic and linear models, with age and smoking history included in the logistic model. Both provided acceptable fits and yielded comparable risk estimates of about 6 percent for rounded opacities and 8 percent for irregular opacities for an average 50-year old worker with a cumulative exposure of 2 mg/m^3-years. Ng and Chan (1994) stated that, although their risk estimates accounted for the prevalence of disease that developed post-employment, there was likely to be a selection bias since only about half of eligible survivors participated in the survey. They noted that silicosis was the underlying cause of death in 17 of the 53 workers known to have died, and that some of the survivors who refused to participate felt that they were not at risk of disease because of low dust exposure. For these reasons, Ng and Chan (1994) believed that silicosis prevalence was probably underestimated in the more highly exposed workers, and overestimated among those with low exposure.

The male population of a small Colorado mining community was invited to participate in a cross sectional study by Kreiss and Zhen (1996). Ninety percent of the population participated and included 100 hardrock miners over 40 years of age and 34 control subjects from the general population. Subjects were administered a standard respiratory questionnaire and given a chest x-ray unless one was available from the preceding 2 years. Radiographs for all but 10 subjects were read independently by three B-readers and a case was defined as those subjects for whom at least two readers classified the radiograph as 1/0 or greater using the 1980 ILO system. For the remaining 10 subjects, films were read by one reader who classified one film as abnormal with small opacity profusion of 1/1.

Most (97%) miners had been first exposed more than 20 years prior to the study and were last exposed an average of 10 years before the survey. Job-specific gravimetric dust measurements taken from 1974 to 1982 were used to estimate silica exposure of the subjects. Particle count data was available for earlier years but was sparse and there was no correlation between particle counts and gravimetric measurements for 32 jobs where both types of measurements were available. Using the gravimetric exposure data, job-specific dust indices were developed by the mining company industrial hygienist, ventilation engineer, and by others familiar with the history of the mine. Job-specific dust indices were converted to silica indices based on the data describing the quartz content of the ore. Silica exposure data were not available for 6 of the 100 miners.

The investigators used logistic regression to model silicosis risk as a function of average or cumulative exposure, age, years of exposure, years since last exposure, pack-years of smoking, and their interactions. The authors found a high prevalence rate of silicosis (32%) among miners aged 40 years or more and who were exposed to an average silica concentration of 0.064 mg/m^3. Silicosis risk was best predicted by a model

incorporating cumulative exposure and time since last exposure, or a model incorporating average exposure, duration of exposure, and time since last exposure. Predicted risks were higher using the cumulative silica exposure indices compared to the dust indices. For a miner with 25 years of work history and exposed to an average of 0.05 mg/m^3, Kreiss and Zhen (1996) predicted silicosis risk to be 9 percent by end of employment, 36 percent after 20 years post-exposure, and 67 percent by end of life (an additional 15 years). Using the logistic regression model by Kreiss and Zhen (1996), NIOSH estimated that the risk of silicosis for a 45-year exposure to 0.1 mg/m^3 or to 0.05 mg/m^3 to be 90 and 30 percent, respectively.

Finkelstein (2000) questioned whether there might have been a selection bias in this study due to over-representation of men with lung disorders. That is, those without such disorders might have been more likely to leave the town for employment elsewhere and not be included in the study. Such a selection bias would tend to overstate risk. However, Kreiss and Zhen (1996) argued that selection bias could also have resulted in an underestimate of risk in that symptomatic miners might have left the region for lower-altitude areas. They reported that available information on outmigrants following closure of the mine provided no evidence of bias in either direction since there was no observed difference in chest complaints or spirometry results from those who remained in the area. The authors also point out the similarity of their risk estimates with those of others who had similar length of follow up (i.e., Hnizdo and Sluis-Cremer, 1993; Ng and Chan, 1994; Steenland and Brown, 1995b), although their estimates were somewhat higher. Kreiss and Zhen (1996) believed that their estimates were higher in large measure because of the availability of job-specific silica measurements for their study, as opposed to having to rely on dust measurements and assume a constant silica content of the dust. Use of the silica index in their exposure-response analysis resulted in almost a doubling of the risk as compared to using the dust index alone.

The prevalence of silicosis among black South African miners was investigated by Churchyard et al. (2004) in a cross-sectional study. A sample of 520 miners employed at one company was recruited to participate in a medical surveillance exam, including a chest x-ray, over a 5-month period in 2000-2001. All miners were over 37 years of age (range 37.1-59.9) and averaged 21.8 years on the job (range 6.3-34.5). Detailed work histories were obtained by interview with verification from company records, and x-ray films were read by one current and another former B-reader. A finding of silicosis was made where x-ray findings were consistent with an ILO classification of 1/1 or higher.

Data on exposures to quartz were evaluated from two sources. First, Churchyard et al. (2004) obtained 506 personal respirable dust measurements from over 100 workers during the period that the research was being conducted. All samples were analyzed for quartz content by x-ray diffraction. These data covered 26 of the 85 jobs represented by the 520 study subjects. Data for additional jobs was obtained from the mining company's routine dust surveillance activities in which personal respirable dust samples are obtained semi-annually from representative workers grouped into job categories; a random sample of dust samples from each job category were analyzed for quartz content. A total of 715 sample records were selected to represent the jobs not covered by the investigators'

sampling efforts. Cumulative exposures of study subjects were estimated via construction of a job exposure matrix.

Results of the research dust samples showed a high degree of concordance with data from the company's routine monitoring. The mean cumulative exposure to respirable quartz for the study group overall was 8.2 mg/m^3-years, with a mean intensity of 0.053 mg/m^3. The observed prevalence of silicosis (> = ILO 1/1) was 18.3 percent from one reader and 19.9 percent from the other. Of these, nearly half were classified as ILO category 2 or 3 level of profusion. The authors noted that the observed silicosis prevalence was likely an under-estimate because workers with tuberculosis are required under law to be excluded from dusty work, and would have been selected out of the workforce over time.

Logistic regression analysis showed highly statistically significant trend between silicosis prevalence and cumulative exposure to respirable dust, respirable quartz, average exposure intensity of both dust and quartz, and length of service. Among the more highly exposed subjects, who had cumulative exposures to respirable quartz in the range of 1.48 to 3.08 mg/m^3-years, the prevalence of silicosis was 33 percent. The authors also pointed out that 90 percent of the study subjects experienced mean exposures to respirable quartz below 0.1 mg/m^3, a level below the current OSHA formula PEL for general industry.

This study had the benefit of detailed occupational histories and high-quality exposure data derived from personal dust samples representing all of the jobs worked by the study group. There are two limitations of this study. First, there was a lack of historical dust monitoring data that would have allowed for better characterization of exposures over the working life of the cohort. However, the authors believed that the available exposure data provided a reasonable estimate of past exposures, citing other earlier studies of South African mines that reported mean dust concentrations only slightly higher than that estimated by the authors from their data. Second, this was a cross-sectional study of active workers only, albeit those with fairly long work tenures, and therefore cannot be used to characterize additional silicosis risk post exposure. Noting that Hnizdo and Sluis-Cremer (1993) (discussed below) reported finding that most cases of silicosis in their study were detected among retired miners, Chuchyard et al. (2004) concluded that the prevalence of silicosis found in their cohort was "certainly an underestimate of lifetime cumulative incidence."

Love et al. (1999) conducted a cross-sectional study to determine the quantitative relationship between cumulative exposure to respirable crystalline silica and risk of radiographic abnormalities and respiratory symptoms among workers in the heavy clay industry in the United Kingdom. Eighteen facilities in England and Scotland were chosen where industrial processes were deemed to have changed little over recent decades. Factories produced bricks, clay pipes, and tiles, but not refractory brick. Exposures of workers in over 300 jobs were assessed by personal sampling for respirable dust conducted over a 5- or 10-day period at each plant. A total of 1,465 samples were collected, of which 1,403 were analyzed for quartz by x-ray diffraction or infrared analysis. Workers were invited to participate in a medical survey consisting of a work history, respiratory symptom questionnaire, and chest x-ray. Medical information and x-

ray films for 1,831 male workers were available for analysis. X-ray films were read by three physicians experienced in classifying pneumoconiosis according to the ILO system. Cumulative exposure indices for respirable dust and respirable quartz were estimated for each worker based on geometric mean exposure and time spent in each job. Exposure-response relationships were examined by multiple logistic regression.

Quartz was detected in 97 percent of the samples, and respirable quartz concentrations ranged from 0.01 to 3.8 mg/m^3, with 97 percent below 0.4 mg/m^3, the maximum allowable limit in the U.K. at the time. Of the 1,831 workers included in the study, 1,337 (73 percent) had cumulative exposures of less than 2 mg/m^3-yrs respirable quartz, and 120 (6.6 percent) had cumulative exposures exceeding 4 mg/m^3-yrs. The observed prevalence of chest roentgenograms with small opacities was low; based on the median readings of the three physicians, 3.7 percent of films were classified as ILO category 0/1 or higher, and 1.4 percent as category 1/0 or higher. Only seven films were classified as 2/1 or higher, with the highest classification being 2/3.

The prevalence of workers with films classified as 0/1 or higher increased with age (from zero at age $\leq$ 24 years to 8.5 percent at age $\geq$ 55 years) and cumulative exposure (from 1.0 percent among workers exposed to $\leq$ 0.5 mg/m^3-yrs to 10 percent among those exposed to 4 mg/m^3-yrs or more). Logistic regression analysis showed that the risk of acquiring a radiograph classified as category 0/1 or higher increased significantly with age and cumulative exposure to respirable quartz. Risk was further increased among current smokers but the effect was not statistically significant. Based on the regression model, the authors estimated the odds ratio for acquiring a radiologic abnormality (classified under ILO as $\geq$ 0/1) to be 4.3 for a 55-year-old man exposed to 1.0 mg/m^3-yrs respirable silica; given a reported baseline odds of 0.0062 for the lowest-exposed worker, this equates to a risk to age 55 of 2.6 percent. Similarly, the odds ratio for a 55-year-old non-smoker having a cumulative exposure of 4 mg/m^3-yrs was estimated to be 8.2, which equates to a risk of 4.9 percent. The model was not used by the authors to estimate odds of acquiring a radiographic abnormality classified as 1/0 or higher since only 25 workers had films so classified.

The authors concluded that the prevalence of abnormal radiographs tended toward the lower range of prevalence reported in other cross-sectional studies of brick workers. For example, they cited studies by Sluis-Cremer (1972), who reported a 2.3-percent prevalence of silicosis among South African brick workers; Palmer et al. (1980) who found a 5-percent prevalence of silicosis among brick workers in North Carolina; and Myers (1989), who reported a silicosis prevalence of 4 percent among South African brick workers. Love et al. (1999) suggested that the presence of clay minerals on quartz particles could have been responsible for reducing the toxicity of quartz in these plants, and they also acknowledged that the cross-sectional nature of the study could have biased the study towards understating the risk due to the preferential departure of workers previously affected by dust exposure. Despite these considerations, the authors believed that the exposure-response analysis "…suggests considerable risks of radiologic abnormality even at concentrations of 0.1 mg/m^3 of quartz."

Most recently, an unpublished study of silicosis prevalence among American brick workers was conducted for the Brick Industry Association (BIA) (Hessel, 2006) and reported finding no radiologic evidence of silicosis. The study population included 974 workers from 14 U.S. structural brick manufacturing facilities (13 selected at random from BIA member establishments and 1 that volunteered to provide medical information and chest x-ray films). Chest roentgenograms were obtained from 701 (72 percent) workers and medical questionnaires from 691 (71 percent) workers. X-ray films were read by two B-readers and disagreements were resolved by a third B-reader. Chest x-rays were taken in 2005 for all but 84 workers for whom previous films were available (dating back to 1999). No measurements of exposure to respirable crystalline silica were presented.

None of the x-ray films were considered consistent with silicosis. A consensus of the readers classified three films as 1/0 or higher but none were read as showing rounded opacities. Eight other films were classified as 1/0 or higher by only one of the primary readers and a consensus reading could not be obtained. Furthermore, six of these eight films were read as having only irregular opacities and the remaining two as having mixed shapes.

Hessel (2006) concluded that the study was consistent with other reports finding no evidence of silicosis among structural brick workers (citing Rajhans and Budlovsky, 1972; Zuskin et al., 1998; and Wiecek et al., 1983), as well as with the Love et al. (1999) study discussed above. However, OSHA believes that the cross-sectional study design and lack of quantitative exposure data limit the utility of this study.

II.F.2.b. Cumulative risk studies with little or no post-employment follow up.

Muir et al. (1989 a, 1989b; Verma et al., 1989) conducted a study of 2,109 active hardrock miners from Ontario assembled in 1940 and followed to 1982; retired and former workers were not included. Thirty-two workers were classified as having silicosis. Investigators used particle-count exposure measurements made by konimeter and converted them to mass respirable crystalline silica values based on data from side-by-side sampling. The study subjects had been employed for an average of 26 years and were exposed to dust containing 6 to 8.4% silica. Of the 2,109 miners, all but 63 (3%) were estimated to have had cumulative exposures of 2 mg/m^3-years or less, and 1,313 (62%) had exposures below 0.5 mg/m^3-years (Muir et al., 1989b). Chest x-ray films, which were taken annually on the miners, were examined by five readers using the following approach. First, four readers independently examined the two most recent films to screen out miners whose films clearly showed an absence of any evidence of silicosis. Based on the initial screening, the films of 650 miners were examined further by having each of the five readers classify the films using the 1980 ILO standard reference films; readers were provided these films in random order. If two readers classified the same zone of the same film as 1/1 or greater, all films for that miner were subjected to a final examination by all five readers. Films from 48 miners were selected for final examination, of which 32 were considered by one or more readers to have silicosis. Risk estimates were made for various cumulative exposure levels based on a fitted Weibull model and incorporating a 5-year exposure lag.

Muir et al. (1989b) estimated that the cumulative risk of developing silicosis as a result of 40 years of exposure to 0.1 mg/m^3 was 2.7 percent based on a positive finding from at least one reader, or 1.2 percent based on agreement of three or more readers; results based on findings from each of the five readers ranged from 0.5 to 2 percent. For an exposure level of 0.05 mg/m^3, they estimated the risk to be 0.9 percent based on at least one reader and 0.4 percent based on three or more readers. The investigators remarked that the x-ray films were of very variable quality, which was the reason for devising their strategy for evaluating the films (Muir et al., 1989a).

In his review of available risk studies for silicosis, Finkelstein (2000) stated that the results from this study were not sufficiently reliable for risk assessment because the period of follow up was too short. He pointed out that the latest x-ray for nearly half of the subjects was obtained less than 15 years from the start of exposure and that in his earlier study of Ontario miners who started exposure in 1950 or later, less than 20% of the silicosis cases were diagnosed earlier than 20 years from first exposure (Finkelstein, 1994). He also believed that the results understated the true risk because there was no adjustment for time since first exposure; that is, the calculation of the risk included miners with latencies less than 10-15 years and, consequently, who should be regarded as not being at risk.

Hughes et al. (1998) reported the results of their retrospective cohort study of 2,342 workers employed at a diatomaceous earth mining and processing facility for at least one year between 1942 and 1987. Exposure estimates were made from respirable dust monitoring data and estimates of the percent crystalline silica content of the product. Estimates of dust concentrations prior to 1948 when measurements were first made were based on relative rankings of exposures in different jobs and documented changes in processes and dust controls. From this assessment, average respirable silica exposures were estimated to be 0.9 mg/m^3 in 1932-43 and declined to 0.4 mg/m^3 in 1944-1953, 0.15 mg/m^3 in 1954-1973, and 0.10 mg/m^3 in 1974-1994. An x-ray surveillance program (at initial hire and periodically thereafter) was initiated in the 1930s; participation was not required and only a few films were available from some of the earlier workers. In all, films were available for 1,983 workers; however, only the films from 1,809 workers who had films taken more than one-month post-hire were included in the exposure-response analysis. In addition, only 82 workers participated in the surveillance program post-employment. All available films for the cohort were screened by one reader to select the latest film for each worker having acceptable quality. These films were read independently by three B-readers according to the 1980 ILO system; a silicosis case was defined if at least two readers scored the film as 1/0 or greater, or if large opacities were identified. All films for each worker identified from the latest film as having silicosis were read by the three readers to ascertain the dates of the last negative and first positive film. Silicosis incidence within the cohort was assessed by Poission regression, followed by life table analysis and parametric failure-time models to evaluate the exposure-response relationship.

Overall, opacities in films were observed in 4.5 percent of the cohort. The relative risk of silicosis increased significantly with cumulative exposure to silica and was best described by a log-logistic model. However, the investigators found that

average concentration of silica, defined as the cumulative exposure divided by the number of years worked up to the final or first positive x-ray, was also an important determinant. This finding was based on analysis of incidence rates and relative risks after dividing the cohort into those whose average exposure exceeded 0.5 mg/m^3 and those whose average exposure was below or equal to 0.5 mg/m^3. The value of 0.5 mg/m^3 was chosen based on the average exposure among 357 workers who had cumulative exposure of 3 mg/m^3-years and for whom a relatively high incidence of disease was found. Hughes et al. (1998) estimated that the cumulative risks of opacities at a cumulative exposure of 4.0 mg/m^3-years (equal to a 40-year exposure to 0.1 mg/m^3 respirable crystalline silica) were 3.3 and 12.4 percent for workers exposed below or above an average concentration of 0.5 mg/m^3, respectively. For a cumulative exposure of 2 mg/m^3-years (equal to a 40-year exposure to 0.05 mg/m^3), the estimated cumulative risks were 1.1 and 3.7 percent for workers exposed below or above 0.5 mg/m^3, respectively. Hughes et al. (1998) found that subdividing the cohort based on other average exposure values below 0.5 mg/m^3 did not have any meaningful effect on the relationship between relative risk and cumulative exposure.

According to the investigators, the finding of a steeper exposure-response relationship with cumulative exposure for the subgroup of workers exposed to an average concentration of 0.5 mg/m^3 or more suggests that exposure concentration is a risk factor for silicosis. However, they also suggested that the observed difference could reflect an underestimation of exposure levels for early hires, who comprised the majority of workers exposed to the higher concentrations. If that was the case, then the risk associated with a given cumulative exposure would have been lower than observed among workers exposed to the higher concentrations, and thus would have been closer to the risk among workers exposed at lower concentrations but at the same cumulative exposure.

As with the Muir et al. (1989b) study, this study of diatomaceous earth workers is weakened by a short follow up period. There were only 394 workers (22 percent of the cohort) for whom the latest chest radiograph was taken 20 or more years post-hire. For the cohort overall, the latest chest film was taken an average of 11.5 years after hire, a period too short for silicosis to have developed. Hughes et al. (1998) recognized this limitation and acknowledged the possibility that this led to an underestimation of risk, but they also argued that risk would have been understated only if there was a higher rate of disease among workers who left employment (for whom chest x-ray films were not generally available) compared to workers who continued employment. Essentially, this would reflect a healthy worker effect.

Park et al. (2002) conducted exposure-response analyses of a previously assembled cohort of 2,342 white male workers in a diatomaceous earth plant, all of whom had worked for at least a year between 1942 and 1994; this analysis was described in detail above in Section II.C with respect to their analysis of non-malignant respiratory disease mortality. Evaluation of silicosis morbidity was based on 70 incident cases of silicosis. Chest x-ray films dating back to the 1930s were available for the cohort, however almost all radiography ended with employment. Silicosis cases were defined as

radiographs classified ILO 1/0 or greater by two of three B readers. The median date of the first positive film was used in Poisson regression and proportional hazards analysis.

The investigators observed a skewed distribution in calendar time in which 73 percent of cases occurred during the first 13 of 53 years of follow-up. They considered this to be a reflection of increased surveillance after 1942 during which many previously undetected cases were revealed. According to the authors, this expansion of the surveillance program might have resulted in cases identified after 1942 that were present earlier but not detected. The extent to which such cases were ascertained late could have resulted in a bias toward underestimating risk.

Risks were estimated for the cohort overall and for the cohort excluding the highest-exposed (>10 mg/m^3-years) group of workers (as with the case for the mortality analysis). With the high-exposure group excluded, the excess lifetime risk estimates of radiographic silicosis for a 45-year exposure to 0.1 mg/m^3 and 0.05 mg/m^3 were 14 and 7.5 percent, respectively. With the high-exposure group included, the estimated lifetime risks for these exposure levels were 10 and 6.8 percent, respectively.

II.F.2.c. Cumulative risk studies with post-employment follow up.

Hnizdo and Sluis-Cremer (1993) described the results of a retrospective cohort study of 2,235 white gold miners in South Africa. These workers had received annual examinations and chest x-rays while employed; most returned for occasional examinations after employment. Radiographs were interpreted by a single reader and a case was defined as one classified as ILO 1/1 or greater. A total of 313 miners had developed silicosis and had been exposed for an average of 27 years at the time of diagnosis. Forty-three percent of the cases were diagnosed while employed and the remaining 57 percent were diagnosed an average of 7.4 years after leaving the mines. The average latency for the cohort was 35 years (range of 18-50 years) from start of exposure to diagnosis.

Cumulative exposures of the miners were estimated by converting particle count measurements made in the 1960's to respirable dust measurements (Du Toit 1991) and assuming a 30-percent quartz content of the dust. The average respirable dust exposure for the cohort overall was 0.29 mg/m^3 (range 0.11-0.47); this corresponds to an average respirable silica concentration of 0.09 mg/m^3 (range 0.033-0.14). The average cumulative dust exposure for the overall cohort was 6.6 mg/m^3-years (range 1.2-18.7), or an average cumulative silica exposure of 1.98 mg/m^3 (range 0.36-5.61).

Gibbs and Du Toit (2002) argued that the exposure estimates were understated by about a factor of two since a higher silica content should have been assumed. According to a footnote in Table II of Hnizdo-Slius-Cremer (1993), the assumption of a 30-percent quartz content applied to heat-treated and acid-washed dust; Gibbs and DuToit believed after their review that this assumption was erroneous, and that a 54-percent quartz content value should have been used to estimate the exposures of miners to respirable quartz.

The California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA, 2005) examined this issue in detail by reviewing the underlying data presented by Page-Shipp and Harris (1972) and comparing those data to the quartz exposures calculated by Hnizdo and Slius-Cremer based on a 30 percent quartz content and to the exposure estimates that would result from assuming a 54 percent quartz content, as asserted by Gibbs and DuToit. OEHHA (2005) found that the use of a 30 percent quartz value yielded exposure estimates that were consistent with those calculated originally by Page-Shipp and Harris (1972), indicating that the assumption by Hnizdo and Slius-Cremer of a 30 percent quartz content for untreated dust was more likely correct. (This suggests that the footnote in Table II of Hnizdo and Sluis-Cremer is in error and the data presented are for untreated rather than acid-washed dust.) In addition, OEHHA (2005) cite evidence that more recent investigations have found the quartz content of respirable dust in South African gold mines is even less than 30 percent. For example, they cite Kielblock et al. (1997), who reported that mine dust sampled between the late 1980's and early 1990's contains about 15 percent crystalline silica, and that a summary by Hnizdo of other measurements made in the 1970's and 1980's have found a quartz content to be about 20 percent. Most recently, Churchyard et al. (2003, 2004, discussed above) found a median quartz content of 13.2 percent among 506 personal dust samples taken in 2000-2001, and a median of 16.1 among almost 700 measurements made by employers. These findings indicate that the quartz content of dust collected in South African gold mines was in fact likely to be less than the 30 percent assumed by Hnizdo and Sluis-Cremer (1993). Thus, OSHA is not persuaded by the analysis of Gibbs and Du Toit (2002) suggesting that the exposure estimates in the Hnizdo et al. (1997) study were understated, and other data suggests that the assumed quartz content of the dust, and hence worker exposures, might have been overstated. However, the need to rely on particle count data that was generated over a fairly narrow production period and the need to make assumptions about the quartz content of the dust to which workers were exposed does add uncertainty to the exposure estimates.

Silicosis risk increased exponentially with cumulative exposure to respirable dust and was modeled using log-logistic regression. Using the exposure-response relationship developed by Hnizdo and Sluis-Cremer (1993), and assuming a quartz content of 30 percent in respirable dust, Rice and Stayner (1995) and NIOSH (2002) estimated the risk of silicosis to be 70 percent and 13 percent for a 45-year exposure to 0.1 and 0.05 mg/m^3 respirable crystalline silica, respectively.

According to Finkelstein (2000), this study had good statistical power because of the relatively large number of cases identified in the cohort. In addition, this study had good follow up of miners post-employment as evidenced by more than half the cases being diagnosed after employment. Finkelstein (2000) also pointed to uncertainties in the exposure estimates as well as potential uncertainty introduced by the radiographs having been read by a single reader. However, autopsy data presented by Hnizdo and Sluis-Cremer (1993) indicated that the classification of radiographs most likely understated the true prevalence of silicosis in this cohort since the sensitivity of the coding relative to autopsy findings was 0.99 (i.e., almost no false-positive readings), whereas the specificity was only 0.39 (i.e., a high rate of false negatives).

Three thousand three hundred thirty South Dakota gold miners who had worked at least a year underground between 1940 and 1965 were studied by Steenland and Brown (1995b). Workers were followed though 1990 with 1,551 having died. X-rays taken in cross-sectional surveys in 1960 and 1976 and death certificates were used to ascertain cases of silicosis. One hundred twenty eight cases were found via death certificate, 29 by x-ray, and 13 by both. Nine percent of deaths had silicosis mentioned on the death certificate. The loss to follow up was quite low (2%). Exposure was estimated by conversion of impinger (particle count) data and was based on measurements indicating an average of 13% silica in the dust. Based on these data, the authors estimated the mean exposure concentration to be 0.05 mg/m^3 for the overall cohort, with those hired before 1930 exposed to an average of 0.15 mg/m^3. The average duration of exposure for cases was 20 years (sd = 8.7) compared to 8.2 years (sd = 7.9) for the rest of the cohort. This study found that cumulative exposure was the best disease predictor, followed by duration of exposure and average exposure. Risk analysis was based on Poisson regression to calculate silicosis rates (cases per person-year at risk) for seven cumulative exposure categories. Lifetime risks to age 75 were calculated from these rates using standard life table techniques. The authors estimated a risk of 47 percent associated with 45 years of exposure to 0.09 mg/m^3 respirable crystalline silica, which reduced to 35 percent after adjustment for age and calendar time. OSHA used the same life table approach as described above for estimating lung cancer and NMRD mortality risks to estimate silicosis risk based on the silicosis rates, adjusted for age and calendar time, calculated by Steenland and Brown (1995b, Table 2). Silicosis risk was estimated through age 85, assuming exposure from age 20 through 65, and assuming that the silicosis rate remains constant after age 65. All-cause mortality rates to all males for calendar year 2006 were used to account for background competing risk. From this analysis, OSHA estimates the risk from exposure to the current general industry PEL of 0.1 mg/m^3 to be 43 percent; this is somewhat higher than estimated by Steenland and Brown (1995b) because of the use by OSHA of more recent mortality data and calculation of risk through age 85 rather than 75. For exposure to the proposed PEL of 0.05 mg/m^3, OSHA estimates the lifetime risk to be 7 percent.

Inclusion of death certificate diagnoses complicates interpretation of the risk estimate from this study since, as noted by Finkelstein (2000), it is not known how well such diagnoses correlate with ILO radiographic interpretations; as such, the risk estimates derived from this study may not be directly comparable to others that rely exclusively on radiographic findings to evaluate silicosis morbidity risk.

Miller et al. (1995, 1998) and Buchanan et al. (2003) reported on a 1990/1991 follow-up study of 547 survivors of a 1,416-member cohort of Scottish coal workers from a single mine. These men had all worked in the mine during a period between early 1971 and mid 1976, during which they had experienced "unusually high concentrations of freshly cut quartz in mixed coalmine dust. The population's exposures to quartz dust had been measured in unique detail, for a substantial proportion of the men's working lives." The 1,416 men had all had previous radiographs dating from before, during, or just after this high exposure period. Of these 1,416 men, 384 were identified as having died by 1990/1991. Of the 1,032 remaining men, 156 were untraced, and, of the 876 who were traced and replied, 711 agreed to participate in the study. Of these, the total number of

miners who were surveyed was 551. Four of these were omitted, two because of a lack of chest radiograph. The 547 surviving miners (age range of 29 to 85 years, mean = 59 years) were interviewed and received their follow-up chest x-rays between November 1990 and April 1991. The interviews consisted of questions on current and past smoking habits, and occupational history since leaving the coal mine, which closed in 1981. They were also asked about respiratory symptoms and were given a spirometry test.

Exposure characterization was based on extensive respirable dust sampling; samples were analyzed for quartz content by infrared spectroscopy. Between 1969 and 1977, two coal seams were mined; one of them had produced quarterly mean concentrations of silica substantially less than 1 mg/m^3 (only 10 percent exceeded 0.3 mg/m^3), while the other more unusual seam (mined between 1971 and 1976) lay in sandstone strata and generated air levels of silica such that quarterly mean exposures exceeded 1 mg/m^3 (10% of the quarterly measurements were over 10 mg/m^3). Thus, this cohort allowed study of the effects of both higher and lower silica concentrations, and exposure-rate effects on the development of silicosis.

Three physicians read each chest film taken during the current survey as well as films from the surveys conducted in 1974 and 1978. Films from the 1970 survey were read only if none were available from the subsequent two surveys. Silicosis cases were identified as such if the median classification of the three readers indicated an ILO (1980) class of 1/0 or greater, plus a progression from the earlier reading. Of the 547 men, 203 (38%) showed progression of at least one ILO category from the 1970's surveys to the 1990-91 survey; in 128 of these (24%) there was progression of two or more steps. In the 1970's survey 504 men had normal chest x-rays; of these 120 (24%) acquired an abnormal x-ray consistent with ILO category 1/0 or greater at the follow-up. Of the 36 men whose x-rays were consistent with ILO category 1/0 or greater in the 1970's surveys, 27 (75%) exhibited further progression at the 1990/1991 follow-up. Only one subject showed a regression from any earlier reading, and that was slight, from 1/0 to 0/1. The earlier Miller et al. (1995) report presented results for cases classified as having x-ray films consistent with either 1/0+ and 2/1+ degree of profusion; the Miller et al. (1998) analysis and the Buchanan et al. (2003) reanalyses emphasize the results from cases having x-rays classified as 2/1+.

Evaluation of exposure-response was performed by logistic regression using cumulative exposure expressed as g/m^3-hours, assuming 1,740 work hours per year. Thus, to estimate risk for OSHA's purposes, exposure to 0.1 mg/m^3 for 45 years is about equal to 9.00 g/m^3-hours (0.0001 g/m^3 * 45 years * 2000 hours/year). Covariates in the regression included smoking, age, amount of coal dust, and percent of quartz in the coal dust during various previous survey periods. Both Miller et al. (1995 and 1998) papers present the results of numerous regression models, and they compare the results of the partial regression coefficients using Z statistics of the coefficient divided by the standard error. Also presented are the residual deviances of the models and the residual degrees of freedom. In the introduction to the results section, Miller et al. (1995) stated that, "… in none of the models fitted was there a significant effect of smoking habit (current, ex-smoker, and never smoker), nor was there any evidence of any difference between

smoking groups in their relationship of response with age." They therefore presented the results of the regression analyses without terms for smoking effects.

The logistic models developed by Miller et al., (1995) included terms for cumulative exposure and age. In their later publication, Miller et al. (1998), presented models similar to their 1995 report, but without the age variable included. Using logistic regression model A from Table 7 of their report, which included only an intercept (-4.32) and the quartz cumulative exposure variable (0.416), they estimated that exposure to crystalline silica at an average concentration of 0.10 mg/m^3 for 15 years (2.6 g/m^3-hr assuming 1,750 hours worked per year) would result in an increased risk of silicosis (ILO$\geq$2/1) of 5 percent. Using these same model coefficients, OSHA estimates that exposure to the current general industry PEL of 0.1 mg/m^3 for 45 years (9.0 g/m^3-hours assuming 2,000 hours worked per year) would result in an excess risk of about 0.36, or 360 workers per 1000. Exposure to the proposed PEL of 0.05 mg/m^3 for 45 years (4.5 g/m^3-hours) results in an estimated excess risk of about 80 cases per 1,000 workers.

A later paper and reanalysis by these same authors (Buchanan et al., 2003) provided strong evidence of an exposure-rate effect for silicosis in this cohort. To estimate exposure-rate effects, exposure was categorized as pre- and post-1964, the latter period being that of generally higher quartz concentrations. For the purpose of this analysis the results were presented for the 371 men (out of the original 547) who were between the ages of 50 and 74 at the time of the 1990/1991 follow-up, "since they had experienced the widest range of quartz concentrations, and showed the strongest exposure-response relations." Thus, combined with their exposure history, which went back to pre- 1954, many of these men had 30 to 40+ years of highly detailed occupational exposure histories. Of these 371, there were 35 (9.4%) who had x-ray films consistent with ILO category 2/1+ , with at least 29 of these having progressed from less severe silicosis since the previous follow-up during the 1970's (from Miller et al., 1998).

The Buchanan et al. (2003) reanalysis presented logistic regression models in stages. In the first stage they compared the effect of pre- vs. post 1964 cumulative quartz exposures on odds ratios. This yielded a statistically significant odds ratio estimate for post-, but not pre-1964 cumulative exposures. In the second stage, including first these post-1964 cumulative quartz exposures in the model, the authors then added total dust levels both pre- and post-1964, age, smoking status, and number of hours worked pre-1954. In this second stage, only post-1964 cumulative exposures remained statistically significant. Finally, in their third stage of modeling, starting with only the statistically significant post-1964 cumulative exposures, the authors separated these exposures into, "two quartz concentration bands, defined by the cut point 2.0 mg/m^3." This yielded the final equation:

$$\text{Prob}(2/1+) = 1/ (1+\exp-(-4.83 + 0.443*\text{Cum.Expos}_{<2} + 01.323 * \text{Cum.Exp}_{>2})$$

In this model both the cumulative exposure concentration exposure variables were "highly statistically significant in the presence of the other." Since these variables were in the same units, g–hr/m^3, the authors noted that coefficient for exposure concentrations >2.0 mg/m^3 is 3 times that for the concentrations <2.0 mg/m^3, and concluded that their

latest analysis has shown that "the risk of silicosis over a working lifetime can rise dramatically with exposure to such high concentrations over a timescale of merely a few months."

Buchanan et al. (2003) also used this model to estimate the risk of acquiring a chest x-ray classified as ILO category 2/1+, 15 years after exposure ends, as a function of both low (<2.0 mg/m^3) and high (>2.0 mg/m^3) quartz concentrations. OSHA has chosen to use this model to estimate the risk of radiological silicosis consistent with an ILO category 2/1+ chest x-ray for several exposure scenarios, assuming 45 years of exposure, 2000 hours/year of exposure, and no exposure above a concentration of 2.0 mg/m^3. These are presented in Table II-11. The results show that occupational exposures to the proposed PEL of 0.05 mg/m^3 lead to an estimated risk of 5.5 cases per 100 workers. Exposure at the current general industry PEL of 0.100 mg/m^3 increases the estimate to 30.1 cases per 100 workers. At higher exposure levels the risk estimates rise quickly to near certainty.

Buchanan et al., (2003) provided analysis and risk estimates only for cases having x-ray films consistent with ILO category 2/1+ extent of profusion of opacities, after adjusting for the disproportionately severe effect of exposure to high concentrations of silica. Estimating the risk of 1/0+ profusions from the Buchanan (2003) or the earlier Miller et al. (1995, 1998) publications can only be roughly approximated because of the summary information included. This is done as follows: From Miller et. al., (1998), Table 4 presents a cross tabulation of radiograph progression, using the 12-point ILO scale, from the last baseline exam to the 1990/1991 follow-up visit for the 547 men at the Scottish coal mine. From this table, among workers for whom there were early x-ray films as well as follow-up films, there were 44 men who had progressed to 2/1+ by the last follow up, and an additional 105 who had experienced onset of silicosis (i.e., x-rays films were classified as 1/0, 1/1, or 1/2). Thus, by the time of the follow-up, there were 3-times more miners with silicosis consistent with ILO category 1 than there were miners with a category 2+ level of severity ((105 + 44)/44 = 3.38). This suggests that the risk estimates derived from the Buchanan et al. (2003) model, which reflects the risk of progressing to ILO category 2+, understates the risk of acquiring radiological silicosis by about 3-fold in this population of workers.

OSHA has a high degree of confidence in the estimates of silicosis morbidity risk from this Scotland coal mine study, mainly because of the highly detailed and extensive exposure measurements, the radiographic records, and the detailed analyses of high exposure-rate effects. However, in another paper, the authors (Soutar et al., 2004) noted that:

> If the effects of silica vary according to the conditions of exposure, these risks are probably towards the high end of the risk spectrum, since the silica was freshly fractured from massive sandstone, and not derived from dirt bands where the quartz grains are aged and accompanied by clay minerals.

In contrast to the risk estimates that reflect an ILO 2/1+ degree of profusion of small opacities, OSHA could only crudely assess the risk of less severe silicosis from the

Table II-11. Summary of Silicosis Morbidity Risk Estimates

Study	Predicted Risk From Exposure Over 45 Years (Cases per 100 Workers)	
	0.1 mg/m^3	0.05 mg/m^3
Cross-Sectional Studies		
Rosenman et al., 1996	3[a]	2[a]
Ng and Chan, 1994	NE	6[b]
Kreiss and Zhen, 1996	90	30
Churchyard et al., 2003	NE	33[c]
Love et al., 1999	4.9[d]	NE
Cumulative Risk Studies, Little or No Post-Employment Follow Up		
Muir et al., 1989a, 1989b; Verma et al., 1989	2.7[a,e]	0.9[a,e]
	1.2[a,f]	0.4[a,f]
Hughes et al., 1998	3.3[a,g]	1.1[a,g]
	12.4[a,h]	3.7[a,h]
Park et al., 2002	14	7.5
Cumulative Risk Studies With Post-Employment Follow Up		
Hnizdo and Sluis-Cremer, 1993[i]	77	13
Steenland and Brown, 1995b[i]	43	7
Miller et al., 1998[i]	36	8
Buchanan et al., 2003[i]	30	5.5
Chen et al., 2001[j]	59	17
Chen et al., 2005[k]		
Tin miners	32	9
Tungsten miners	12	2
Pottery workers	6	2

Footnotes for Table II-11

[a] Risk assuming a 40-year working life
[b] Risk for an average 50-year old worker exposed to 2 mg/m^3-years
[c] Risk of ≥0/1 x-ray to age 55 for cumulative exposure of 4 mg/m^3-years
[d] Prevalence of ≥ 1/1 x-ray for cumulative exposure of 1.48 - 3.08 mg/m^3-years
[e] Estimates based on findings from at least one reader
[f] Estimates based on agreement by three or more readers
[g] Risk for workers exposed to average concentrations <= 0.5 mg/m^3
[h] Risk for workers exposed to average concentrations > 0.5 mg/m^3
[i] Estimated by OSHA, see text and Table II-12
[j] Estimated from the Weibull model parameters reported by Chen et al., 2001
[k] Estimated from Figure 2B of Chen et al., 2005

information available. However, it is obvious from the available information that the risk of acquiring radiological silicosis consistent with ILO category 1/0+ (i.e., the risk of onset of disease) are significantly greater than that for progressing to more severe disease. From the Buchanan et al. (2003) and Miller et al. (1998) studies, the risk of acquiring silicosis would be of the same magnitude as that reported by Hnizdo and Sluis-Cremer, (1993).

Another factor, study participant recruitment could also affect these risk estimates. Finkelstein (2000), commenting on Miller et al. (1998), raised the issue of whether selection bias might have affected the risk estimates, given that only about 50 percent of the cohort participated in the interview and radiological surveillance. He also questioned whether lung clearance impairment might have been a factor during the period of very high silica exposure experienced by these miners. OSHA acknowledges that both these may be factors in estimating risks from this study, but concludes that, at worst, effects would probably tend to be in opposite directions and offset each other. First, with respect to selection bias, this is a survivor cohort studied at least 15 years after the period of high quartz exposure. About 10 percent of the 1,416 had already died by 1990. Considering the high silicosis incidence and the known association of silicosis with increased risk of both lung cancer and NMRD, this survivor cohort should lead to an underestimate of silicosis risks. Further, selection of the 50-75 age group for use in the latest reanalysis would tend to accentuate the survivorship effect of underestimating risks. Second, with respect to an exposure-rate effect of high silica exposure possibly due to lung clearance impairment, OSHA agrees that these have to be taken into account with this cohort. OSHA concludes that the results of the Buchanan et al. (2003) regression model showing statistically significant and differential effects of exposure to both high and low quartz concentrations during the same exposure periods, provide superior estimates of silicosis for OSHA's risk assessment purposes.

OSHA also acknowledges that using these logistic regression models for projecting risk estimates with these data has limitations and uncertainties, especially using models with only one, two or three variables. There are significant differences in risk estimates using different models, as displayed both here and in the Miller et al. and Buchanan et al. papers. However, use of these models with these data has shown several significant results. First, there is the lack of significance of smoking in producing radiographs with silicosis profusions. Second, the models show an established cumulative quartz exposure effect for silicosis in coal miners, and independent of the presence of coal dust. Third there is an independent high exposure-rate effect for silicosis, which is accounted for in the risk estimates derived from the Buchanan et al. (2003) model.

In 2001, Chen et al. reported the results of a retrospective study of a Chinese cohort of 3,010 underground miners who had worked in tin mines at least one year between 1960 and 1965. They were followed through 1994, by which time 2,426 (80.6%) workers had either retired or died, and only 400 (13.3%) remained employed at the mines.

The mines provided occupational histories, dust measurement and medical examination records. Exposure data consisted of high-flow, short-term gravimetric total dust measurements made routinely since 1950; the authors used data from 1950 to represent earlier exposures since dust control measures were not implemented until 1958. Conversion of total dust measurements to respirable silica values was based on respirable dust samples taken during a survey in 1988-1989; results from this survey indicated that respirable silica measurements were 3.6 percent (sd = 2.5 percent) of total dust measurements. Annual radiographs were taken since 1963 and all cohort members continued to have chest x-rays taken every 2 or 3 years after leaving work. Silicosis was diagnosed when at least 2 of 3 radiologists classified a radiograph as being a "suspected case" or at Stage I, II, or III under the 1986 Chinese pneumoconiosis roentgen diagnostic criteria. According to Chen et al. (2001), these four categories under the Chinese system were found to agree closely with ILO categories 0/1, Category 1, Category 2, and Category 3, respectively, based on studies comparing the Chinese and ILO classification systems. Silicosis was observed in 33.7% of the group; 67.4% of the cases developed after exposure ended.

The investigators found that a Weibull model provided the best fit to relate cumulative silicosis risk to eight categories of cumulative total dust exposure. The risk of silicosis was strongly related to cumulative silica exposure. The investigators predicted a 55-percent risk of silicosis associated with 45 years of exposure to 0.1 mg/m^3. The paper did not report the risk associated with a 45-year exposure to 0.05 mg/m^3, but OSHA estimates the risk to be about 17 percent (based on the parameters of the Weibull model provided in Chen et al., 2001).

In a later study, Chen et al. (2005) investigated silicosis morbidity risks among three cohorts to determine if the risk varied among workers exposed to silica dust having different characteristics. The cohorts consisted of 4,547 pottery workers, 4,028 tin miners, and 14,427 tungsten miners selected from a total of 20 workplaces. Cohort members included all males employed after January 1, 1950 and who worked for at least one year between 1960 and 1974. Radiological follow-up was through December 31, 1994 and x-rays were scored according to the Chinese classification system as described previously by Chen et al. (2001) for the tin miner study. Exposure estimates of cohort members to respirable crystalline silica were based on the same data as described by Chen et al. (2001), i.e., short-term area samples for total dust with respirable silica dust exposures estimated from side-by-side measurements taken in 1988-1989 of total dust using the Chinese sampling method and respirable dust using the U.S. method. In addition, the investigators measured the extent of surface occlusion of crystalline silica particles by alumino-silicate from 47 dust samples taken at 13 worksites using multiple-voltage scanning electron microscopy and energy dispersive X-ray spectroscopy (Harrison et al., 2005); this technique measures the silicon-to-aluminum ratio for both the whole particle (using high voltage) and the particle surface (using low voltage), which yields estimates of the percent of particle surface that is occluded.

Compared to tin and tungsten miners, pottery workers were exposed to significantly higher mean total dust concentrations (8.2 mg/m^3, compared to 3.9 mg/m^3 for tin miners and 4.0 mg/m^3 for tungsten miners), worked more net years in dusty

occupations (mean of 24.9 years compared to 16.4 years for tin miners and 16.5 years for tungsten miners), and had higher mean cumulative dust exposures (205.6 mg/m^3-years compared to 62.3 mg/m^3-years for tin miners and 64.9 mg/m^3-years for tungsten miners) (Chen et al., 2005). Applying the authors' conversion factors to estimate respirable crystalline silica from Chinese total dust measurements, the approximate mean cumulative exposures to respirable silica for pottery, tin, and tungsten workers are 6.4 mg/m^3-years, 2.4 mg/m^3-years, and 3.2 mg/m^3-years, respectively. Measurement of particle surface occlusion indicated that, on average, 45 percent of the surface area of respirable particles collected from pottery factory samples was occluded, compared to 18 percent of the particle surface area for tin mine samples and 13 percent of particle surface area for tungsten mines.

The relationship between respirable silica exposure and silicosis morbidity (defined as Stage I or higher classification of chest x-ray films under the Chinese system) was analyzed using the Weibull model (details not provided), the results of which were provided in graphic form. Based on Figure 2B of Chen et al. (2005), OSHA estimated the cumulative silicosis risk associated with a cumulative exposure of 4.5 mg/m^3-years respirable silica to be 6 percent for pottery workers, 12 percent for tungsten miners, and 32 percent for tin miners. For a cumulative exposure of 2.25 mg/m^3-years (i.e., 45 years of exposure to 0.05 mg/m^3), cumulative silicosis morbidity risks were estimated to be 2, 2, and 9 percent for pottery, tungsten, and tin miners, respectively. When cumulative silica exposure was adjusted to reflect exposure to surface-active quartz particles (i.e., not occluded), the estimated cumulative risk among pottery workers more closely approximated those of the tin and tungsten miners, suggesting to the authors that alumino-silicate occlusion of the crystalline particles in pottery factories at least partially explained the lower risk seen among workers, despite their having been more heavily exposed.

II.F.3. Summary of Risk Estimates.

Table II-11 presents a summary of the risk estimates provided by the studies reviewed in this section. It is clear from this table and it has been pointed out by others (Chen et al., 2001; Finkelstein, 2000; NIOSH, 2002) that lack of follow up of retired workers consistently resulted in lower risk estimates compared to studies that included retired workers. OSHA believes that the most reliable estimates of silicosis morbidity, as detected by chest radiographs, come from the five studies that evaluated radiographs over time, included radiographic evaluation of workers after they left employment, and derived cumulative or lifetime estimates of silicosis disease risk: the U.S. gold miner cohort studied by Steenland and Brown (1995b), the Scottish coal miner cohort studied by Miller et al. (1995, 1998) and Buchanan et al. (2003), the Chinese tin mining cohort studied by Chen et al. (2001), the tin, tungsten, and pottery worker cohorts studies by Chen et al. (2005), and the South African gold miner cohort studied by Hnizdo and Sluis-Cremer (1993).

These five studies evaluated silicosis risks in seven cohorts (with the two tin miner cohorts overlapping). The estimates derived from the U.S. gold miner cohort (Steenland and Brown, 1995b), the Scottish coal mining cohort (Miller et al., 1998;

Buchanan et al., 2003), Chinese tin mining cohorts (Chen et al., 2001; Chen et al., 2005), and South African gold miner cohorts (Hnizdo and Sluis-Cremer, 1993) are all in reasonable agreement and range from 30 to 77 percent for a 45-year exposure to 0.1 mg/m^3 respirable crystalline silica. Of these studies, OSHA believes that the study of coalworkers by Miller et al. (1995, 1998) and Buchanan et al. (2003) is of the best overall quality, in large part due to the availability of respirable quartz measurements taken over several years that provided the basis for estimating exposures of individual cohort members. In contrast, the study of U.S. gold miners (Steenland and Brown, 1995b) required estimation of mass quartz exposures from particle count data and limited side-by-side respirable dust sampling, and the studies by Chen et al. (2001) and Chen et al. (2005) relied on short-term total dust samples, also with limited side-by-side sampling, to estimate exposures to respirable quartz dust. However, it is important to note that risk estimates based on the Miller et al. (1995, 1998) and Buchanan et al. (2003) studies reflect the risk that nodular profusion will progress such that a chest x-ray would be classified as ILO major category 2 or higher. Such estimates understate the risk of developing lesser degrees of profusion (i.e., ILO 1/0 or 1/1).

The highest estimate comes from the Hnizdo and Sluis-Cremer (1993) study, from which OSHA estimates silicosis risks of 77 and 13 percent for 45 years of exposure to 0.1 and 0.05 mg/m^3, respectively. It has been suggested that the exposure estimates were understated in this study by a factor of about two (Gibbs and Du Toit, 2002). As explained in Section II.F.2.c above, OSHA is not convinced that the exposures of the South African miners were necessarily systematically understated in this study; nevertheless, it must be acknowledged that there is uncertainty in the exposure estimates of the South African miner study. The low end of the range is reflected by the risk estimates from the two cohorts studied by Chen et al. (2005), the Chinese tungsten miners and pottery workers. For the pottery workers, it is possible that the presence of alumino-silicate surface occlusion resulted in reduced toxicity of the quartz particles; there is substantial evidence in animals that such coatings can reduce the fibrogenic potency of quartz (see Section I.F of the Health Effects section), and Chen et al. (2005) found that differences in the exposure-response relationship for pottery workers compared to miners was at least partially mitigated after adjusting cumulative silica exposure to account for surface occlusion. The studies by Love et al. (1999) of U.K. heavy clay workers and by Hessel (2006) of U.S. brick industry workers also suggest that silicosis risks are lower than has been seen in other industries, despite the cross-sectional nature of these studies. Recently, Miller and Soutar (2007) applied the model developed from the Scottish coal worker cohort by Buchanan et al. (2003) to compare predicted and observed silicosis cases in the cohort studied by Love et al (1999), and found that the model predicted about 4-fold more cases of silicosis (defined as ILO 2/1+ x-ray findings) than were observed (about 31 predicted compared to 8 observed). Miller and Soutar (2007) concluded that the predictive model was probably not relevant for the clay industry.

There is no apparent explanation for why tungsten miners appeared to have lower silicosis risk than tin miners, although their risk per unit cumulative silica exposure was higher than that of pottery workers. It is possible that the difference in observed exposure-response relationships seen among tungsten and tin miners reflects exposure misclassification due to the need to estimate full-shift exposures to respirable quartz from

short-term total dust samples, or that the difference is the result of unidentified workplace-specific factors that influenced the relative toxicities of the quartz particles found in the tungsten and tin mines.

The considerations described above make it difficult to estimate the risk of silicosis morbidity with a high degree of precision. However, because these five studies examined the morbidity experience of retired workers, OSHA believes that these studies come closest to reflecting the lifetime risk of experiencing radiological opacities faced by workers who are exposed to crystalline silica. For crystalline silica dust that is generated using high-energy processes (i.e., freshly cut or fractured) and not occluded, silicosis morbidity risk associated with exposure to the current PEL over 45 years is estimated to range between 12 and 77 cases per 100 workers, based on five studies that were judged to have sufficient follow-up of retired workers. The range in estimated risk associated with exposure to 0.05 mg/m^3 is from 2 to 17 cases per 100 workers. Of these studies, OSHA believes that the Miller et al. (1998) and Buchanan et al. (2003) studies provide the most reliable basis for estimating silicosis morbidity risk due to the high quality of the underlying exposure data for the cohort, and the capability of the Buchanan et al. model to account for possible effects of exposures to very high concentrations of respirable silica. OSHA estimated the risk from that study to be 30 cases per 100 workers for exposure to the current general industry PEL of 0.1 mg/m^3 and 5.5 cases per 100 workers for exposure to the proposed PEL of 0.05 mg/m^3. However, these estimates reflect the risk of developing more advanced stages of silicosis than do the remaining studies, and thus underestimate the actual risk of radiological silicosis.

II.G. Issues Related to Assessing Crystalline Silica-Related Risk.

II.G.1. Choice of Cumulative Dose as the Dose Metric.

Each of the analyses presented in this section have relied on cumulative exposure as the exposure metric used to quantify exposure-response relationships. Some studies have also reported finding positive exposure-response relationships based on exposure intensity rather than, or in addition to, cumulative exposure. Such findings could suggest that the relationship between exposure to crystalline silica and lung cancer or silicosis reflects a dose-rate effect, where for a given cumulative exposure level, exposure to higher concentrations would have a greater health impact than exposure to lower concentrations. Kuempel et al. (2001) argued that a dose-rate effect is biologically plausible given that quartz is cytotoxic and may interfere directly with the lung's antioxidant defenses resulting in a series of events that lead to disease. Among the studies relied on by OSHA, only the Buchanan et al. (2003) study of silicosis risks among Scottish coal miners has adjusted the cumulative exposure metric to account for the effects of exposures to high concentrations.

For lung cancer, a few studies have reported finding positive exposure-response relationships with exposure metrics other than cumulative exposure. Cherry et al. (1998) in their case-referent study of U.K. pottery workers reported that odds ratios for lung cancer increased with increasing concentration of crystalline silica, but not with cumulative exposure or exposure duration (after controlling for smoking and employing

lags of 0, 10, and 20 years). However, the prevalence of small opacities increased with both cumulative exposure and exposure concentration. These investigators stated that the lack of an exposure-response relationship for lung cancer and cumulative exposure arose directly from the cases having generally shorter durations of exposure than did controls, which were matched on date of birth and date of first exposure. Almost half (49.2 percent) of the controls were exposed for more than 15 years compared to 38.4 percent of cases, and more than one-third of the cases (37 percent) had less than 5 years of exposure, compared to only 27 percent of cases. This study was of a relatively small size, including a total of 52 lung cancer cases.

Two other studies reported finding increased lung cancer risk with increasing exposure intensity. Hughes et al. (2001) conducted a nested case-control study of 95 lung cancer deaths in nine industrial sand plants and found significant exposure-response trends with both cumulative exposure and average crystalline silica concentration, after controlling for smoking. In a separate study of industrial sand workers, Steenland et al. (2001b) found borderline significant trends with cumulative exposure and a significant positive trend with average exposure.

In contrast to these studies, most other epidemiological studies that examined relationships with cumulative exposure found positive associations; for example, nine of the ten epidemiological studies included in the pooled analysis by Steenland et al. (2001a) showed positive exposure coefficients when exposure was expressed as cumulative exposure (the one exception being the U.S. gold mining cohort).

Similarly, with a few notable exceptions, most of the studies of silicosis mortality and morbidity demonstrated positive exposure-response trends with cumulative exposure; these include each of the six cohort studies used in the pooled analysis by Mannetje et al. (2002b) and all of the silicosis morbidity studies summarized in Section II.F.2 above. In their analysis of diatomaceous earth workers and lung disease other than cancer, Park et al. (2002) specifically examined the fit of several models to alternative exposure metrics and found that in only one case did a model provide an adequate fit with average exposure intensity (log-linear model with the highest cumulative-exposure workers included); otherwise, most models performed best with cumulative exposure as the exposure metric.

Two studies provide some evidence for a dose-rate effect and silicosis morbidity as evidenced by the appearance of small opacities on chest roentgenograms. The Buchanan et al., (2003) reanalysis of the Miller et al., (1998) Scottish coal worker study has already been discussed in several sections above; that reanalysis found an approximately 3-fold increased silicosis risk resulting from exposure to concentrations above 2 mg/m^3 vs. that associated with equivalent cumulative exposures but to concentrations below 2 mg/m^3.

Hughes et al. (1998) found that exposure concentration was an important determinant of the risk to diatomaceous earth workers, where the relationship between cumulative exposure and risk of silicosis was considerably steeper among workers hired prior to 1950 and exposed to average concentrations above 0.5 mg/m^3, compared to that

for workers hired after 1950 and exposed to lower average concentrations. However, the authors also suggested that the observed difference could have been the result of underestimating exposure levels of workers hired early in the observation period when exposures were higher but less well characterized than for later years. In addition, the results of this study are made uncertain by a lack of follow up; for the cohort overall, the latest chest film was taken an average of 11.5 years after hire, a period too short to ensure that all, or nearly all, cases of silicosis that will develop could be detected.

The studies by Hughes et al. (1998) and Buchanan et al. (2003) provide evidence for a dose-rate effect for silicosis morbidity (as defined by the appearance of small opacities) in instances where workers are exposed to crystalline silica concentrations several-fold to orders of magnitude above the current OSHA PEL (i.e., above approximately 0.1 mg/m^3). OSHA believes that such an effect is biologically plausible given the cytotoxic nature of crystalline silica and its ability to interfere with its clearance by alveolar macrophages and fuel a persistent inflammatory reaction in the lung. However, there is little evidence that such a dose-rate effect exists at concentrations in the range of the current PEL. As summarized in the earlier parts of this section, the majority of studies of lung cancer and silicosis morbidity and mortality have consistently found significant positive relationships between risk and cumulative exposure. Lacking strong evidence of an exposure-rate effect in other studies, OSHA has chosen cumulative exposure unadjusted for any exposure-rate effect as a reasonable exposure metric on which to base estimates of risk to workers exposed to crystalline silica in the range of the current PEL.

II.G.2. Physical Factors That May Influence Toxicity of Crystalline Silica.

Much research has been conducted to investigate the influence of certain physical factors on the toxicologic potency of crystalline silica; such factors include crystal polymorphism, particle surface characteristics, the age of fractured surfaces of the crystal particle, the presence of impurities on particle surfaces, and coating of the particle. These factors may vary among different workplace settings suggesting that the risk to workers exposed to a given level of respirable crystalline silica may not be equivalent in different work environments. These findings are summarized in this section. Further details and discussion of additional studies may be found in Section I.F. of the Health Effects literature review.

These physical factors primarily affect the surface of silica particles. Researchers believe that surface characteristics of respirable crystalline particles play an important role in the mechanism by which silica causes lung damage. Thus, any factor that influences or modifies these surface characteristics may alter the toxicity of silica by affecting the mechanistic process. A silica particle entering the lung has reactive sites on its surface consisting of silicon-based free radicals. When these free radicals react with aqueous (water-based) constituents in the lung, they generate reactive oxygen species, or ROS, that can react with and damage cellular constituents such as DNA, proteins, lipids and carbohydrates. Silica surface contact with water also results in the formation of surface silanol groups. It is hypothesized that cellular response, and particularly macrophage activation and death, is mediated by strong interactions between reactive

sites on the particle surface and cell membrane components. These reactive species can cause cellular injury leading to fibrosis by several proposed mechanisms, including by direct cytotoxicity and by stimulating alveolar macrophages leading to release of cytotoxic enzymes, ROS, inflammatory factors (which lead to recruitment of polymorphonuclear leukocytes and cytokine release), and other factors that initiate fibroblast production and collagen synthesis (NIOSH, 2002). In addition, generation of ROS from silica directly or by stimulated cells may damage the lung epithelia and may play a role in silica-induced DNA damage or cell proliferation contributing to carcinogenesis (Fubini et al., 2004; Shi et al., 1989; Shi et al., 1998).

IARC (1997) has determined that "crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is carcinogenic to humans." In making this determination, the IARC Working Group noted that "carcinogenicity was not detected in all industrial circumstances studied." The Working Group also stated that "carcinogenicity may be dependent on inherent characteristics of the crystalline silica or on external factors affecting its biological activity or distribution of its polymorphs." Thus, while IARC has determined that cristobalite and quartz are both carcinogenic to humans, there has been considerable discussion among researchers as to whether the toxicological and carcinogenic potency of crystalline silica might vary depending on crystalline structure or surface chemistry of the particles.

Very early animal studies appeared to suggest that the crystal polymorphs cristobalite and tridymite were more toxic to the lung than quartz. King et al. (1953), who exposed rats by single intratracheal injection to quartz, cristobalite, or tridymite, described the action of cristobalite as "perhaps slightly faster than quartz," and tridymite as having a "spectacular" fibrotic effect. However, Bolsaitis and Wallace (1996) reviewed more recent studies showing the effect of different polymorphs on hemolytic activity and on inflammation and fibrosis in mouse lungs induced by quartz, cristobalite, or tridymite. The results showed that hemolytic activities were within the range of experimental error and lung fibrosis was essentially the same among the three polymorphs.

A difference in toxicity between cristobalite and quartz has not been observed in epidemiologic studies (exposure to tridymite has not been the subject of epidemiologic study). In their study of diatomaceous earth workers whose predominant exposure was to cristobalite, Rice et al. (2001) reiterated that differential polymorph toxicity has not been confirmed by results of epidemiological studies; however, citing results from studies of pottery workers, they also believed that there may be some evidence of increased mortality from lung cancer in industries with high temperature processes. These authors concluded that differences in the carcinogenic potential of various crystalline silica polymorphs have not been established and therefore cancer risks from workplace exposure to silica cannot yet be attributed or limited to a particular polymorph. Steenland et al. (2001a) also addressed the debate regarding whether the risk of lung cancer might be higher for cristobalite vs. quartz, since one of their cohorts was primarily exposed to cristobalite (diatomaceous earth workers). It was observed that the exposure-response trends within this cohort did not differ notably from trends in the remaining cohorts.

A number of investigators have addressed the relationship between the age of fractured crystal surfaces on respirable silica particles and their toxicologic potency. When crystalline silica is subjected to high energy forces, as occurs in work processes such as abrasive blasting, rock drilling, tunneling, stone carving and the production of silica flour, the silica particles are said to be "freshly fractured." Silica that is not fractured by the work process is said to be "aged." A number of studies have examined the question of whether freshly fractured silica is more toxic than aged silica. It has been noted that acute silicosis is associated with the generation of freshly fractured silica dust in these occupations (Castranova et al., 1996).

Early in vitro studies demonstrated that freshly fractured silica caused more cytotoxicity in cells than did aged silica (Vallyathan et al., 1988). Freshly fractured silica has been shown to possess an increased ability to activate respiratory bursts in alveolar macrophages (Shi et al., 1989), and it was found to be 4.6-fold more potent than aged particles in the release by activated alveolar macrophages of reactive oxygen species (Vallyathan et al.,1992). Vallyathan et al. (1988) hypothesized that freshly fractured silica is more potent due to formation of silicon-based radicals from cleavage of the crystal surfaces, as well as from propagation of other oxygenated radicals in aqueous environments. They suggested that the presence of these newly formed radicals along with those generated by macrophages may overwhelm pulmonary defense mechanisms. However, Vallyathan et al. (1988) noted that silica aged for years still retained the ability to stimulate alveolar macrophages and cause cytotoxicity, suggesting that silicon-based reactive oxygen species can only partly explain the biologic reactivity of silica.

The presence of moisture also appears to affect the generation of free radicals on particle surfaces. Elias et al. (2000) found that grinding quartz in a wet atmosphere greatly reduced its cytotoxic and transforming potency in Syrian hamster embryo cells, compared to that of dry-ground quartz.

Several in vivo studies have also been done to compare the effects of freshly fractured and aged silica. Representative is a study by Vallyathan et al. (1995) (also reported in Shoemaker et al., 1995 and Castranova et al., 1996) in which they exposed rats to freshly fractured or aged silica for 2 weeks by inhalation. Controls were exposed only to filtered air. In exposed rats, there were changes indicative of damage at the alveolar blood-air barrier level) and an inflammatory response. These indices were significantly elevated in the rats exposed to aged silica as compared to controls, and inhalation of freshly fractured silica resulted in a substantially greater pulmonary reaction than aged silica. The authors suggested that their study results indicated that the pulmonary reactions of rats to short duration exposure to freshly fractured silica mimic those seen in acute silicosis in humans.

The differential potency of freshly fractured vs. aged quartz may be dose dependent. In a recent study, Porter et al. (2002) treated rats by intratracheal instillation with either aged or freshly fractured silica at a dose of either 5 or 20 μg once a week for 12 weeks. These doses, which are lower than has been used in other animal studies, were chosen because they approximated exposures of surface miners to silica aerosols. Exposure to the low dose caused the same degree of inflammatory response and alveolar

macrophage activation for both aged and freshly fractured quartz. At the higher dose, freshly fractured silica was significantly more potent than aged silica in stimulating the activation of alveolar macrophages, but both caused a similar degree of pulmonary damage. The authors believed that their results suggested that the difference in potency between aged and freshly fractured silica occurs only after a threshold burden of silica is reached.

In the above in vitro and in vivo studies, silica was fractured by several different methods such as crushing or grinding in an agate mortar and pestle or generating in a air jet mill fitted with a polyurethane liner and stainless steel jets. However, it has been reported that the toxicity of silica can vary depending on the method of preparation. It was found that the toxicity of quartz particles increased when the sample was ground in a mill rather than in a press (Shi et al., 1989). It was suggested that after crushing in a press, the particle has a smooth surface, while the milled particle has sharp edges and a larger surface area. It is unclear what this finding means for the many different work processes that can create freshly fractured silica.

Castranova et al. (1998) demonstrated in rats that exposure to silica by intratracheal instillation or by inhalation results in an increase in messenger RNA for inducible nitric oxide synthase in bronchoalveolar lavage cells, elevated nitric oxide production by bronchoalveolar lavage cells and an increase in nitric oxide dependent chemiluminescence from alveolar macrophages. Freshly fractured silica was a more potent stimulant of nitric oxide-dependent chemiluminescence than aged silica. This study also compared similar endpoints in a healthy volunteer, a silica-exposed coal miner with a normal chest X-ray and a silica-exposed miner with an abnormal chest X-ray with an ILO reading of 1/0. There was some messenger RNA for inducible nitric oxide synthase in the bronchoalveolar lavage cells of the miner with the normal chest X-ray, there was much more in the cells of the miner with the abnormal chest X-ray. There was also more nitric oxide-dependent chemiluminescence in cells from the miner with the abnormal chest X-ray. Both endpoints were increased above control even in the miner with a normal chest X-ray.

The studies described above suggest generally that exposure to freshly fractured crystalline silica may be more hazardous than exposure to aged silica particles, and that the difference may be attributed to formation of reactive species on the surfaces of fractured quartz particles. However, aging quartz under laboratory conditions has not been shown to render the silica biologically inactive, and the difference in potency between freshly fractured and aged quartz may be dose dependent. Although studies have demonstrated that workers in jobs where they are likely to be exposed to freshly fractured silica show similar cellular effects to those seen in experimental animals, there are no studies that compare workers in those jobs to workers in jobs likely to have exposure to predominately aged silica. OSHA believes that it is not possible to determine from the available evidence at what point or under what conditions aged silica reduces in biological activity such that lung cancer and silicosis risks would be substantially diminished (e.g., by an order of magnitude or more).

Metal impurities can also modify the surface reactivity of silica (IARC, 1997). Transition metal ions (typically iron), adsorbed at the surface, activate the production of free radicals in aqueous suspensions. There have been a number of studies on the effect of metal impurities on silica toxicity. For example, in a follow-up to the Vallyathan et al. (1995) study cited above, the investigators altered the level of iron contamination of the freshly-fractured silica (Castranova et al., 1997). Surface radicals on freshly fractured silica are thought to generate hydroxyl radicals upon contact with water. Since iron chelation reduces the number of hydroxyl radicals, it is thought that trace contamination of silica with ferrous iron can enhance hydroxyl radical generation via a Fenton-like reaction. The finding that the production of both hydroxyl radical and silica-induced biological reaction decrease in a similar fashion with time after fracturing suggests that a relationship exists between hydroxyl radical generation and toxicity. The investigators hypothesized that trace contamination with iron would increase the pulmonary responses to inhaled silica. The study found that silica with high iron contamination produced more reactive species, significantly more damage to the alveolar air-blood barrier, more inflammation, increased macrophage activity and a greater level of lipid peroxidation in the lung tissues of experimental animals than did silica with low iron contamination. The authors concluded that the results support the hypothesis that trace iron contamination can augment the generation of oxidants by silica and enhance its inflammatory and cytotoxic potency in the lung. They also suggested that trace contamination of silica with iron may occur in occupational circumstances such as rock drilling and sandblasting, leading to increased lung damage and inflammation in workers in these occupations.

Donaldson and Borm (1998) reviewed this and other studies on the effect of iron or aluminum contamination associated with the quartz structure. They reported that, in contrast to the findings above, other studies have shown that iron can also reduce the toxicity of quartz. Metallic iron was found to diminish the ability of quartz to cause inflammation in the lungs of rats following instillation. Donaldson and Borm (1998) pointed out, however, that the state of iron may be important. Ferrous or ferric iron contamination was involved in the Castranova et al. (1997) study above showing increased toxicity as opposed to metallic iron. The quantity of iron may also be important with trace amounts increasing toxicity and a large excess decreasing toxicity. Aluminum was also shown to lower the toxicity of quartz in several studies. Co-treatment with aluminum attenuated the fibrogenic response to the inhalation of quartz in rats and reduced inflammation in sheep lung quartz instillation and in rats. Donaldson and Borm (1998) proposed that the biological effects of quartz (such as silicosis and cancer) could be understood in terms of surface reactivity and noted that a range of substances including minerals could modify the ability of quartz to generate free radicals and cause oxidative stress. They proposed that the hazard posed by quartz is not a constant entity, but one that may vary depending on the origin of the silica sample or its contact with other chemicals or minerals.

One of the authors of studies reviewed by Donaldson and Borm (1998) has recently published a further study of the state of the surface of quartz and its relationship to biological activity in vitro and in vivo. Fubini et al. (2004) examined the surface properties of four commercial quartz flours. Two of the samples had been shown in previous studies to be inflammogenic in vivo and to activate macrophages in vitro. The

two active samples were also genotoxic in vivo. The other two samples, which were mostly inert, contained a higher content of impurities, including aluminum, potassium, carbon, and iron. The authors suggested that their results were consistent with a model in which the difference in behavior of the four dusts are mainly caused by a different level and dispersion of contaminants on the silica surface (mainly aluminum and potassium and possibly also iron), which changed the silanol patches that correlate with cell damage.

Another physical factor relevant to the toxicologic potency of silica is the presence of a mineral coating, or "occlusion" of the silica surface that might affect the biological availability of the quartz component of the dust to which workers are exposed. This issue has been discussed by Wallace et al. (1996), who described research suggesting that contaminants on the surface may diminish the biological availability of toxic surface sites by gross occlusion of the silica surface, for example, by aluminosilicate clay. However, previous research by this author demonstrated comparable in vitro cytotoxicity for quartz and clay-occluded quartz. Thus, Wallace et al. (1996) commented that comparisons of pathologic potential and silica exposure must be made on the basis of worker population epidemiological data, for which surface properties of dust exposures typically are not investigated, or on the basis of in vivo animal model studies. An additional factor is the persistence of the contaminating material under conditions of particle deposition and residence in the lung. Limited tests on the durability of occluded silica particles upon a few hours incubation in surrogate pulmonary surfactant demonstrated the existence of aluminosilicate coating on quartz particles. Thus, in the opinion of the authors, relatively soluble clay occlusion would be expected to persist at least until phagocytosis, but that longer-term persistence under conditions of residence in interstitial tissue or the lymphatics was an open question. The authors, therefore, called for additional research to detail the nature of such occluded particle surfaces, the geological and processing factors which affect such occlusion, and the durability of such particles in tissue. More recently, Fubini et al. (2004), have commented that kaolin contamination, known to reduce quartz toxicity (citing the studies of Wallace et al., 1996 discussed above), may leave aluminum ions at the abraded quartz surface during grinding, which would inhibit the reactivity of silanols.

Although it is evident that a number of factors can act to mediate the toxicological potency of crystalline silica, it is not clear how such considerations should be taken into account to evaluate lung cancer and silicosis risks to exposed workers. After evaluating many in vitro studies that had been conducted to investigate the surface characteristics of crystalline silica particles and their influence on fibrogenic activity, NIOSH (2002) concluded that further research is needed to associate specific surface characteristics that can affect potency with specific occupational exposure situations and consequent health risks to workers. According to NIOSH, such exposures may include work processes that produce freshly fractured silica surfaces or that involve quartz contaminated with trace elements such as iron. NIOSH called for further in vitro and in vivo studies of the toxicity and pathogenicity of quartz compared with its polymorphs, quartz contaminated with trace elements, and further research on the association of surface properties with specific work practices and health effects.

In discussing the heterogeneity shown across the 10 studies used in the pooled lung cancer risk analysis, Steenland et al. (2001a) pointed to hypotheses that physical differences in silica exposure (e.g., freshness of particle cleavage) between cohorts may be a partial explanation of observed differences in exposure-response coefficients derived from those cohort studies. However, the authors did not have specific information on whether or how these factors might have actually influenced the observed differences. Similarly, in the pooled analysis and risk assessments for silicosis mortality conducted by Mannetje et al. (2002b), differences in biological activity of different types of silica dust could not be specifically taken into account. Mannetje et al. (2002b) determined that the exposure-response relationship between silicosis and log-transformed cumulative exposure to crystalline silica was comparable between studies and no significant heterogeneity was found. The authors therefore concluded that their findings were relevant for different circumstances of occupational exposure to crystalline silica.

Therefore, OSHA preliminarily concludes that it is not yet possible to use available information on factors that mediate the potency of silica to refine available quantitative estimates of the lung cancer and silicosis mortality risks, and that the estimates from the pooled analyses are fairly representative of a wide range of workplaces reflecting differences in silica polymorphism, surface properties, and impurities.

II.H. Preliminary Conclusions.

Table II-12 summarizes all of OSHA's risk estimates based on the studies reviewed in this section and OSHA's implementation of the various risk models. OSHA's preliminary conclusions are discussed below for lung cancer, silicosis mortality (including non-malignant lung disease risks), renal disease mortality, and silicosis morbidity.

Lung Cancer. Risk estimates were derived from the pooled risk analysis conducted by Steenland et al. (2001a); from studies of diatomaceous earth workers (Rice et al., 2001) and granite workers (Attfield and Costello, 2004), which were among the ten cohorts included in the pooled analysis; and from studies of North American industrial sand workers (Hughes et al., 2001) and British coal miners (Miller and MacCalman, 2009). Each of these studies shows a significant exposure-response relationship with cumulative occupational exposure to silica, which strengthens the evidence for a causal relationship between exposure to crystalline silica and lung cancer mortality.

For exposures in the range of the current general industry PEL and the proposed PEL, estimates of lifetime lung cancer risks are reasonably consistent among the five data sets and seven models employed. For 45 years of exposure to the current general industry PEL of 0.100 mg/m^3, OSHA estimates the risk to be between 13 and 60 deaths per 1,000 workers; the risk is estimated to range from 6 to 26 deaths per 1,000 for 45 years of exposure to the proposed PEL of 0.05 mg/m^3. Lung cancer risk is estimated to range from 3 to 22 deaths per 1,000 at the proposed action level. In the range of the current general industry PEL and proposed PEL, OSHA believes that the estimates from

Table II-12. Summary of Lifetime or Cumulative Risk Estimates for Crystalline Silica

	Risk Associated with 45 Years of Occupational Exposure (per 1,000 Workers)				
Health Endpoint (Source)	Respirable Crystalline Silica Exposure Level (mg/m^3)				
	0.025	0.05	0.100	0.250	0.500
Lung Cancer Mortality (Lifetime Risk)					
Pooled Analysis, Toxichemica, Inc (2004)[a,b]	9-23	18-26	22-29	27-34	36-38
Diatomaceous Earth Worker study (Rice et al., 2001)[a,c]	9	17	34	81	152
U.S. Granite Worker study (Attfield and Costello, 2004)[a,d]	11	25	60	250	653
North American Industrial Sand Worker study (Hughes et al., 2001)[a,e]	7	15	34	120	387
British Coal Miner study (Miller and MacCalman, 2009)[a,f]	3	6	13	37	95
Silicosis and Non-Malignant Lung Disease Mortality (Lifetime Risk)					
Pooled Analysis (Toxichemica, Inc., 2004) (silicosis)[g]	4	7	11	17	22
Diatomaceous Earth Worker study (Park et al., 2002) (NMRD)[h]	22	43	83	188	321
Renal Disease Mortality (Lifetime Risk)					
Pooled Cohort study (Steenland et al., 2002a)[i]	25	32	39	52	63

Silicosis Morbidity (Cumulative Risk)					
Chest x-ray category of 2/1 or greater (Buchanan et al., 2003)[j]	21	55	301	994	1,000
Silicosis mortality and/or x-ray of 1/1 or greater (Steenland and Brown, 1995b)[k]	31	74	431	593	626
Chest x-ray category of 1/1 or greater (Hnizdo and Sluis-Cremer, 1993)[l]	6	127	773	995	1,000
Chest x-ray category of 1or greater (Chen et al., 2001)[m]	40	170	590	1,000	1,000
Chest x-ray category of 1or greater (Chen et al., 2005)[n]					
Tin miners	40	100	400	950	1,000
Tungsten miners	5	20	120	750	1,000
Pottery workers	5	20	60	300	700

Footnotes to Table II-12

[a] Lifetime risks through age 85 calculated from a life table that accounts for competing causes of death (see Appendix). Background all-cause and lung cancer mortality rates are 2006 rates for all males (National Center for Health Statistics, 2009). Background lung cancer mortality rate is based on ICD-10 categories C-33-C34, malignant neoplasms of trachea, bronchus, lung. Exposure to crystalline silica is assumed to begin at age 20 through age 65.

[b] Range based on three models (see Table II-2).

c. Based on the linear relative risk model with exposures lagged 10 years, RR = 1 + (0.1441*E) where E is cumulative respirable crystalline silica exposure in mg/m^3-years.

[d] Based on the log-linear relative risk model with exposures lagged 15 years, RR = exp(0.19*E) where E is cumulative respirable crystalline silica exposure in mg/m^3-years.

[e] Based on the log-linear relative risk model with exposures lagged 15 years, RR = exp(0.13*E) where E is cumulative respirable crystalline silica exposure in mg/m^3-years.

[f] Based on the log-linear relative risk model with exposures lagged 15 years, RR = exp(0.0524*E) where E is cumulative respirable crystalline silica exposure in mg/m^3-years.

[g] Estimates derived from rate ratios based on the categorical model after accounting for exposure measurement uncertainty, from Table 7 of Toxichemica, Inc. (2004). Absolute risk calculated as 1 – exp(-∑time*rate), where rate is the rate ratio for a given cumulative exposure times a base rate of 4.7E-5.

[h] Estimated by OSHA based on the Park et al. (2002) linear relative rate model, RR = 1 + (0.5469*E) where E is cumulative respirable crystalline silica exposure in mg/m^3-years. Lifetime risks through age 85 calculated from a life table that accounts for competing causes of death. Background all-cause and non-malignant lung disease mortality rates are 2006 rates for all males (National Center for Health Statistics, 2009). Non-malignant lung disease mortality rates reflect those for ICD-10 disease codes J40-J47 (chronic lower respiratory diseases) and J60-J66 (pneumoconioses and chemical effects). Exposure to crystalline silica is assumed to begin at age 20 through age 65.

[i] Estimated by OSHA based on the Steenland et al. (2002a) log-linear model with log cumulative exposure, RR = exp(0.269(lnE)) where E is cumulative respirable crystalline silica exposure in mg/m^3-days. Lifetime risks through age 85 calculated from a life table that accounts for competing causes of death. Background all-cause and end-stage renal disease (ESRD) are 1998 rates for all males (National Center for Health Statistics, 2005). Background ESRD mortality rates reflect those for ICD-9 disease codes 580-589. Exposure to crystalline silica is assumed to begin at age 20 through age 65 with 250 days per year of exposure.

[j] Estimated by OSHA from the equation Prob(2/1+) = 1/ (1+exp-(-4.83 + 0.443*cum. quartz$_{<2.0\ mg/m^3}$)), where quartz is cumulative respirable silica exposure in ghm^{-1}, with one year of work = 2000 hours (250 days per year x 8 hours per day). Exposure to crystalline silica is assumed to begin at age 20 through age 65. Age of cohort at follow-up was between 50 and 74 years.

[k] Lifetime risks through age 85 calculated from a life table that accounts for competing causes of death (see Appendix). Background all-cause and lung cancer mortality rates are 2006 rates for all males (National Center for Health Statistics, 2009). Silicosis rate is age- and calendar-time-adjusted, from Table 2 of Steenland et al. (2002). Exposure to crystalline silica is assumed to begin at age 20 through age 65, with no exposure lag.

[l] Estimated by OSHA from the equation CR = 1 – {1/[1 + exp(2.439/.2199)*CDE$^{1/.2199}$]}, CR is cumulative risk and CDE is cumulative respirable dust exposure in mg/m^3-years; assumed quartz content of respirable dust is 30 percent. Assumed 45 years of exposure. Mean age of cohort at onset was 55.9 years (range 38-74)

[m] Estimated by OSHA from the equation CR = 1-exp(-0.0076*E)$^{2.23}$ where E is cumulative exposure to total dust. Respirable crystalline silica reported by Chen et al. (2001) to be 3.6 percent of total dust. Assumed 45 years of exposure. Mean age at onset was 48.3 years.

[n] Estimated from Figure 2B in Chen et al. (2005) showing cumulative risk vs. cumulative exposure to respirable crystalline silica. Mean age at onset was 47.9, 41.8, and 52.5 years for tin, tungsten, and pottery workers, respectively.

the five data sets and model approaches are in very close agreement, which adds a degree of confidence in the risk estimates.

OSHA did not rely on the spline model originally used by Steenland et al. (2001a) in the pooled analysis because this model was not monotonic in the exposure range of between 0.05 and 0.25 mg/m^3; from this spline model, risk estimates remain between 15 and 17 deaths per 1,000 workers in this exposure range and do not increase consistently with increasing exposure over this range. The lack of a monotonic response from this spline model in this region of exposure is inconsistent with the findings from the four single-cohort studies used for quantitative assessment of lung cancer risk (Attfield, 2004; Rice et al., 2001; Hughes et al., 2001; Miller and MacCalman, 2009), each of which found a strong linear lung cancer response in this region of exposure. Of the two model forms employed originally by Steenland et al. (2001a), OSHA believes that the log-linear model based on log cumulative exposure is the more plausible because it remains monotonic from the origin and thus reflects that risk consistently increases with increasing exposure. Other linear models fit the pooled data set as consistently; these were a 2-piece spline model with untransformed cumulative exposure, and a linear relative risk model with log-transformed cumulative exposure (Steenland, personal communication, 2010).

Estimates of risk associated with higher exposures in the range of OSHA's current construction PEL are more uncertain. Estimates based on the four single-cohort studies are 37 to 250 deaths per 1,000 for exposure to 0.25 mg/m^3 over 45 years, and 95 to 653 deaths per 1,000 at 0.5 mg/m^3. However, estimates based on the model from the pooled analysis (which relied on a log transform of cumulative exposure) yielded lower estimates, (27-34 deaths per 1,000 at 0.25 mg/m^3 and 36-38 deaths per 1,000 at 0.5 mg/m^3). The use of the log-transformed exposure metric in the pooled study, which reflects an exposure-response model that rises more quickly at low exposures and subsequently flattens out at high exposures, was employed to reduce significant heterogeneity between the 10 worker cohorts that was evident with a model based on untransformed cumulative exposure. It is not known whether the heterogeneity between these cohorts reflected real differences between the studies in the cancer responses at high exposures, perhaps reflecting differences in the toxicity of crystalline silica in different workplace settings, or other issues common to occupational studies that may have differentially affected the cohorts, such as a survivor effect in some of the cohorts, competing silica-related mortality at high exposures, or exposure misclassification.

A categorical analysis performed by Steenland and Bartell (Steenland, personal communication, 2010) and further modeling with linear models shows that the lung cancer risk attenuates at higher exposures (i.e., at a cumulative exposure above that permitted by OSHA's general industry PEL). This is in contrast to the individual cohort studies, which, with the exception of the high-exposure group in the granite cohort (Attfield and Costello, 2004), do not suggest an attenuation of the exposure-response curve at higher exposures. In the granite cohort, the lung cancer mortality rate among workers exposed to 6 mg/m^3-years or more was less than either of the preceding exposure groups; in contrast, the lung cancer mortality rate was highest among diatomaceous earth workers exposed to about 13 mg/m^3-years or more, and no decline was seen in either the

industrial sand or coal worker cohorts at cumulative exposures of similar magnitude. It is not known whether the decline in cancer risk seen among highly exposed granite workers was the result of a survivor effect, exposure misclassification, or a substantial increase in mortality from competing causes. OSHA believes that the risk estimates based on the Steenland et al. (2001a) pooled cohort study reflect credible central tendency estimates of risk across a range of industrial settings, but these estimates of risk may understate the risk at higher cumulative exposures in at least some industry sectors, based on the analyses derived from the single cohort studies.

Steenland and Bartell (Toxichemica, Inc., 2004) conducted an analysis of the impact on risk estimates of uncertainties in the underlying exposure estimates developed for each of the 10 cohorts in the pooled analysis. A Monte Carlo simulation that explored the potential effects of uncertainties in the assignment of mean job-specific exposures and in the estimation of respirable silica mass from particle count exposure measurements resulted in pooled exposure-response coefficients that were, on average, only slightly smaller than that from the original analysis with essentially no increase in the variance of the estimate. The individual exposure-response coefficients for the diatomaceous earth and U.S. granite cohorts were also reasonably stable with respect to unbiased uncertainty in the exposure estimates. Assuming a biased uncertainty in each of the individual cohorts also had little effect on the pooled exposure-response coefficient. Therefore, OSHA believes that uncertainties in the underlying exposure estimates are not likely to substantially affect its estimates of lung cancer risk.

Silicosis Mortality. There are two published quantitative risk assessments of silicosis mortality; an analysis by Mannetje et al. (2002b) of pooled cohort data from six epidemiological studies (from the ten cohorts that were part of the IARC multi-centric exposure-response study of lung cancer, discussed above), and an exposure-response analysis of diatomaceous earth workers (Park et al., 2002). Also, an additional uncertainty analysis was conducted on the Mannetje et al. (2002b) data by Dr. Steenland for Toxichemica, Inc. (Toxichemica, Inc., 2004).

Mannetje et al. (2002b) found that the best fit was provided by the log of cumulative exposure. No significant heterogeneity was found between studies. A cubic spline model did not fit better than the linear relative risk model with the log of cumulative exposure. Mannetje et al. estimated the lifetime risk of death from silicosis (to age 65), assuming 45 years of exposure to 0.1 mg/m^3 to be 13 deaths per 1,000 workers; at an exposure of 0.05 mg/m^3, the estimated lifetime risk was 6 per 1,000. The Toxichemica, Inc. (2004) uncertainty analysis yielded modified silicosis rate ratios based on using a case-control design rather than the original categorical analysis performed by Mannetje et al. (2002b). The corresponding estimated risks to age 65 (as used by Mannetje et al.) were 7 (95% CI 2-23) and 4 (95% CI 2-12) per 1,000. The confidence intervals of the risk estimates using the log cumulative exposure model lie within those using the categorical model. According to Toxichemica, Inc., the decrease in estimated risk from the original Mannetje et al. results is partly due to the incorporation of measurement error and partly due to the use of a nested case-control analysis here versus the Poisson regression originally performed by Mannetje et al. Based on these modified rate ratios, OSHA estimates risks to age 85 to be 11 and 7 deaths per 1,000 for exposure

to the current PEL of 0.10 mg/m^3 or the proposed PEL of 0.05 mg/m^3, respectively. For exposure at the proposed action level, OSHA estimates the silicosis mortality risk to be 4 deaths per 1,000. For exposure in the range of the current construction PEL, the range in estimated risk is from 17 to 22 deaths per 1,000.

Park et al. (2002) analyzed the California diatomaceous earth cohort data to quantify the relationship between exposure to cristobalite and mortality from chronic lung disease other than cancer (LDOC); diseases in this category included pneumoconiosis, chronic bronchitis, and emphysema. Based on its superior fit to the cohort data, Park et al. (2002) selected the linear relative rate model with external adjustment and use of cumulative exposure as the exposure metric as the basis for estimating LDOC mortality risks. Based on their model, OSHA estimates the excess lifetime risk associated with a 45-year exposure to the proposed PEL of 0.05 mg/m^3 respirable crystalline silica dust to be 43 per 1,000 (95% CI 17-150) and, for exposure to the current general industry PEL of 0.1 mg/m^3, 83 per 1,000. The estimated risk at the proposed action level is 22 deaths per 1,000. At the higher exposure levels of 0.25 and 0.50 mg/m^3, OSHA estimates the risk to be 188 and 321 deaths per 1000, respectively. These estimates are considerably higher than those calculated for the pooled analysis of Mannetje et al. (2002b), but are based on 67 deaths from LDOC. The Mannetje et al. analysis included only 15 deaths from this cohort where the cause of death was coded as silicosis or other pneumoconiosis.

Based on the available risk assessments for silicosis mortality, OSHA believes that the estimates from the pooled study represent credible central tendency estimates of mortality risk from silicosis across a range of industrial settings, but are likely to understate the actual risk due to silicosis being misclassified as a cause of death. OSHA believes that the risk estimates derived from the Park et al. (2002) study reasonably reflects the total respiratory disease mortality risk due to exposure to respirable crystalline silica since LDOC, as defined by this study, would capture much of this misclassification and include risks from other lung diseases (emphysema, chronic bronchitis) that have been associated with exposure to crystalline silica.

Renal Disease Mortality. OSHA is basing its estimates of renal disease mortality on a case-control study performed by Steenland et al. (2002a) on the combined cohorts from a U.S. gold miner study (Steenland and Brown, 1995a), a U.S. industrial sand study (Steenland et al., 2001b), and a Vermont granite worker study (Costello and Graham, 1998). This is a large combined cohort (13,382) where exposure and job history data were available for about 95 percent of the study subjects. The job-exposure matrices had been used previously in studies showing positive exposure-response trends for silicosis mortality and morbidity, thus lending credibility to the underlying exposure assessments. A statistically significant excess mortality from renal disease was seen in the combined cohort, and the case-control analysis showed statistically significant exposure-response trends for both multiple-cause mortality (with either cumulative exposure or log of cumulative exposure) and for underlying cause mortality (with log cumulative exposure only). Based on the log-linear model with log cumulative exposure derived from the underlying cause analysis, OSHA estimates that exposure for 45 years to the current general industry and construction/shipyard PELs results in an excess risk of 39 and 52-63

deaths per 1,000 workers, respectively. Exposure to the proposed PEL of 0.05 mg/m^3 results in an excess estimated risk of 32 deaths per 1,000. At the proposed action level, the excess risk is estimated to be 25 deaths per 1,000. Although these estimates are based on only 50 renal disease deaths in the pooled cohort, and are therefore less robust than risk estimates for the other health effects discussed in this assessment, OSHA believes that the risk estimates for renal disease are credible given the large size of the pooled cohort study and quality of underlying exposure and job history information.

Silicosis Morbidity. OSHA has reviewed the principal studies available that have characterized the risk to exposed workers of acquiring lung fibrosis as evidenced by the appearance of opacities on chest radiographs. Several of these studies did not include follow up of workers who had left employment, and some were of a cross-sectional design that cannot provide information on disease onset or permit evaluation of disease incidence. More useful in estimating long-term risks are those retrospective cohort studies that included a large proportion of retired workers in the cohort and that were able to evaluate disease status over time. OSHA identified six such studies (Chen et al., 2001; Chen et al., 2005; Hnizdo and Sluis-Cremer, 1993; Miller et al., 1998; Buchanan et al., 2003; Steenland and Brown, 1995b), which analyzed data from six mining cohorts exposed to freshly cut (fractured) quartz and one pottery cohort exposed to quartz particles for which a significant fraction of the surface was occluded by alumino-silicates. For freshly cut crystalline silica, the range of risk associated with 45 years of exposure to the current general industry PEL of 0.1 mg/m^3 is estimated to be between 120 and 773 cases per 1,000. For a 45-year exposure to the proposed PEL of 0.05 mg/m^3, the range in estimated risk is from 20 to 170 cases per 1,000 workers. At exposures at the current construction/shipyard PEL, (0.25-0.5 mg/m^3) for 45 years, the risk of acquiring an abnormal chest x-ray approaches unity.

As is the case with the lung cancer and silicosis mortality studies, one of the principal sources of uncertainty in the silicosis morbidity studies is the estimation of respirable silica exposures of the cohorts. Two of the studies (Hnizdo and Sluis-Cremer, 1993; Steenland and Brown, 1995b) relied on particle count data, requiring use of a conversion factor to estimate exposures to dust mass. The Chen et al. studies (2001, 2005) were based on gravimetric total dust sampling and use of side-by-side respirable dust sampling to estimate historical exposures to respirable crystalline silica. Only the studies by Miller et al. (1998) and Buchanan et al. (2003) was able to rely exclusively on respirable dust sampling and quartz analysis performed over the entire period of significant quartz exposure; as such, OSHA believes that risk estimates derived from that study are the least susceptible to uncertainties in the underlying exposure assessment. From that study, OSHA estimated the risk of silicosis (defined as ILO 2/1 or greater or the presence of large opacities) to be 301 and 55 cases per 1,000 workers exposed to 0.1 or 0.05 mg/m^3, respectively.

Another source of potential uncertainty lies in the use of chest roentgenograms to ascertain cases. OSHA believes that the uncertainty associated with the subjective reading of chest films by trained health professionals was likely to be mitigated by each of the studies having relied on panels of at least three readers (except for Steenland and Brown, 1995b) and by the use of a common reference system (i.e., the ILO system) for

classifying x-ray findings. Although the Chen et al. studies (2001, 2005) did not use the ILO system, they presented data indicating that their use of the Chinese classification system was comparable to the use of the ILO. Furthermore, the work of Hnizdo et al. (1993) shows that reading of chest films is more likely to result in missing silicosis cases (defined by autopsy findings) than in falsely identifying cases, due to the relative insensitivity of chest roentgenograms, indicating that risk estimates based on reading of chest films would likely understate the true risk.

Despite these uncertainties, the risk findings from these studies appear to be reasonably consistent. Studies that did not have significant post-employment follow-up resulted in lower risk estimates than did the studies that included a substantial proportion of retired workers. In fact, the population of the study reporting the highest risk estimate (Kreiss and Zhen, 1996) consisted exclusively of workers whose last exposure occurred 10 years or more prior to the study and who were first exposed at least 20 years before their health status was assessed. The finding that estimated risks are higher when retired workers are included in the study cohort is consistent with what one would expect given the chronic nature of silicosis, and provides greater credibility in the resulting risk estimates.

OSHA believes that risk estimates based on the Miller et al. (1993) and Buchanan et al. (2003) study are the most reliable overall because of the availability of high-quality exposure data, post-exposure follow up, and extensive analysis. In addition, the Buchanan et al. study accounted for the effects of exposure to very high concentrations of respirable quartz (i.e., > 2 mg/m^3). However, these may understate the risk of developing early signs of silicosis (i.e., corresponding to ILO x-ray film classifications of 1/0 and 1/1). The study of British coal miners by Miller et al. (1998) suggests that the risk of disease onset in this population could be three times as high as suggested by the risk estimates derived from the Buchanan et al. (2003) study. Thus, risk estimates that reflect onset as well as progression of disease lies in the range of risks derived from the four studies that included as cases those workers whose chest radiographs were categorized as consistent with ILO major category 1.

These risk estimates reflect those associated with exposure to quartz-containing material that has been freshly cut (fractured). One study of pottery workers (Chen et al., 2005) suggests that the presence of significant surface occlusion by alumino-silicates may be partly responsible for the observed decrease in silicosis morbidity risk; this is supported by animal studies that have shown reduced fibrogenic activity of clay-coated quartz particles. Risk estimates based on the pottery cohort are 60 and 20 cases per 1,000 workers exposed for 45 years to 0.1 and 0.05 mg/m^3, respectively, which is substantially below most of the risk estimates derived from the mining studies. Other studies have also found silicosis risks among clay workers to be lower than is often seen in other industry settings (Love et al., 1999; Hessel, 2006; Miller and Soutar, 2007). However, OSHA believes that additional study is needed to more fully characterize the effect of workplace-specific factors that affect the surface properties of crystalline silica and their effect on silicosis risks.

OSHA has estimated silicosis morbidity risks associated with 45 years of exposure to the proposed action level of 0.025 mg/m^3; these estimates range from 5 to 40 cases per 1,000 workers. OSHA regards these estimates as more uncertain than those derived for the proposed and current PELs as a result of considering available evidence concerning a threshold for lung inflammation. Kuempel et al. (2001) employed a rat-based toxicokinetic/toxicodynamic model with extrapolation to humans using a human lung deposition/clearance model to estimate a minimum lung burden necessary to cause the precursor events that can lead to adverse physiological effects in the lung. These adverse physiological effects can then lead to lung fibrosis and an indirect genotoxic cause of lung cancer. They estimated that the threshold effect level of lung burden associated with this inflammation (M_{crit}) is the equivalent of exposure to 0.036 mg/m^3 for 45 years; thus, exposures below this level would presumably not lead to an excess lung cancer risk (based on an indirect genotoxic mechanism) nor to silicosis, at least in the "average individual." This might suggest that exposures to a concentration of silica at the proposed action level would not be associated with an excess silicosis, and possible cancer, risk. However, OSHA does not believe that the analysis by Kuemple et al. is definitive with respect to a threshold for silica-related disease. First, since the critical quartz burden is a mean value derived from the model, the authors estimated that a 45-year exposure to a concentration as low as 0.005 mg/m^3, or 5 times below the proposed action level, would result in a lung quartz burden that was equal to the 95-percent lower confidence limit on M_{crit}. Therefore, the existence of a threshold lung burden that is below that resulting from exposure to the proposed action level cannot be ruled due to statistical uncertainty in the estimate of critical lung burden. In addition, with respect to silica-related lung cancer, if at least some of the risk is from a direct genotoxic mechanism (see section II.F), then this threshold value is not relevant. Although OSHA acknowledges that a threshold exposure level might lie within the range of the proposed action level, and thus add uncertainty to the estimated risks associated with exposure to the action level, available information cannot firmly establish a threshold exposure for silica-related effects.

APPENDIX A

Life Tables Used for Assessments of Lung Cancer, Non-Malignant Respiratory Disease, and Renal Disease Mortality Risks

Appendix A-1

Health endpoint: Lung cancer mortality
Data source: Steenland et al. (2001) Pooled Cohort Analysis
Model: Log-linear relative risk
Dose metric: Log-transformed cumulative exposure, 15-yr lag
Exposure level: 0.1 mg/m^3

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
interval number (i)	age interval	all cause mortality (x 10^5/year)	lung cancer mortality (x 10^5/year)	all-cause hazard rate (h*)	prob of surviving interval i (q_i)	prob of surviving up to interval i (S_i)	lung cancer hazard rate (h)	cond prob of lung cancer mortality in interval	exposure duration through end of interval (xtime)	cum exp at end of interval (mg/m^3-d) (xdose)	exposed lung cancer hazard rate (h_x)	exposed all cause hazard rate (h^*_x)	exposed prob of surviving interval (qx)	exposed prob of surviving up to interval (Sx)	exposed cond prob of lung cancer in interval
1	<1	756.3	0	0.0076	0.9925	1.0000	0.00000	0.00000	0	1	0.0000	0.0076	0.9925	1.0000	0.0000
2	1-4	30.5	0	0.0012	0.9988	0.9925	0.00000	0.00000	0	1	0.0000	0.0012	0.9988	0.9925	0.0000
3	5-9	15.4	0	0.0008	0.9992	0.9913	0.00000	0.00000	0	1	0.0000	0.0008	0.9992	0.9913	0.0000
4	10-14	19.6	0	0.0010	0.9990	0.9905	0.00000	0.00000	0	1	0.0000	0.0010	0.9990	0.9905	0.0000
5	15-19	90.7	0	0.0045	0.9955	0.9895	0.00000	0.00000	0	1	0.0000	0.0045	0.9955	0.9895	0.0000
6	20-24	148	0	0.0074	0.9926	0.9850	0.00000	0.00000	0	1	0.0000	0.0074	0.9926	0.9850	0.0000
7	25-29	143.4	0.2	0.0072	0.9929	0.9778	0.00001	0.00001	0	1	0.0000	0.0072	0.9929	0.9778	0.0000
8	30-34	150.4	0.6	0.0075	0.9925	0.9708	0.00003	0.00003	0	1	0.0000	0.0075	0.9925	0.9708	0.0000
9	35-39	189	2	0.0095	0.9906	0.9635	0.00010	0.00010	5	126	0.0001	0.0095	0.9906	0.9635	0.0001
10	40-44	285.9	7.3	0.0143	0.9858	0.9545	0.00037	0.00035	10	251	0.0005	0.0144	0.9857	0.9544	0.0005
11	45-49	435.3	21.6	0.0218	0.9785	0.9409	0.00108	0.00101	15	376	0.0015	0.0222	0.9780	0.9407	0.0014
12	50-54	659.7	47.5	0.0330	0.9676	0.9207	0.00238	0.00215	20	501	0.0034	0.0341	0.9665	0.9201	0.0031
13	55-59	920	88.3	0.0460	0.9550	0.8908	0.00442	0.00384	25	626	0.0065	0.0481	0.9531	0.8893	0.0056
14	60-64	1373.6	167.8	0.0687	0.9336	0.8507	0.00839	0.00690	30	751	0.0125	0.0728	0.9298	0.8475	0.0102
15	65-69	2040.2	272.4	0.1020	0.9030	0.7943	0.01362	0.01028	35	876	0.0205	0.1088	0.8969	0.7880	0.0153
16	70-74	3117.5	378.8	0.1559	0.8557	0.7172	0.01894	0.01258	40	1001	0.0287	0.1656	0.8474	0.7068	0.0187
17	75-79	4944.6	486	0.2472	0.7810	0.6137	0.02430	0.01321	45	1126	0.0370	0.2600	0.7711	0.5989	0.0195
18	80-84	7942.7	544.1	0.3971	0.6722	0.4793	0.02721	0.01076	45	1126	0.0415	0.4114	0.6627	0.4618	0.0157
							sum = Ro =	0.0612						sum = Rx =	0.0902
										Rx - Ro	0.0290				

Appendix A-1 (Continued)

column A: interval index number (i)
column B: 5-year age intervals up to age 85
column C: all-cause mortality rate (x 10^5/year) (2006 data from NCHS, total males)
column D: lung and bronchus cancer (invasive) mortality rate (x 10^5/year) (2006 NCHS data, total males)
column E: all-cause hazard rate (h) (= all-cause mortality rate X number of years in age interval)*
column F: probability of surviving interval (q) (= exp(-h))*
column G: probability of surviving up to interval (S_i) ($S(_1)$=1; $S(_i)$=$S(_{i-1})$ X $q(_{i-1})$)
column H: lung cancer hazard rate for interval I (h) (= lung cancer mortality rate X number of years in interval)
column I: conditional probability of dying from lung cancer in interval I (= (h/h) X $S(_i)$ X (1-$q(_i)$))*
[Ro, the background lifetime probability of dying from lung cancer, = sum of conditional probabilities across all intervals]
column J: exposure duration at end of interval (includes 15-year lag beginning at age 20 thru age 65) (xtime)
column K: cumulative exposure (xdose) at end of interval (= exposure level (mg/m^3) X 250 days/yr exposed X xtime)
column L: lung cancer hazard rate in exposed (h_x) (= h X exp(β X ln(xdose+1))), where
[β is the regression coefficient for the pooled analysis from Steenland et al. (2001), after correcting the original data set (β = 0.06, se = 0.015 from Table 1 of Toxichemica, 2004)
column M: all-cause hazard rate in exposed workers for interval i (h^*x_i) (= h^*_i + (hx_i - h_i))
column N: probability of surviving interval I for exposed workers (q_x) (= exp(-h^*x_i))
column O: probability of surviving up to interval for exposed (Sx) (Sx_1=1; Sx_i=Sx_{i-1} X qx_{i-1})
column P: conditional probability of dying from lung cancer in interval I for exposed workers
(= (hx_i/h^*x_i) X Sx_i X (1-qx_i))
[Rx, the lifetime probability of dying from lung cancer for exposed workers, = sum of conditional probabilities across all intervals

Appendix A-2

Health endpoint: Lung cancer mortality
Data source: Steenland et al. (2001) Pooled Cohort Analysis
Model: Linear relative risk
Dose metric: Log-transformed cumulative exposure, 15-yr lag
Exposure level: 0.1 mg/m^3

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
interval number (i)	age interval	all cause mortality (x 10^5/year)	lung cancer mortality (x 10^5/year)	all-cause hazard rate (h*)	prob of surviving interval i (q_i)	prob of surviving up to interval i (S_i)	lung cancer hazard rate (h)	cond prob of lung cancer mortality in interval	exposure duration through end of interval (xtime)	cum exp at end of interval (mg/m^3-d) (xdose)	exposed lung cancer hazard rate (h_x)	exposed all cause hazard rate (h^*_x)	exposed prob of surviving interval (qx)	exposed prob of surviving up to interval (Sx)	exposed cond prob of lung cancer in interval
1	<1	756.3	0	0.0076	0.9925	1.0000	0.00000	0.00000	0	1	0.0000	0.0076	0.9925	1.0000	0.0000
2	1-4	30.5	0	0.0012	0.9988	0.9925	0.00000	0.00000	0	1	0.0000	0.0012	0.9988	0.9925	0.0000
3	5-9	15.4	0	0.0008	0.9992	0.9913	0.00000	0.00000	0	1	0.0000	0.0008	0.9992	0.9913	0.0000
4	10-14	19.6	0	0.0010	0.9990	0.9905	0.00000	0.00000	0	1	0.0000	0.0010	0.9990	0.9905	0.0000
5	15-19	90.7	0	0.0045	0.9955	0.9895	0.00000	0.00000	0	1	0.0000	0.0045	0.9955	0.9895	0.0000
6	20-24	148	0	0.0074	0.9926	0.9850	0.00000	0.00000	0	1	0.0000	0.0074	0.9926	0.9850	0.0000
7	25-29	143.4	0.2	0.0072	0.9929	0.9778	0.00001	0.00001	0	1	0.0000	0.0072	0.9929	0.9778	0.0000
8	30-34	150.4	0.6	0.0075	0.9925	0.9708	0.00003	0.00003	0	1	0.0000	0.0075	0.9925	0.9708	0.0000
9	35-39	189	2	0.0095	0.9906	0.9635	0.00010	0.00010	5	126	0.0001	0.0095	0.9906	0.9635	0.0001
10	40-44	285.9	7.3	0.0143	0.9858	0.9545	0.00037	0.00035	10	251	0.0005	0.0144	0.9857	0.9544	0.0005
11	45-49	435.3	21.6	0.0218	0.9785	0.9409	0.00108	0.00101	15	376	0.0016	0.0222	0.9780	0.9407	0.0015
12	50-54	659.7	47.5	0.0330	0.9676	0.9207	0.00238	0.00215	20	501	0.0035	0.0341	0.9665	0.9200	0.0031
13	55-59	920	88.3	0.0460	0.9550	0.8908	0.00442	0.00384	25	626	0.0065	0.0481	0.9530	0.8892	0.0057
14	60-64	1373.6	167.8	0.0687	0.9336	0.8507	0.00839	0.00690	30	751	0.0126	0.0728	0.9297	0.8474	0.0103
15	65-69	2040.2	272.4	0.1020	0.9030	0.7943	0.01362	0.01028	35	876	0.0205	0.1089	0.8968	0.7879	0.0153
16	70-74	3117.5	378.8	0.1559	0.8557	0.7172	0.01894	0.01258	40	1001	0.0287	0.1657	0.8473	0.7066	0.0187
17	75-79	4944.6	486	0.2472	0.7810	0.6137	0.02430	0.01321	45	1126	0.0371	0.2600	0.7710	0.5987	0.0196
18	80-84	7942.7	544.1	0.3971	0.6722	0.4793	0.02721	0.01076	45	1126	0.0415	0.4115	0.6627	0.4616	0.0157
							sum = Ro =	0.0612						sum = Rx =	0.0905
										Rx - Ro	0.0293				

Appendix A-2 (Continued)

column A: interval index number (i)
column B: 5-year age intervals up to age 85
column C: all-cause mortality rate (x 10^5/year) (2006 data from NCHS, total males)
column D: lung and bronchus cancer (invasive) mortality rate (x 10^5/year) (2006 NCHS data, total males)
column E: all-cause hazard rate (h) (= all-cause mortality rate X number of years in age interval)*
column F: probability of surviving interval (q) (= exp(-h))*
column G: probability of surviving up to interval (S_i) ($S(_1)=1$; $S(_i)=S(_{i-1})$ X $q(_{i-1})$)
column H: lung cancer hazard rate for interval I (h) (= lung cancer mortality rate X number of years in interval)
column I: conditional probability of dying from lung cancer in interval I (= (h/h) X $S(_i)$ X $(1-q(_i))$*
[Ro, the background lifetime probability of dying from lung cancer, = sum of conditional probabilities across all intervals]
column J: exposure duration at end of interval (includes 15-year lag beginning at age 20 thru age 65) (xtime)
column K: cumulative exposure (xdose) at end of interval (= exposure level (mg/m^3) X 250 days/yr exposed X xtime)
column L: lung cancer hazard rate in exposed (h_x) (= h X (1+(β X ln(xdose+1))), where
[β is the regression coefficient for the pooled analysis from Steenland (personal communication, 2010) (β = 0.07495, se = 0.02412)
column M: all-cause hazard rate in exposed workers for interval i (h^*x_i) (= h^*_i + (hx_i - h_i))
column N: probability of surviving interval I for exposed workers (q_x) (= exp(-h^*x_i))
column O: probability of surviving up to interval for exposed (Sx) ($Sx_1=1$; $Sx_i=Sx_{i-1}$ X qx_{i-1})
column P: conditional probability of dying from lung cancer in interval I for exposed workers
(= (hx_i/h^*x_i) X Sx_i X $(1-qx_i)$)
[Rx, the lifetime probability of dying from lung cancer for exposed workers, = sum of conditional probabilities across all intervals

Appendix A-3

Health endpoint: Lung cancer mortality
Data source: Steenland et al. (2001) Pooled Cohort Analysis
Model: 2-piece linear spline
Dose metric: Cumulative exposure, 15-yr lag
Exposure level: 0.1 mg/m^3

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
interval number (i)	age interval	all cause mortality (x 10^5/year)	lung cancer mortality (x 10^5/year)	all-cause hazard rate (h*)	prob of surviving interval i (q_i)	prob of surviving up to interval i (S_i)	lung cancer hazard rate (h)	cond prob of lung cancer mortality in interval	exposure duration through end of interval (xtime)	cum exp at end of interval (mg/m^3-yr) (xdose)	exposed lung cancer hazard rate (h_x)	exposed all cause hazard rate (h^*_x)	exposed prob of surviving interval (qx)	exposed prob of surviving up to interval (Sx)	exposed cond prob of lung cancer in interval
1	<1	756.3	0	0.0076	0.9925	1.0000	0.00000	0.00000	0	0	0.0000	0.0076	0.9925	1.0000	0.0000
2	1-4	30.5	0	0.0012	0.9988	0.9925	0.00000	0.00000	0	0	0.0000	0.0012	0.9988	0.9925	0.0000
3	5-9	15.4	0	0.0008	0.9992	0.9913	0.00000	0.00000	0	0	0.0000	0.0008	0.9992	0.9913	0.0000
4	10-14	19.6	0	0.0010	0.9990	0.9905	0.00000	0.00000	0	0	0.0000	0.0010	0.9990	0.9905	0.0000
5	15-19	90.7	0	0.0045	0.9955	0.9895	0.00000	0.00000	0	0	0.0000	0.0045	0.9955	0.9895	0.0000
6	20-24	148	0	0.0074	0.9926	0.9850	0.00000	0.00000	0	0	0.0000	0.0074	0.9926	0.9850	0.0000
7	25-29	143.4	0.2	0.0072	0.9929	0.9778	0.00001	0.00001	0	0	0.0000	0.0072	0.9929	0.9778	0.0000
8	30-34	150.4	0.6	0.0075	0.9925	0.9708	0.00003	0.00003	0	0	0.0000	0.0075	0.9925	0.9708	0.0000
9	35-39	189	2	0.0095	0.9906	0.9635	0.00010	0.00010	5	0.5	0.0001	0.0095	0.9906	0.9635	0.0001
10	40-44	285.9	7.3	0.0143	0.9858	0.9545	0.00037	0.00035	10	1	0.0004	0.0144	0.9857	0.9545	0.0004
11	45-49	435.3	21.6	0.0218	0.9785	0.9409	0.00108	0.00101	15	1.5	0.0013	0.0220	0.9782	0.9409	0.0013
12	50-54	659.7	47.5	0.0330	0.9676	0.9207	0.00238	0.00215	20	2	0.0032	0.0338	0.9668	0.9203	0.0029
13	55-59	920	88.3	0.0460	0.9550	0.8908	0.00442	0.00384	25	2.5	0.0060	0.0476	0.9535	0.8898	0.0052
14	60-64	1373.6	167.8	0.0687	0.9336	0.8507	0.00839	0.00690	30	3	0.0115	0.0718	0.9307	0.8484	0.0094
15	65-69	2040.2	272.4	0.1020	0.9030	0.7943	0.01362	0.01028	35	3.5	0.0188	0.1072	0.8983	0.7896	0.0141
16	70-74	3117.5	378.8	0.1559	0.8557	0.7172	0.01894	0.01258	40	4	0.0263	0.1633	0.8494	0.7093	0.0172
17	75-79	4944.6	486	0.2472	0.7810	0.6137	0.02430	0.01321	45	4.5	0.0340	0.2569	0.7735	0.6025	0.0180
18	80-84	7942.7	544.1	0.3971	0.6722	0.4793	0.02721	0.01076	45	4.5	0.0380	0.4080	0.6650	0.4660	0.0145
							sum = Ro =	0.0612						sum = Rx =	0.0832
										Rx - Ro	0.0220				

Appendix A-3 (Continued)

column A: interval index number (i)
column B: 5-year age intervals up to age 85
column C: all-cause mortality rate (x 10^5/year) (2006 data from NCHS, total males)
column D: lung and bronchus cancer (invasive) mortality rate (x 10^5/year) (2006 NCHS data, total males)
column E: all-cause hazard rate (h) (= all-cause mortality rate X number of years in age interval)*
column F: probability of surviving interval (q) (= exp(-h))*
column G: probability of surviving up to interval (S_i) ($S(_1)=1$; $S(_i)=S(_{i-1})$ X $q(_{i-1})$)
column H: lung cancer hazard rate for interval I (h) (= lung cancer mortality rate X number of years in interval)
column I: conditional probability of dying from lung cancer in interval I (= (h/h) X $S(_i)$ X $(1-q(_i))$*
[Ro, the background lifetime probability of dying from lung cancer, = sum of conditional probabilities across all intervals]
column J: exposure duration at end of interval (includes 15-year lag beginning at age 20 thru age 65) (xtime)
column K: cumulative exposure (xdose) at end of interval (= exposure level (mg/m^3) X xtime)
column L: lung cancer hazard rate in exposed (h_x) (= h X (1+(β_1 X xdose)), for xdose < 2.19 mg/m^3-yrs) or
(= h X [1+(β_1 X 2.19) + ((β_1 + β_2)(xdose - 2.19))] for xdose >= 2.19)*
β_1 = .13498, se = .065335
β_2 = -0.149285, se = .0657
from Steenland, personal communication, March 17, 2010
column M: all-cause hazard rate in exposed workers for interval i (h^*x_i) (= h^*_i + (hx_i - h_i))
column N: probability of surviving interval I for exposed workers (q_x) (= exp(-h^*x_i))
column O: probability of surviving up to interval for exposed (Sx) ($Sx_1=1$; $Sx_i=Sx_{i-1}$ X qx_{i-1})
column P: conditional probability of dying from lung cancer in interval I for exposed workers
(= (hx_i/h^*x_i) X Sx_i X $(1-qx_i)$)
[Rx, the lifetime probability of dying from lung cancer for exposed workers, = sum of conditional probabilities across all intervals

Appendix A-4

Health endpoint: Lung cancer mortality
Data source: Rice et al. (2001)
Model: Linear relative risk
Dose metric: Cumulative exposure, 10-yr lag
Exposure level: 0.1 mg/m^3

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
interval number (i)	age interval	all cause mortality (x 10^5/year)	lung cancer mortality (x 10^5/year)	all-cause hazard rate (h*)	prob of surviving interval i (q_i)	prob of surviving up to interval i (S_i)	lung cancer hazard rate (h)	cond prob of lung cancer mortality in interval	exposure duration through end of interval (xtime)	cum exp at end of interval (mg/m^3-yr) (xdose)	exposed lung cancer hazard rate (h_x)	exposed all cause hazard rate (h^*_x)	exposed prob of surviving interval (qx)	exposed prob of surviving up to interval (Sx)	exposed cond prob of lung cancer in interval
1	<1	756.3	0	0.0076	0.9925	1.0000	0.00000	0.00000	0	0	0.0000	0.0076	0.9925	1.0000	0.0000
2	1-4	30.5	0	0.0012	0.9988	0.9925	0.00000	0.00000	0	0	0.0000	0.0012	0.9988	0.9925	0.0000
3	5-9	15.4	0	0.0008	0.9992	0.9913	0.00000	0.00000	0	0	0.0000	0.0008	0.9992	0.9913	0.0000
4	10-14	19.6	0	0.0010	0.9990	0.9905	0.00000	0.00000	0	0	0.0000	0.0010	0.9990	0.9905	0.0000
5	15-19	90.7	0	0.0045	0.9955	0.9895	0.00000	0.00000	0	0	0.0000	0.0045	0.9955	0.9895	0.0000
6	20-24	148	0	0.0074	0.9926	0.9850	0.00000	0.00000	0	0	0.0000	0.0074	0.9926	0.9850	0.0000
7	25-29	143.4	0.2	0.0072	0.9929	0.9778	0.00001	0.00001	0	0	0.0000	0.0072	0.9929	0.9778	0.0000
8	30-34	150.4	0.6	0.0075	0.9925	0.9708	0.00003	0.00003	5	0.5	0.0000	0.0075	0.9925	0.9708	0.0000
9	35-39	189	2	0.0095	0.9906	0.9635	0.00010	0.00010	10	1	0.0001	0.0095	0.9906	0.9635	0.0001
10	40-44	285.9	7.3	0.0143	0.9858	0.9545	0.00037	0.00035	15	1.5	0.0004	0.0144	0.9857	0.9544	0.0004
11	45-49	435.3	21.6	0.0218	0.9785	0.9409	0.00108	0.00101	20	2	0.0014	0.0221	0.9782	0.9408	0.0013
12	50-54	659.7	47.5	0.0330	0.9676	0.9207	0.00238	0.00215	25	2.5	0.0032	0.0338	0.9667	0.9203	0.0029
13	55-59	920	88.3	0.0460	0.9550	0.8908	0.00442	0.00384	30	3	0.0063	0.0479	0.9532	0.8897	0.0055
14	60-64	1373.6	167.8	0.0687	0.9336	0.8507	0.00839	0.00690	35	3.5	0.0126	0.0729	0.9297	0.8480	0.0103
15	65-69	2040.2	272.4	0.1020	0.9030	0.7943	0.01362	0.01028	40	4	0.0215	0.1099	0.8960	0.7884	0.0160
16	70-74	3117.5	378.8	0.1559	0.8557	0.7172	0.01894	0.01258	45	4.5	0.0312	0.1682	0.8452	0.7064	0.0203
17	75-79	4944.6	486	0.2472	0.7810	0.6137	0.02430	0.01321	45	4.5	0.0401	0.2630	0.7688	0.5971	0.0210
18	80-84	7942.7	544.1	0.3971	0.6722	0.4793	0.02721	0.01076	45	4.5	0.0448	0.4148	0.6605	0.4590	0.0168
							sum = Ro =	0.0612						sum = Rx =	0.0948
										Rx - Ro	0.0336				

Appendix A-4 (Continued)

column A: interval index number (i)
column B: 5-year age intervals up to age 85
column C: all-cause mortality rate (x 10^5/year) (2006 data from NCHS, total males)
column D: lung and bronchus cancer (invasive) mortality rate (x 10^5/year) (2006 NCHS data, total males)
column E: all-cause hazard rate (h) (= all-cause mortality rate X number of years in age interval)*
column F: probability of surviving interval (q) (= exp(-h))*
column G: probability of surviving up to interval (S_i) ($S(_1)=1$; $S(_i)=S(_{i-1})$ X $q(_{i-1})$)
column H: lung cancer hazard rate for interval I (h) (= lung cancer mortality rate X number of years in interval)
column I: conditional probability of dying from lung cancer in interval I (= (h/h) X $S(_i)$ X $(1-q(_i))$*
[Ro, the background lifetime probability of dying from lung cancer, = sum of conditional probabilities across all intervals]
column J: exposure duration at end of interval (includes 10-year lag beginning at age 20 thru age 65) (xtime)
column K: cumulative exposure (xdose) at end of interval (= exposure level (mg/m^3) X xtime)
column L: lung cancer hazard rate in exposed (h_x) (= h X (1+(β X xdose)), β = .1441
column M: all-cause hazard rate in exposed workers for interval i (h^*x_i) (= h^*_i + (hx_i - h_i))
column N: probability of surviving interval I for exposed workers (q_x) (= exp(-h^*x_i))
column O: probability of surviving up to interval for exposed (Sx) ($Sx_1=1$; $Sx_i=Sx_{i-1}$ X qx_{i-1})
column P: conditional probability of dying from lung cancer in interval I for exposed workers
(= (hx_i/h^*x_i) X Sx_i X $(1-qx_i)$)
[Rx, the lifetime probability of dying from lung cancer for exposed workers, = sum of conditional probabilities across all intervals

Appendix A-5

Health endpoint: Lung cancer mortality
Data source: Attfield and Costello (2004)
Model: Log-linear relative risk
Dose metric: Cumulative exposure, 15-yr lag
Exposure level: 0.1 mg/m^3

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
interval number (i)	age interval	all cause mortality (x 10^5/year)	lung cancer mortality (x 10^5/year)	all-cause hazard rate (h*)	prob of surviving interval i (q_i)	prob of surviving up to interval i (S_i)	lung cancer hazard rate (h)	cond prob of lung cancer mortality in interval	exposure duration through end of interval (xtime)	cum exp at end of interval (mg/m^3-yr) (xdose)	exposed lung cancer hazard rate (h_x)	exposed all cause hazard rate (h^*_x)	exposed prob of surviving interval (qx)	exposed prob of surviving up to interval (Sx)	exposed cond prob of lung cancer in interval
1	<1	756.3	0	0.0076	0.9925	1.0000	0.00000	0.00000	0	0	0.0000	0.0076	0.9925	1.0000	0.0000
2	1-4	30.5	0	0.0012	0.9988	0.9925	0.00000	0.00000	0	0	0.0000	0.0012	0.9988	0.9925	0.0000
3	5-9	15.4	0	0.0008	0.9992	0.9913	0.00000	0.00000	0	0	0.0000	0.0008	0.9992	0.9913	0.0000
4	10-14	19.6	0	0.0010	0.9990	0.9905	0.00000	0.00000	0	0	0.0000	0.0010	0.9990	0.9905	0.0000
5	15-19	90.7	0	0.0045	0.9955	0.9895	0.00000	0.00000	0	0	0.0000	0.0045	0.9955	0.9895	0.0000
6	20-24	148	0	0.0074	0.9926	0.9850	0.00000	0.00000	0	0	0.0000	0.0074	0.9926	0.9850	0.0000
7	25-29	143.4	0.2	0.0072	0.9929	0.9778	0.00001	0.00001	0	0	0.0000	0.0072	0.9929	0.9778	0.0000
8	30-34	150.4	0.6	0.0075	0.9925	0.9708	0.00003	0.00003	0	0	0.0000	0.0075	0.9925	0.9708	0.0000
9	35-39	189	2	0.0095	0.9906	0.9635	0.00010	0.00010	5	0.5	0.0001	0.0095	0.9906	0.9635	0.0001
10	40-44	285.9	7.3	0.0143	0.9858	0.9545	0.00037	0.00035	10	1	0.0004	0.0144	0.9857	0.9545	0.0004
11	45-49	435.3	21.6	0.0218	0.9785	0.9409	0.00108	0.00101	15	1.5	0.0014	0.0221	0.9781	0.9408	0.0013
12	50-54	659.7	47.5	0.0330	0.9676	0.9207	0.00238	0.00215	20	2	0.0035	0.0341	0.9665	0.9202	0.0031
13	55-59	920	88.3	0.0460	0.9550	0.8908	0.00442	0.00384	25	2.5	0.0071	0.0487	0.9525	0.8894	0.0062
14	60-64	1373.6	167.8	0.0687	0.9336	0.8507	0.00839	0.00690	30	3	0.0148	0.0751	0.9276	0.8471	0.0121
15	65-69	2040.2	272.4	0.1020	0.9030	0.7943	0.01362	0.01028	35	3.5	0.0265	0.1149	0.8915	0.7858	0.0197
16	70-74	3117.5	378.8	0.1559	0.8557	0.7172	0.01894	0.01258	40	4	0.0405	0.1774	0.8374	0.7006	0.0260
17	75-79	4944.6	486	0.2472	0.7810	0.6137	0.02430	0.01321	45	4.5	0.0571	0.2801	0.7557	0.5867	0.0292
18	80-84	7942.7	544.1	0.3971	0.6722	0.4793	0.02721	0.01076	45	4.5	0.0640	0.4339	0.6480	0.4434	0.0230
							sum = Ro =	0.0612						sum = Rx =	0.1212
										Rx - Ro	0.0600				

Appendix A-5 (Continued)

column A: interval index number (i)
column B: 5-year age intervals up to age 85
column C: all-cause mortality rate (x 10^5/year) (2006 data from NCHS, total males)
column D: lung and bronchus cancer (invasive) mortality rate (x 10^5/year) (2006 NCHS data, total males)
column E: all-cause hazard rate (h) (= all-cause mortality rate X number of years in age interval)*
column F: probability of surviving interval (q) (= exp(-h))*
column G: probability of surviving up to interval (S_i) ($S(_1)=1$; $S(_i)=S(_{i-1})$ X $q(_{i-1})$)
column H: lung cancer hazard rate for interval I (h) (= lung cancer mortality rate X number of years in interval)
column I: conditional probability of dying from lung cancer in interval I (= (h/h) X $S(_i)$ X $(1-q(_i))$*
[Ro, the background lifetime probability of dying from lung cancer, = sum of conditional probabilities across all intervals]
column J: exposure duration at end of interval (includes 15-year lag beginning at age 20 thru age 65) (xtime)
column K: cumulative exposure (xdose) at end of interval (= exposure level (mg/m^3) X xtime)
column L: lung cancer hazard rate in exposed (h_x) (= h X exp(β X xdose)), β = .19
column M: all-cause hazard rate in exposed workers for interval i (h^*x_i) (= h^*_i + (hx_i - h_i))
column N: probability of surviving interval I for exposed workers (q_x) (= exp(-h^*x_i))
column O: probability of surviving up to interval for exposed (Sx) ($Sx_1=1$; $Sx_i=Sx_{i-1}$ X qx_{i-1})
column P: conditional probability of dying from lung cancer in interval I for exposed workers
(= (hx_i/h^*x_i) X Sx_i X $(1-qx_i)$)
[Rx, the lifetime probability of dying from lung cancer for exposed workers, = sum of conditional probabilities across all intervals

Appendix A-6

Health endpoint: Lung cancer mortality
Data source: Hughes et al. (2001)
Model: Log-linear relative risk
Dose metric: Cumulative exposure, 15-yr lag
Exposure level: 0.1 mg/m^3

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
interval number (i)	age interval	all cause mortality (x 10^5/year)	lung cancer mortality (x 10^5/year)	all-cause hazard rate (h*)	prob of surviving interval i (q_i)	prob of surviving up to interval i (S_i)	lung cancer hazard rate (h)	cond prob of lung cancer mortality in interval	exposure duration through end of interval (xtime)	cum exp at end of interval (mg/m^3-yr) (xdose)	exposed lung cancer hazard rate (h_x)	exposed all cause hazard rate (h^*_x)	exposed prob of surviving interval (qx)	exposed prob of surviving up to interval (Sx)	exposed cond prob of lung cancer in interval
1	<1	756.3	0	0.0076	0.9925	1.0000	0.00000	0.00000	0	0	0.0000	0.0076	0.9925	1.0000	0.0000
2	1-4	30.5	0	0.0012	0.9988	0.9925	0.00000	0.00000	0	0	0.0000	0.0012	0.9988	0.9925	0.0000
3	5-9	15.4	0	0.0008	0.9992	0.9913	0.00000	0.00000	0	0	0.0000	0.0008	0.9992	0.9913	0.0000
4	10-14	19.6	0	0.0010	0.9990	0.9905	0.00000	0.00000	0	0	0.0000	0.0010	0.9990	0.9905	0.0000
5	15-19	90.7	0	0.0045	0.9955	0.9895	0.00000	0.00000	0	0	0.0000	0.0045	0.9955	0.9895	0.0000
6	20-24	148	0	0.0074	0.9926	0.9850	0.00000	0.00000	0	0	0.0000	0.0074	0.9926	0.9850	0.0000
7	25-29	143.4	0.2	0.0072	0.9929	0.9778	0.00001	0.00001	0	0	0.0000	0.0072	0.9929	0.9778	0.0000
8	30-34	150.4	0.6	0.0075	0.9925	0.9708	0.00003	0.00003	0	0	0.0000	0.0075	0.9925	0.9708	0.0000
9	35-39	189	2	0.0095	0.9906	0.9635	0.00010	0.00010	5	0.5	0.0001	0.0095	0.9906	0.9635	0.0001
10	40-44	285.9	7.3	0.0143	0.9858	0.9545	0.00037	0.00035	10	1	0.0004	0.0143	0.9858	0.9545	0.0004
11	45-49	435.3	21.6	0.0218	0.9785	0.9409	0.00108	0.00101	15	1.5	0.0013	0.0220	0.9782	0.9409	0.0012
12	50-54	659.7	47.5	0.0330	0.9676	0.9207	0.00238	0.00215	20	2	0.0031	0.0337	0.9669	0.9204	0.0028
13	55-59	920	88.3	0.0460	0.9550	0.8908	0.00442	0.00384	25	2.5	0.0061	0.0477	0.9534	0.8899	0.0053
14	60-64	1373.6	167.8	0.0687	0.9336	0.8507	0.00839	0.00690	30	3	0.0124	0.0727	0.9299	0.8485	0.0101
15	65-69	2040.2	272.4	0.1020	0.9030	0.7943	0.01362	0.01028	35	3.5	0.0215	0.1099	0.8960	0.7890	0.0160
16	70-74	3117.5	378.8	0.1559	0.8557	0.7172	0.01894	0.01258	40	4	0.0319	0.1688	0.8447	0.7069	0.0207
17	75-79	4944.6	486	0.2472	0.7810	0.6137	0.02430	0.01321	40	4	0.0409	0.2638	0.7681	0.5971	0.0215
18	80-84	7942.7	544.1	0.3971	0.6722	0.4793	0.02721	0.01076	40	4	0.0458	0.4157	0.6599	0.4586	0.0172
							sum = Ro =	0.0612						sum = Rx =	0.0954
										Rx - Ro	0.0342				

Appendix A-6 (Continued)

column A: interval index number (i)
column B: 5-year age intervals up to age 85
column C: all-cause mortality rate (x 10^5/year) (2006 data from NCHS, total males)
column D: lung and bronchus cancer (invasive) mortality rate (x 10^5/year) (2006 NCHS data, total males)
column E: all-cause hazard rate (h) (= all-cause mortality rate X number of years in age interval)*
column F: probability of surviving interval (q) (= exp(-h))*
column G: probability of surviving up to interval (S_i) ($S(_1)$=1; $S(_i)$=$S(_{i-1})$ X $q(_{i-1})$)
column H: lung cancer hazard rate for interval I (h) (= lung cancer mortality rate X number of years in interval)
column I: conditional probability of dying from lung cancer in interval I (= (h/h) X $S(_i)$ X (1-$q(_i)$))*
[Ro, the background lifetime probability of dying from lung cancer, = sum of conditional probabilities across all intervals]
column J: exposure duration at end of interval (includes 15-year lag beginning at age 20 thru age 65) (xtime)
column K: cumulative exposure (xdose) at end of interval (= exposure level (mg/m^3) X xtime)
column L: lung cancer hazard rate in exposed (h_x) (= h X exp(β X xdose))
β = .13, se = 0.074
column M: all-cause hazard rate in exposed workers for interval i (h^*x_i) (= h^*_i + (hx_i - h_i))
column N: probability of surviving interval I for exposed workers (q_x) (= exp(-h^*x_i))
column O: probability of surviving up to interval for exposed (Sx) (Sx_1=1; Sx_i=Sx_{i-1} X qx_{i-1})
column P: conditional probability of dying from lung cancer in interval I for exposed workers
(= (hx_i/h^*x_i) X Sx_i X (1-qx_i))
[Rx, the lifetime probability of dying from lung cancer for exposed workers, = sum of conditional probabilities across all intervals

Appendix A-7

Health endpoint: Lung cancer mortality
Data source: Miller and MacCalman (2009)
Model: Log-linear relative risk
Dose metric: Cumulative exposure, 15-yr lag
Exposure level: 0.1 mg/m^3

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
interval number (i)	age interval	all cause mortality (x 10^5/year)	lung cancer mortality (x 10^5/year)	all-cause hazard rate (h*)	prob of surviving interval i (q_i)	prob of surviving up to interval i (S_i)	lung cancer hazard rate (h)	cond prob of lung cancer mortality in interval	exposure duration through end of interval (xtime)	cum exp at end of interval (mg/m^3-yr) (xdose)	exposed lung cancer hazard rate (h_x)	exposed all cause hazard rate (h^*_x)	exposed prob of surviving interval (qx)	exposed prob of surviving up to interval (Sx)	exposed cond prob of lung cancer in interval
1	<1	756.3	0	0.0076	0.9925	1.0000	0.00000	0.00000	0	0	0.0000	0.0076	0.9925	1.0000	0.0000
2	1-4	30.5	0	0.0012	0.9988	0.9925	0.00000	0.00000	0	0	0.0000	0.0012	0.9988	0.9925	0.0000
3	5-9	15.4	0	0.0008	0.9992	0.9913	0.00000	0.00000	0	0	0.0000	0.0008	0.9992	0.9913	0.0000
4	10-14	19.6	0	0.0010	0.9990	0.9905	0.00000	0.00000	0	0	0.0000	0.0010	0.9990	0.9905	0.0000
5	15-19	90.7	0	0.0045	0.9955	0.9895	0.00000	0.00000	0	0	0.0000	0.0045	0.9955	0.9895	0.0000
6	20-24	148	0	0.0074	0.9926	0.9850	0.00000	0.00000	0	0	0.0000	0.0074	0.9926	0.9850	0.0000
7	25-29	143.4	0.2	0.0072	0.9929	0.9778	0.00001	0.00001	0	0	0.0000	0.0072	0.9929	0.9778	0.0000
8	30-34	150.4	0.6	0.0075	0.9925	0.9708	0.00003	0.00003	0	0	0.0000	0.0075	0.9925	0.9708	0.0000
9	35-39	189	2	0.0095	0.9906	0.9635	0.00010	0.00010	5	0.5	0.0001	0.0095	0.9906	0.9635	0.0001
10	40-44	285.9	7.3	0.0143	0.9858	0.9545	0.00037	0.00035	10	1	0.0004	0.0143	0.9858	0.9545	0.0004
11	45-49	435.3	21.6	0.0218	0.9785	0.9409	0.00108	0.00101	15	1.5	0.0012	0.0219	0.9784	0.9409	0.0011
12	50-54	659.7	47.5	0.0330	0.9676	0.9207	0.00238	0.00215	20	2	0.0026	0.0332	0.9673	0.9206	0.0024
13	55-59	920	88.3	0.0460	0.9550	0.8908	0.00442	0.00384	25	2.5	0.0050	0.0466	0.9545	0.8905	0.0044
14	60-64	1373.6	167.8	0.0687	0.9336	0.8507	0.00839	0.00690	30	3	0.0098	0.0701	0.9323	0.8499	0.0081
15	65-69	2040.2	272.4	0.1020	0.9030	0.7943	0.01362	0.01028	35	3.5	0.0164	0.1048	0.9005	0.7923	0.0123
16	70-74	3117.5	378.8	0.1559	0.8557	0.7172	0.01894	0.01258	40	4	0.0234	0.1603	0.8519	0.7135	0.0154
17	75-79	4944.6	486	0.2472	0.7810	0.6137	0.02430	0.01321	45	4.5	0.0308	0.2537	0.7759	0.6079	0.0165
18	80-84	7942.7	544.1	0.3971	0.6722	0.4793	0.02721	0.01076	45	4.5	0.0344	0.4044	0.6674	0.4717	0.0134
							sum = Ro =	0.0612						sum = Rx =	0.0740
										Rx - Ro	0.0128				

Appendix A-7 (Continued)

column A: interval index number (i)
column B: 5-year age intervals up to age 85
column C: all-cause mortality rate (x 10^5/year) (2006 data from NCHS, total males)
column D: lung and bronchus cancer (invasive) mortality rate (x 10^5/year) (2006 NCHS data, total males)
column E: all-cause hazard rate (h) (= all-cause mortality rate X number of years in age interval)*
column F: probability of surviving interval (q) (= exp(-h))*
column G: probability of surviving up to interval (S_i) ($S(_1)=1$; $S(_i)=S(_{i-1})$ X $q(_{i-1})$)
column H: lung cancer hazard rate for interval I (h) (= lung cancer mortality rate X number of years in interval)
column I: conditional probability of dying from lung cancer in interval I (= (h/h) X $S(_i)$ X $(1-q(_i))$*
[Ro, the background lifetime probability of dying from lung cancer, = sum of conditional probabilities across all intervals]
column J: exposure duration at end of interval (includes 15-year lag beginning at age 20 thru age 65) (xtime)
column K: cumulative exposure (xdose) at end of interval (= exposure level (mg/m^3) X xtime)
column L: lung cancer hazard rate in exposed (h_x) (= h X exp(β X xdose))
β = .0524, se = 0.0188
column M: all-cause hazard rate in exposed workers for interval i (h^*x_i) (= h^*_i + (hx_i - h_i))
column N: probability of surviving interval I for exposed workers (q_x) (= exp(-h^*x_i))
column O: probability of surviving up to interval for exposed (Sx) ($Sx_1=1$; $Sx_i=Sx_{i-1}$ X qx_{i-1})
column P: conditional probability of dying from lung cancer in interval I for exposed workers
(= (hx_i/h^*x_i) X Sx_i X $(1-qx_i)$)
[Rx, the lifetime probability of dying from lung cancer for exposed workers, = sum of conditional probabilities across all intervals

Appendix A-8

Health endpoint: Non-malignant respiratory disease (NMRD) mortality
Data source: Park et al. (2002)
Model: Linear relative risk
Dose metric: Cumulative exposure, no lag
Exposure level: 0.1 mg/m^3

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
interval number (i)	age interval	all cause mortality (x 10^5/year)	NMRD mortality (x 10^5/year)	all-cause hazard rate (h*)	prob of surviving interval i (q_i)	prob of surviving up to interval i (S_i)	NMRD hazard rate (h)	cond prob of NMRD mortality in interval	exposure duration through end of interval (xtime)	cum exp at end of interval (mg/m^3-yr) (xdose)	exposed NMRD hazard rate (h_x)	exposed all cause hazard rate (h^*_x)	exposed prob of surviving interval (qx)	exposed prob of surviving up to interval (Sx)	exposed cond prob of NMRD in interval
1	<1	756.3	0.9	0.0076	0.9925	1.0000	0.00001	0.00001	0	0	0.0000	0.0076	0.9925	1.0000	0.0000
2	1-4	30.5	0.3	0.0012	0.9988	0.9925	0.00001	0.00001	0	0	0.0000	0.0012	0.9988	0.9925	0.0000
3	5-9	15.4	0.3	0.0008	0.9992	0.9913	0.00002	0.00001	0	0	0.0000	0.0008	0.9992	0.9913	0.0000
4	10-14	19.6	0.4	0.0010	0.9990	0.9905	0.00002	0.00002	0	0	0.0000	0.0010	0.9990	0.9905	0.0000
5	15-19	90.7	0.4	0.0045	0.9955	0.9895	0.00002	0.00002	0	0	0.0000	0.0045	0.9955	0.9895	0.0000
6	20-24	148	0.5	0.0074	0.9926	0.9850	0.00003	0.00002	5	0.5	0.0000	0.0074	0.9926	0.9850	0.0000
7	25-29	143.4	0.6	0.0072	0.9929	0.9778	0.00003	0.00003	10	1	0.0000	0.0072	0.9928	0.9778	0.0000
8	30-34	150.4	0.7	0.0075	0.9925	0.9708	0.00004	0.00003	15	1.5	0.0001	0.0075	0.9925	0.9708	0.0001
9	35-39	189	1	0.0095	0.9906	0.9635	0.00005	0.00005	20	2	0.0001	0.0095	0.9905	0.9635	0.0001
10	40-44	285.9	2.6	0.0143	0.9858	0.9545	0.00013	0.00012	25	2.5	0.0003	0.0145	0.9856	0.9544	0.0003
11	45-49	435.3	5.5	0.0218	0.9785	0.9409	0.00028	0.00026	30	3	0.0007	0.0222	0.9780	0.9406	0.0007
12	50-54	659.7	13.4	0.0330	0.9676	0.9207	0.00067	0.00061	35	3.5	0.0020	0.0343	0.9663	0.9200	0.0018
13	55-59	920	27.6	0.0460	0.9550	0.8908	0.00138	0.00120	40	4	0.0044	0.0490	0.9522	0.8890	0.0038
14	60-64	1373.6	62.4	0.0687	0.9336	0.8507	0.00312	0.00257	45	4.5	0.0108	0.0764	0.9265	0.8465	0.0088
15	65-69	2040.2	121	0.1020	0.9030	0.7943	0.00605	0.00457	45	4.5	0.0209	0.1169	0.8897	0.7842	0.0155
16	70-74	3117.5	221.1	0.1559	0.8557	0.7172	0.01106	0.00734	45	4.5	0.0383	0.1831	0.8327	0.6977	0.0244
17	75-79	4944.6	369.8	0.2472	0.7810	0.6137	0.01849	0.01005	45	4.5	0.0640	0.2927	0.7462	0.5810	0.0322
18	80-84	7942.7	551.5	0.3971	0.6722	0.4793	0.02758	0.01091	45	4.5	0.0954	0.4650	0.6281	0.4335	0.0331
							sum = Ro =	0.0378						sum = Rx =	0.1209
										Rx - Ro	0.0830				

Appendix A-8 (Continued)

column A: interval index number (i)
column B: 5-year age intervals up to age 85
column C: all-cause mortality rate (x 10^5/year) (2006 data from NCHS, total males)
column D: NMRD mortality rate (x 10^5/year) (2006 NCHS data for ICD J40-J47 (chronic lower respiratory disease) and J60-J66 (pneumoconioses), total males)
column E: all-cause hazard rate (h) (= all-cause mortality rate X number of years in age interval)*
column F: probability of surviving interval (q) (= exp(-h))*
column G: probability of surviving up to interval (S_i) ($S(_1)=1$; $S(_i)=S(_{i-1})$ X $q(_{i-1})$)
column H: NMRD hazard rate for interval I (h) (= NMRD mortality rate X number of years in interval)
column I: conditional probability of dying from NMRD in interval I (= (h/h) X $S(_i)$ X $(1-q(_i))$*
[Ro, the background lifetime probability of dying from NMRD, = sum of conditional probabilities across all intervals]
column J: exposure duration at end of interval (beginning at age 20 thru age 65) (xtime)
column K: cumulative exposure (xdose) at end of interval (= exposure level (mg/m^3) X xtime)
column L: NMRD hazard rate in exposed (h_x) (= h X (1+(β X xdose)), β = .5469)
column M: all-cause hazard rate in exposed workers for interval i (h^*x_i) (= h^*_i + (hx_i - h_i))
column N: probability of surviving interval I for exposed workers (q_x) (= exp(-h^*x_i))
column O: probability of surviving up to interval for exposed (Sx) ($Sx_1=1$; $Sx_i=Sx_{i-1}$ X qx_{i-1})
column P: conditional probability of dying from NMRD in interval I for exposed workers
(= (hx_i/h^*x_i) X Sx_i X $(1-qx_i)$)
[Rx, the lifetime probability of dying from NMRD for exposed workers, = sum of conditional probabilities across all intervals

Appendix A-9

Health endpoint: End-stage renal disease (ESRD) mortality
Data source: Steenland et al. (2002)
Model: Log-linear relative risk
Dose metric: Log cumulative exposure, no lag
Exposure level: 0.1 mg/m^3

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
interval number (i)	age interval	all cause mortality (x 10^5/year)	ESRD mortality (x 10^5/year)	all-cause hazard rate (h*)	prob of surviving interval i (q_i)	prob of surviving up to interval i (S_i)	ESRD hazard rate (h)	cond prob of ESRD mortality in interval	exposure duration through end of interval (xtime)	cum exp at end of interval (mg/m^3-d) (xdose)	exposed ESRD hazard rate (h_x)	exposed all cause hazard rate (h^*_x)	exposed prob of surviving interval (qx)	exposed prob of surviving up to interval (Sx)	exposed cond prob of ESRD in interval
1	<1	756.3	0	0.0076	0.9925	1.0000	0.00000	0.00000	0	1	0.0000	0.0076	0.9925	1.0000	0.0000
2	1-4	30.5	0	0.0012	0.9988	0.9925	0.00000	0.00000	0	1	0.0000	0.0012	0.9988	0.9925	0.0000
3	5-9	15.4	0	0.0008	0.9992	0.9913	0.00000	0.00000	0	1	0.0000	0.0008	0.9992	0.9913	0.0000
4	10-14	19.6	0	0.0010	0.9990	0.9905	0.00000	0.00000	0	1	0.0000	0.0010	0.9990	0.9905	0.0000
5	15-19	90.7	0	0.0045	0.9955	0.9895	0.00000	0.00000	0	1	0.0000	0.0045	0.9955	0.9895	0.0000
6	20-24	142.3	0	0.0071	0.9929	0.9850	0.00000	0.00000	5	126	0.0000	0.0071	0.9929	0.9850	0.0000
7	25-29	139.4	0.3	0.0070	0.9931	0.9781	0.00002	0.00001	10	251	0.0001	0.0070	0.9930	0.9781	0.0001
8	30-34	163.1	0.5	0.0082	0.9919	0.9713	0.00003	0.00002	15	376	0.0001	0.0083	0.9918	0.9712	0.0001
9	35-39	213.5	0.9	0.0107	0.9894	0.9634	0.00005	0.00004	20	501	0.0002	0.0109	0.9892	0.9632	0.0002
10	40-44	305.3	1.6	0.0153	0.9849	0.9531	0.00008	0.00008	25	626	0.0005	0.0156	0.9845	0.9528	0.0004
11	45-49	450.8	3	0.0225	0.9777	0.9387	0.00015	0.00014	30	751	0.0009	0.0233	0.9770	0.9380	0.0008
12	50-54	654.1	3.9	0.0327	0.9678	0.9178	0.00020	0.00018	35	876	0.0012	0.0337	0.9668	0.9165	0.0011
13	55-59	1022.4	6.9	0.0511	0.9502	0.8883	0.00035	0.00030	40	1001	0.0022	0.0530	0.9484	0.8861	0.0019
14	60-64	1634	11.8	0.0817	0.9215	0.8440	0.00059	0.00048	45	1126	0.0039	0.0850	0.9185	0.8403	0.0031
15	65-69	2508.6	21	0.1254	0.8821	0.7778	0.00105	0.00077	45	1126	0.0070	0.1313	0.8769	0.7718	0.0050
16	70-74	3867	41	0.1934	0.8242	0.6861	0.00205	0.00128	45	1126	0.0136	0.2049	0.8148	0.6769	0.0083
17	75-79	5719.7	70	0.2860	0.7513	0.5655	0.00350	0.00172	45	1126	0.0232	0.3057	0.7366	0.5515	0.0110
18	80-84	9226.6	137.3	0.4613	0.6304	0.4248	0.00687	0.00234	45	1126	0.0454	0.4999	0.6066	0.4062	0.0145
							sum = Ro =	0.0074						sum = Rx =	0.0467
										Rx - Ro	0.0393				

Appendix A-9 (Continued)

column A: interval index number (i)
column B: 5-year age intervals up to age 85
column C: all-cause mortality rate (x 10^5/year) (1998 data from NCHS, total males)
column D: ESRD mortality rate (x 10^5/year) (1998 NCHS data for ICD 580-589, total males)
column E: all-cause hazard rate (h) (= all-cause mortality rate X number of years in age interval)*
column F: probability of surviving interval (q) (= exp(-h))*
column G: probability of surviving up to interval (S_i) ($S(_1)$=1; $S(_i)$=$S(_{i-1})$ X $q(_{i-1})$)
column H: ESRD hazard rate for interval I (h) (= ESRD mortality rate X number of years in interval)
column I: conditional probability of dying from ESRD in interval I (= (h/h) X $S(_i)$ X (1-$q(_i)$)*
[Ro, the background lifetime probability of dying from ESRD, = sum of conditional probabilities across all intervals]
column J: exposure duration at end of interval (beginning at age 20 thru age 65) (xtime)
column K: cumulative exposure (xdose) at end of interval (= exposure level (mg/m^3) X 250 d/yr exposed X xtime)
column L: ESRD hazard rate in exposed (h_x) (= h X exp(β X ln(xdose+1)))
β = 0.269, se = 0.120 (Steenland, personal communication, 2010)
column M: all-cause hazard rate in exposed workers for interval i (h^*x_i) (= h^*_i + (hx_i - h_i))
column N: probability of surviving interval I for exposed workers (q_x) (= exp(-h^*x_i))
column O: probability of surviving up to interval for exposed (Sx) (Sx_1=1; Sx_i=Sx_{i-1} X qx_{i-1})
column P: conditional probability of dying from ESRD in interval I for exposed workers
(= (hx_i/h^*x_i) X Sx_i X (1-qx_i))
[Rx, the lifetime probability of dying from ESRD for exposed workers, = sum of conditional probabilities across all intervals

III. Response to Peer Review Comments.

In 2009, Eastern Research Group, Inc. (ERG), under contract to the Occupational Safety and Health Administration (OSHA)[3], conducted an independent, scientific peer review of two draft documents prepared by OSHA; these were a draft Health Effects Literature Review for Crystalline Silica, and a Preliminary Quantitative Risk Assessment for Crystalline Silica. This section of the background document describes the review process and summarizes peer reviewers' comments and OSHA's responses.

Based on input from OSHA regarding the areas of expertise required for the review, ERG conducted a search for nationally recognized experts in occupational epidemiology, biostatistics and risk assessment, animal and cellular toxicology, and occupational medicine who had no conflict of interest (COI) or apparent bias in performing the review. Interested candidates submitted evidence of their qualifications and responded to detailed COI questions. ERG also searched the Internet to determine whether qualified candidates had made public statements or declared a particular bias regarding silica regulation.

From the pool of qualified candidates, ERG selected seven to conduct the review, based on:

- Their qualifications, including their degrees, years of relevant experience, number of related peer-reviewed publications, experience serving as a peer reviewer for OSHA or other government organizations, and committee and association memberships related to the review topic;

- Lack of bias and lack of any actual, potential, or perceived conflict of interest; and

- The need to ensure that the panel collectively was sufficiently broad and diverse to fairly represent the relevant scientific and technical perspectives and fields of knowledge appropriate to the review.

OSHA reviewed the qualifications of the candidates proposed by ERG to verify that they met the technical selection criteria. Upon receiving OSHA confirmation of the selected reviewers, ERG contracted with the following reviewers to perform the review. Six experts reviewed both documents; Dr. Crump reviewed only the quantitative risk assessment:

[3] Task Order No. 059622303/099P28863, Contract No. GS10F0125P, with a period of performance from May 22, 2009 to May 22, 2010.

Reviewer	Affiliation	Reviewed Health Effects Section	Reviewed Quantitative Risk Assessment
Bruce Allen	Bruce Allen Consulting	√	√
Kenneth Crump	Louisiana Tech University Foundation		√
Murray Finkelstein	McMaster University, Ontario	√	√
Gary Ginsberg	Connecticut Department of Public Health	√	√
Brian Miller	IOM Consulting Ltd., Scotland	√	√
Andrew Salmon	Private Consultant	√	√
Noah Seixas	University of Washington, Seattle	√	√

Reviewers were provided with the charge, review documents, and access to relevant references and given six weeks to conduct the review.

Early in the review schedule, ERG organized and facilitated a briefing call to ensure that reviewers understood the peer review process. OSHA representatives were available on the call to respond to technical questions of clarification. Reviewers were invited to submit any subsequent questions of clarification to ERG via email.

ERG checked reviewers' written comments to ensure that each reviewer had clearly responded to all charge questions and then submitted the individual reviewer comments, unedited, to OSHA. ERG also organized the comments by charge questions for both documents and submitted this version to OSHA and the reviewers in preparation for a follow-up conference call.

The conference call, organized and facilitated by ERG, provided an opportunity for OSHA to clarify individual reviewer's comments. After the call, ERG directed reviewers to revise their written comments to include the clarifications or additional information provided on the call. ERG submitted the revised comments to OSHA, organized by charge question, and prepared a final peer review report that is available in Docket OSHA-2010-0034. In Section

III.A, OSHA summarizes the comments received on the draft health effects literature review and the Agency's responses to those comments. Section III.B presents comments received on the draft Preliminary Quantitative Risk Assessment.

III.A. ***Peer Review of the Health Effects Literature Review.***

In general, OSHA asked the peer reviewers to consider the strengths, weaknesses, interpretations, and inclusion of studies the Agency used to support OSHA's preliminary findings. Overall, the reviewers expressed that OSHA had been very thorough in the Agency's review of the literature and appropriately addressed all known health endpoints. The reviewers also agreed that OSHA was reasonable in its interpretation of the studies with regards to the various endpoints examined, and that its conclusions were generally well founded. A number of reviewers suggested improvements to facilitate use of the document, and OSHA revised the document as appropriate, in particular, adding a table in the lung cancer section to summarize information from the epidemiological studies that were reviewed and revising subheadings to better delineate sections of the document and make it easier to find summary conclusions.

Some reviewers also found that the draft lacked sufficient explanation of how OSHA selected studies for the literature review, or why OSHA selected certain studies but not others for inclusion in the quantitative risk assessment. OSHA agrees with these comments that its selection criteria for the literature review and risk assessment were not always clear and has revised the document throughout to better reflect the Agency's critical evaluation of the literature. In particular, the section on lung cancer (Section I.C.1) describes OSHA's approach for identifying studies and evaluating their quality, and a description of the overall approach is included in Section V of the preamble to the proposed rule (Summary of the Health Effects).

Several reviewers indicated the need for a more developed introduction to the draft that addressed clear definitions, concepts and terminology used throughout the health effects section. OSHA agreed with these recommendations and expanded the Introduction in Section I.A that explains terminology related to crystalline silica, the measurement of dust exposures, and OSHA's current and proposed exposure limits for respirable crystalline silica. The revised section also introduces concepts concerning characterization of long-term exposure (e.g., use of cumulative exposure measures). OSHA also included in the introduction a more extensive review of the analytical techniques used over the years to evaluate silica exposure. Dr. Seixas, Dr. Miller and Dr. Salmon thought that a more thorough description of current and past methodologies employed to measure worker exposures to dust and to crystalline silica was necessary since this understanding is critical to properly evaluate epidemiological studies that have relied on exposure data obtained from the use of different sampling and analytical methods over time. The significance of early efforts to characterize worker exposures to dust on our understanding of chronic respiratory disease was underscored by Dr. Salmon:

It is not that the gravimetric measure [of dust exposure] is intrinsically technically superior, but rather that the availability of particle counts and size- or surface-area measurements as well as gravimetric analysis made an important contribution to the eventual conclusion that 1)

long-term cumulative exposure was the chief determinant of chronic silicosis and 2) the gravimetric measure is the appropriate dose metric related to health effects.

OSHA agreed with these comments and included a more detailed description of the various methodologies employed in these studies and those currently in use.

Dr. Seixas commented that OSHA should explain the choice of a proposed exposure limit based on measurement of respirable crystalline silica in air rather than the formula-based limit currently enforced. OSHA has not included this discussion in its health effects review, but does explain the reasons for its choice of a proposed PEL in the preamble to the proposed rule (Section X., Summary and Explanation for paragraph (c)).

In Section B of the draft document, OSHA presented a discussion of silicosis that focused on summarizing available data from disease surveillance programs and addressed certain issues that are of particular interest to the Agency; these issues included the reliability and sensitivity of chest radiographs for diagnosing silicosis, the relationship between radiological changes indicative of silicosis and pulmonary function, and factors that influence progression of the disease. Dr. Salmon commented that the overall perspective of the section would be improved if it included a description of the key studies used in the risk assessment for evaluating quantitative relationships between exposure to respirable crystalline silica and silicosis (these studies were instead described in detail in the draft quantitative risk assessment). OSHA has retained the detailed description of these studies in the risk assessment discussion, but OSHA agrees that the silicosis discussion would benefit from a demonstration that an exposure-response relationship exists for silicosis and added a summary of the findings from the key studies in Section I.B.

Dr. Salmon also commented that OSHA's exclusive use in the draft of U.S. silicosis mortality and morbidity statistics supported "an assumption of a relationship between silicosis and exposure to silica", but nevertheless provided a "limited perspective" due to their "individual and clinical, rather than statistical" nature and because such data reflect "substantial under-reporting" of disease. He went on to comment that:

> For a start, [the draft discussion]…is largely confined to United States data which itself ignores the international dimension of the problem, and may produce other weaknesses resulting from the peculiarities of the United States health care system. In general, apart from special projects following pre-defined cohorts, United States data are significantly lacking compared to other countries (especially Scandinavia and the [European Union]…where population-wide health care systems exist.

OSHA agrees that the lack of a national disease surveillance system and resulting under-reporting of silicosis deaths and cases in the U.S. limits the utility of the data for exploring further relationships between exposure and disease. However, OSHA's intent on presenting this information was to characterize the extent of the problem in the U.S., recognizing that the prevalence of silicosis mortality and morbidity is under-reported. Silicosis is unusual in that it is one of only a handful of occupational diseases for which there are any surveillance data outside

of the Bureau of Labor Statistics injury and illness reporting system. Despite this under-reporting, OSHA believes that the available statistics indicate that silicosis is still a significant occupational health problem in this country.

Dr. Salmon also suggested that OSHA include a recently published article describing pneumoconiosis among Californian agricultural workers exposed to crystalline silica-containing dusts (Schenker et al., 2009). This study reported finding histological evidence of mixed-dust pneumoconiosis among deceased agricultural workers. OSHA is also aware of a recent article (Swanepoel et al., 2010) that reported finding exposures to respirable crystalline silica exceeding 0.1 mg/m^3 among South African farmworkers. This survey and other literature describing exposures to respirable quartz dust among farmworkers, Swanepoel et al. (2010) concluded that there is convincing evidence of a respirable quartz risk to workers on sandy farms; however, they also reported that there was "scant evidence" of associated disease in the literature, possibly due to a healthy worker effect, underreporting of disease, low cumulative exposures of farmworkers, or that the potency of silica particles in farm soil may be low. OSHA further discusses the issue of silica exposure in the agricultural industry in the preamble to the proposed rule dealing with scope issues (Section X, Summary and Explanation).

In reviewing the available surveillance data on silicosis mortality, Dr. Seixas commented on the implications of the significant decline in mortality seen since the late 1960's:

> Lessons learned from these data systems, along with their limitations, were well discussed. However, one comes away with an important question. Given the rapid and consistent reduction in mortality, and the continuing exposure levels over the current PEL, one must ask if the remaining disease observed is not completely due to illegal (i.e., > PEL) exposures, rather than the inadequacy of the current standard. I think some discussion of this, in particular the limitations in assessing non-silicosis outcomes (e.g., COPD and [lung cancer]…) in relation to silica exposures, is warranted….Given the limitations of the various surveillance data sources (both exposure and outcomes), it should be pointed out that the best information about the disease comes from well constructed epidemiological studies where the cohort can be adequately defined, exposure can be sufficiently quantified, and outcomes can be thoroughly ascertained.

OSHA believes that Dr. Seixas makes a strong point with respect to making inferences from surveillance data, and OSHA has echoed this in its discussion. NIOSH (CDC, 2005) cited two main reasons for the observed decline: (1) many of the early deaths were likely the result of high exposures experienced before national standards were established in 1971, and (2) declining employment in heavy industries where silica exposures were prevalent would be reflected in declining numbers and rates of silica-related mortality. It is not possible from the available data to attribute the remaining risk solely to non-compliance with current exposure limits, nor to draw any conclusions about the adequacy of current exposure limits. As Dr. Seixas indicates, such evaluations are best made from well-conducted epidemiological investigations and analyses of exposure-response relationships as part of a formal risk assessment.

Dr. Salmon and Dr. Seixas believed the discussion on radiographic tools (x-rays, computerized tomography (CT) and high-resolution CT (HRCT) (Section 1.B.1.b) was appropriate, particularly for pointing out the relative insensitivity of radiography in detecting silicosis. Other reviewers suggested various changes be made in the discussion, including updating the literature on the efficacy of CT and HRCT. OSHA amended this section as appropriate and added more recent studies by Sun et al. (2008), Lopes et al. (2008), and Blum et al. (2008) on the use of HRCT for detecting early silicosis. Dr. Seixas pointed out that the discussion contained no conclusions that could be used for recommending silicosis screening or surveillance systems. OSHA has included such a discussion in the preamble to the proposed rule to support its proposed medical surveillance requirements (Section XVI, Summary and Explanation for paragraph (h)).

Reviewers generally thought OSHA's discussion of pulmonary function as it relates to radiological signs of silicosis (Section I.B.3) was reasonable and defensible. Dr. Miller suggested that OSHA emphasize how inter-individual variability in lung function measurements can complicate interpretation of cross-sectional studies and OSHA has added language to that effect.

Dr. Ginsberg commented that the discussions in the draft on the insensitivity of radiology to detect early silicosis and on the relationships between radiographic findings and pulmonary function declines were reasonable, but that OSHA failed to provide any perspective on how these findings influenced the Agency in the interpretation of epidemiological studies or quantitative assessment of health risks. He stated that:

> Does this [information] affect OSHA's case definition of silicosis (e.g., only if there is associated functional decline)? Does it affect the way OSHA interprets the epidemiology? Does OSHA have a degree of silicosis it is trying to prevent….The decision affects how the epidemiology is interpreted and risk assessment conducted. For example, if the dose-response is from a study whose sensitivity was for mild to moderate silicosis, OSHA may not want to weigh that study as heavily as one with a more sensitive case definition.

OSHA believes that Dr. Ginsberg raises issues that the Agency typically addresses as part of its analysis of the significance of risk, a discussion of which is presented in section VII of the preamble to the proposed rule. To promulgate standards dealing with hazardous substances such as crystalline silica, OSHA must make findings that workers are exposed to a significant risk of material impairment of health or loss of functional capacity. OSHA's goal in the health effects analysis and quantitative risk assessment is to provide the information necessary for OSHA to then evaluate at what point a demonstrated health effect or endpoint constitutes material impairment of health, for example, whether an x-ray described as ILO category 1/0 constitutes material impairment in the affected worker. OSHA's approach in its health effects review and risk assessment was to develop the information and analysis necessary to then permit the Agency to combine the scientific findings with the legal and policy considerations that must be dealt with in order to make its material impairment and significant risk findings, which ultimately justify the regulatory decisions made. In the case of silicosis, OSHA's purpose was to characterize the

morbidity risk to the extent that the available information permitted, and to review information that would best inform the Agency on the issues of material impairment, in particular of the health implications of radiographic findings of silicosis.

In the review of lung cancer studies, OSHA concluded in the draft that studies of cohorts in four industry sectors (diatomaceous earth, U.S. granite, North American industrial sand, and British pottery workers) among the more than 20 such cohorts examined provided the strongest evidence for a causal relationship between exposure to respirable crystalline silica and lung cancer mortality. These studies were selected primarily on the strength and quality of underlying exposure data available for these studies, and because investigators adequately adjusted for or otherwise addressed the influence of smoking and co-exposure to potential confounders. Reviewers generally agreed with OSHA's conclusion, but made several remarks. Mr. Allen questioned why OSHA excluded two studies where exposures were low; these were the U.K. industrial sand study by Brown and Rushton (2005a, 2005b) and the Ulm et al. (1999) study of German stone, quarry, and ceramic workers. Mr. Allen commented that "…inclusion of studies with low exposures as part of a dose-response analysis is very useful precisely because such studies help constrain and define the low-dose…shapes that can be considered consistent with the data…." OSHA agrees that such studies can be particularly useful. However, neither of these studies demonstrated an exposure-related effect with respect to lung cancer mortality, and OSHA believed that the lack of an observed effect was largely due to the low exposures experienced by the cohorts and lack of power that these studies had to detect risks associated with these low exposures. The Brown and Rushton study (2005a, 2005b) was of 2,703 industrial sand workers exposed to a geometric mean of 0.09 mg/m^3 respirable quartz. However, cumulative exposures of the cohort were very low. Over half of the 764 cohort deaths had less than 10 years of service and the mean cumulative exposure of the cohort was 0.31 mg/m^3-years, less than one-tenth that permitted by the current OSHA quartz PEL for a 45-year working life. Other reasons were provided by OSHA in the draft, and OSHA also cited remarks by Steenland (2005a) who also noted an unusual distribution of lung cancer deaths among relatively short-term workers as being a reason to discount the study. With respect to the Ulm et al. (1999) case-control study, cases and controls with silicosis were eliminated from the study (thus eliminating higher-exposed workers) and controls had known exposure to silica, which would further reduce the power of the study. OSHA noted that the authors themselves acknowledged that the low exposures may have reduced the power of the study to detect small risks. In addition, OSHA cited possible misclassification of exposure as another reason for discounting the study. OSHA believes that its reasons for discounting these two studies are clear, but agrees with Mr. Allen that it might not have been clear how these reasons related to the selection criteria laid out in the draft. OSHA believes that inclusion of the summary table in Section I.C and its description of how it evaluated the lung cancer studies clarifies the basis upon which OSHA determined which studies provide the strongest evidence for evaluating the carcinogenicity of crystalline silica.

Dr. Finkelstein agreed with OSHA that it is appropriate to weight most highly those studies with the least confounding, but that there was little mention made of exposure misclassification as a cause for heterogeneity (i.e., conflicting observations among studies with respect to finding exposure-related effects or differences in observed exposure-response relationships). In particular, he described the exposure data underlying the studies of Vermont

granite sheds as being "sparse and [requiring] much interpolation of uncertain data." Despite the uncertainties that result from using such studies in risk assessment, he commented that:

> Nevertheless, I believe that it is important to make the best use of whatever data are available. I thus support pooling of data from individual studies [such as was done in the 10-cohort pooled study by Steenland et al. (2001a)]. I recognize that the pooling of poor quality data will tend to obscure any relations between exposure and response. Should an exposure-response relationship emerge from these analyses, despite the weaknesses, then I believe that this supports the existence of a real association between exposure and disease.

Quality of underlying exposure estimates used in the epidemiological studies reviewed by OSHA was a factor in selecting what the Agency believes to be the most reliable studies on which to base its preliminary conclusions, and OSHA has clarified this in Section I.C.

Dr. Miller also agreed that OSHA properly identified the strongest studies available at the time of the review, but identified a recent lung cancer study of British coal miners, which found an increase in lung cancer mortality related to exposure to respirable quartz dust (Miller et al., 2007; Miller and MacCalman, 2009). OSHA has included a review of these studies in the health effects document (Section I.C.2.k) and in the preliminary quantitative risk assessment (Section II).

Dr. Salmon also agreed that the studies identified by OSHA as being of the best quality reflected studies having adequate power and reasonable exposure and health outcome determinations. However, he believed that omission of the South African gold mining studies was a "mistake" despite OSHA's draft containing favorable comments on the later studies of Hnizdo and Sluis-Cremer (1991) and Hnizdo et al. (1997). He further stated that

> While there are some questions about the exposure measurements used and possible confounding by radon exposure it appear[s] that most of these have been addressed by related studies. This group of miners has been an important source of data on silica effects over the years and historically these studies have contributed greatly to the worldwide concern about, and understanding of, silica exposures and health effects. The fact that a modern epidemiological study finds a positive association with lung cancer in this group is an important and persuasive part of the whole jigsaw puzzle. In the last analysis, however, the most persuasive part of the argument is not any of one of the single study reports, but the meta-analysis by Steenland et al. (2001a).

OSHA believes that its health effects literature review places appropriate emphasis on the importance of the South African gold mining studies, and agrees that the findings by Hnizdo and Sluis-Cremer (1991) and Hnizdo et al. (1997) add significantly to the body of evidence that crystalline silica is a human carcinogen. OSHA also believes that the organization of its draft summary discussion of the lung cancer evidence may have suggested that OSHA's preliminary finding of a causal relationship was based solely on the group of studies identified as those with

the least potential for confounding. This was not OSHA's intent and the present discussion (and the Summary of Health Effects in Section V of the preamble) has been reorganized to make clearer that OSHA is relying on the entire body of evidence, including that from the South African mining studies, in making its preliminary conclusions.

Reviewers generally agreed with OSHA's preliminary conclusions that evidence for a relationship between exposure to respirable crystalline silica and cancers at sites other than the lung is too limited and contradictory to address further in the risk assessment.

Section D of the review presented a discussion of studies that have investigated the risk of chronic obstructive pulmonary disease (COPD) as it relates to crystalline silica exposure. Reviewers thought that OSHA should define the relevant health endpoints up front, and the revised document includes definitions for COPD, chronic bronchitis, and emphysema.

Dr. Ginsberg believed that the section made several important points with respect to crystalline silica increasing the risk of COPD independent of silicosis, but thought that the information presented was not sufficiently tied to the risk assessment. In particular, although the health effects review provides evidence that there is an exposure-response relationship for COPD, there was no analysis describing how COPD may add to silicosis risk or "…how this additional respiratory disease burden could be included in a quantitative risk assessment." Dr. Ginsberg pointed to the study by Park et al. (2002) of diatomaceous earth workers as showing an exposure-related response for fatal lung diseases other than cancer (LDOC) (i.e., silicosis plus COPD) roughly 10 times more potent than for silicosis mortality, and commented that this study "represents a reasonable estimate of silica-induced total respiratory mortality" and might more appropriately reflect the totality of silica-induced respiratory mortality.

OSHA agrees with Dr. Ginsberg that the Park et al. (2002) study provides a reasonable basis for evaluating non-malignant respiratory disease risk, which includes both silicosis and COPD-related mortality, and thus would better reflect the total respiratory mortality burden associated with exposure to respirable crystalline silica. OSHA did include the Park et al. study in its draft risk assessment, but erroneously characterized it as an "upper bound" estimate of silicosis-related mortality, where it is more precisely characterized as an estimate of non-malignant respiratory mortality. OSHA has made the appropriate changes to the draft health effects review and risk assessment to more clearly indicate why OSHA believes the Park et al. study is included in the risk assessment and to clearly interpret the meaning of the resulting risk estimates.

Dr. Ginsberg thought it useful that the risk assessment reported the risk estimates derived from the study, but that "it was unclear how much weight will be given to this potency value." On this same point, Dr. Salmon stated that:

> It is important to emphasize that these different pulmonary disease manifestations…are all reflections of an underlying disease process related to silica exposure….It is therefore important to look at all these disease entities in assessing the overall disease burden from exposure to silica dust.

OSHA believes that the revised document clarifies these points as well. In addition, OSHA's discussion Section VII of the preamble to the proposed rule presents the Agency's evaluation of the significance of the health risks, which explains how the health effects information and risk estimates are viewed in light of the scientific and legal findings necessary to support the proposed rule.

In Section E of the draft, OSHA presented its analysis of literature describing the risk of renal and autoimmune disease and their relationships to crystalline silica exposure. Although reviewers agreed with OSHA's overall analysis supporting such relationships, opinions differed with respect to OSHA's preliminary determination that data were insufficient to support a quantitative assessment of renal and autoimmune effects. Three reviewers (Drs. Finkelstein, Ginsberg, and Miller) agreed with the view expressed in the draft. Dr. Seixas also agreed that data were insufficient to support quantitative assessment of risks, but that "…if one were required, it would be feasible, given the available studies." Two reviewers (Mr. Allen and Dr. Salmon) held opposite opinions, that the available data were sufficient and would support a quantitative assessment. Mr. Allen pointed out that OSHA's draft stated that some exposure-response studies were "credible", and that:

> …it is not appropriate to base a determination…on a comparison to what is known about silicosis or lung cancer. Certainly, other compounds have been subjects of quantitative risk assessments with much less data than what is available for silicosis and lung cancer, and they have been considered adequate for some level of quantitative evaluation. One might ask oneself if, in the absence of the silicosis or lung cancer data, one would use the renal and/or autoimmune data for silica as a basis of a quantitative risk assessment and determination of regulatory levels. I suspect that one would.

Dr. Salmon commented that "OSHA's reluctance to consider a quantitative analysis of renal disease and mortality…seems unjustified", and endorsed use of the Steenland et al. (2002a) pooled cohort analysis. Dr. Salmon also stated that, despite the data for autoimmune effects being "less convincing and comprehensive, due in part to the complexity and variability of this type of disease", it is particularly important "to pursue an appropriate quantitative analysis where possible."

OSHA believes that Mr. Allen is correct that OSHA's initial conclusion reflected a viewpoint that data for renal effects were less robust than were available data on silicosis and non-malignant respiratory disease, and lung cancer. In light of his and other reviewers' comments, OSHA has re-evaluated the available information, particularly the Steenland et al. (2002a) pooled cohort study and underlying analyses, and believes that it is appropriate to include an analysis of renal mortality in the preliminary quantitative risk assessment. The present health effects review and risk assessment documents accordingly reflect this change. OSHA continues to believe that available data on autoimmune diseases is insufficient for the purpose of quantitatively assessing risks.

Section F of the draft health effects review evaluated toxicological and mode-of-action information to explore issues regarding the role of pulmonary inflammation and silicosis in promoting lung cancer, the physical factors that can affect the toxicity of crystalline silica particles, and whether cristobalite exhibits a different toxicological potency from quartz. Reviewers generally believed that the discussion accurately reflected scientific opinion on these issues and raised some specific points. Dr. Ginsberg stated that "…while there is substantial evidence that silicosis is not required for oncogenic potential", the extent to which silicosis could enhance the DNA damaging effects of silica, and consequently affect the dose-response for lung cancer, is unclear. Dr. Miller remarked that "[w]hether any excess silica-related lung cancer risk operates through fibrosis or other aspects of the silicotic response is a difficult question, and the text [of the draft] reflects this." Dr. Salmon pointed out that the diagnostic indicators of silicosis (i.e., radiography and post-mortem histology) are "late" indicators of disease and cannot identify initial stages that may or may not be important in development of lung cancer.

In the draft discussion of physical factors affecting the potency of crystalline silica, OSHA had preliminarily concluded that there is good evidence that several factors influence the ability of quartz particles to interact with cells and cause lung damage; such factors include the age of fractured particles and the presence of minerals on particle surfaces. Although such factors may explain differences observed in exposure-response relationships derived from various studies of cohorts in different occupational settings, OSHA's draft analysis stated that the level of understanding was as yet insufficient to determine how such factors are likely affect disease risk in any given workplace setting. Reviewers agreed with this assessment. For example, Mr. Allen commented that "the manner in which [these factors]…act…does not appear to be well understood…and certainly does not appear to be quantifiable." He concluded that basing decisions on a range of risk estimates that reflect some of the variation attributable to physical modifiers of quartz toxicity was a satisfactory approach. Two reviewers (Dr. Miller and Dr. Ginsberg) addressed the regulatory implications of evidence that quartz exhibits varying potency in different industrial settings. Dr. Ginsberg believed that the discussion in the draft raised "an uncertainty that is not really dealt with", and both suggested regulatory approaches that appear to place some emphasis on the higher potency factors seen among the various studies. OSHA agrees that the health effects and risk assessment drafts were probably not clear with respect to how OSHA interprets the risk information in light of the evidence on physical modifiers of quartz toxicity, although the draft did indicate that such factors were at least a partial explanation for the observed heterogeneity seen in exposure-response relationships for lung cancer and silicosis morbidity. OSHA's assessment, and in particular its evaluation of the significance of risk (Section VII of this preamble), make clear that OSHA is relying on a range of risk estimates that probably reflects at least some of the differences in toxic potency attributed to modifying factors.

OSHA's draft analysis preliminarily determined that current evidence did not support that cristobalite was more toxic than quartz, as was historically beleived. Dr. Seixas, the only reviewer to comment on this aspect of the analysis, agreed that current evidence indicates the polymorphs to be of comparable toxicity.

III.B. ***Peer Review of the Preliminary Quantitative Risk Assessment.***

In general, the reviewers agreed that the strengths and weaknesses of the selected studies are adequately discussed. Some reviewers suggested that other studies could be used for quantitative risk assessment and should be included. For example, Dr. Ginsberg commented that the draft was lacking in critical appraisal of studies and that OSHA's selection of four studies for the draft risk assessment, which was largely based on the investigators having developed quantitative exposure-response models, might have introduced a selection bias. For example, Dr. Ginsberg pointed to OSHA's discussion of the study of Danish stone workers by Guénel et al. (1989) and the Cassidy et al. (2007) multi-center case-control study, which he believed did not sufficiently explain why these studies were not considered for quantitative risk assessment.

As explained above in OSHA's responses to comments on the draft health effects analysis, OSHA agrees that the draft did not include sufficient information describing the basis for OSHA's selection of studies for the risk assessment, and has made appropriate clarifying changes throughout both documents. With respect to the studies mentioned by Dr. Ginsberg, the Cassidy et al. study found highly significant trends in odds ratios between several indices of silica exposure and lung cancer cases, adjusted for smoking and other occupational lung carcinogens. OSHA has preliminarily concluded that the results of this study are "particularly compelling" in demonstrating a relationship between exposure to crystalline silica and lung cancer. However, the silica exposure measures were only semi-quantitative and categorized as "low", "medium", and "high", with ranges of exposure levels assigned to each category in order to obtain "standardization in the application of the intensity index", and data were not available on the actual exposures experienced by most of the the study participants. For this reason, OSHA preferred to rely on studies where exposure data were available from the actual work environments and operations from which study cohorts were drawn. The Danish stone worker study also found increased lung cancer risk associated with silica exposure, but there was not enough exposure information presented to permit quantitative risk estimation.

Mr. Allen commented that OSHA's discussion of exposure reconstruction in the studies might not have sufficiently conveyed limitations of the approaches used by investigators. In particular, he referred to OSHA's discussion of the exposure assessment that was used in the Steenland et al. (2001a) pooled cohort study, in which odds ratios for silicosis mortality were reported by exposure quintile to show that serious exposure misclassification was unlikely to have occurred. Mr. Allen believed that the results presented were not convincing, and questioned whether OSHA was relying on the best evidence. The analysis discussed by OSHA was a preliminary analysis reported by Mannetje et al. (2002a), who also published a more rigorous evaluation of the exposure-response for silicosis mortality (Mannetje et al., 2002b). The latter analysis was presented in OSHA's risk assessment and shows a clear and consistent positive response with increasing decile of cumulative exposure, although there is an anomaly in the 9^{th} decile. Overall, these data support a monotonic exposure-response for silicosis. Given that silicosis is known to be strongly related to cumulative exposure, this finding suggests that exposure has been fairly well measured by Mannetje et al (2002a) and, by extension, in Steenland et al. (2001a), which uses the same exposure estimation. OSHA believes that this provides stronger evidence that supports the underlying exposure assessment and has revised the risk assessment document accordingly.

Dr. Salmon commented that, although OSHA's draft adequately evaluated most of the studies included in the risk assessment, the discussion of silicosis morbidity was less convincing in that it omitted certain studies that he believed were particularly useful for evaluating risks at low exposure. In particular, he identified the cross-sectional study by Churchyard et al. (2004) on black South African miners, and an analysis by California OEHHA (2005), which assessed silicosis risks at low exposures based on many studies that were included in OSHA's analysis. In addition, he believed that the risk assessment overall placed undue focus on extreme endpoints such as silicosis mortality and morbidity defined by ILO 2/1+ x-ray changes, thus lessening the sensitivity of the assessment for low-dose extrapolation.

With respect to the Churchyard et al. (2004) study, OSHA has reviewed this study and agrees with Dr. Salmon that it shows a significant prevalence (almost 20%) of silicosis among older in-service black mineworkers. Unlike other studies described in the risk assessment (e.g., Miller et al., 1998; Hnizdo and Sluis-Cremer, 1993), the Churchyard study included prevalence among only active workers and did not include retirees. OSHA included a discussion of the Churchyard et al. study in the revised risk assessment, but continues to believe that the best estimates of silicosis morbidity risk comes from studies that included both current workers and retirees since the resulting estimates will more closely approximate the risk that accumulates over a lifetime.

OSHA is also aware that, in identifying the Mannetje et al. (2002b) analysis of silicosis mortality and the Miller et al. (1998) analysis of morbidity, the draft might have suggested that OSHA would be relying most heavily on fairly insensitive indicators of silicosis in making regulatory decisions. OSHA's interpretation of the significance of the risk findings and how these findings provide the basis for regulation is presented in the preamble to the proposed rule (i.e., section VII, Significance of Risk and section X., Summary and Explanation of the Standard). OSHA has revised potions of the preliminary risk assessment to clarify that OSHA's estimates of the range of silicosis risk at the current and proposed PEL include more sensitive endpoints, in particular x-ray changes consistent with ILO 1/0+ and 1/1+.

Dr. Miller identified a recent lung cancer study on British coal miners (Miller et al., 2007; Miller and MacCalman, 2009) that he believed should be considered for the assessment. OSHA has reviewed these studies and found that this coalminer study had specific strengths in three areas: the detailed time-exposure measurements of both quartz and total mine dust, detailed individual work histories, and individual smoking histories. In addition, the study conduct and the statistical analyses presented in the publications were well done. The results provide risk estimates that are somewhat on the lower side of the range of lung cancer risk estimates derived from other studies, possibly because of the individual adjustments for smoking and coal dust, or the type of silica exposure in the mines.

As a result of further review, OSHA also added quantitative lung cancer risk estimates based on the North American industrial sand worker study presented by Hughes et al. (2001), and McDonald et al. (2001, 2005). OSHA believes that because of the availability of high-quality exposure and work history data for these studies, as well as individual smoking data that allowed for adjustment in the risk model, OSHA based estimates on the Hughes et al. nested

case-control study, which provided sufficient information in the report to reasonably reproduce the model.

For silicosis morbidity estimates, OSHA has added the analysis of Buchanan et al. (2003) to its revised risk assessment. This study is a reanalysis of the coalminer study by Miller et al. (1998), which was discussed in the draft risk assessment and is a follow-up study that could account for incidence, not just prevalence, of silicosis and included both current workers and retirees. The Buchanan et al. reanalysis was designed to account for high exposure rates, and was reviewed in the draft to evaluate evidence for dose-rate effects for silicosis morbidity. Reviewers had suggested that, given the Buchanan et al. model adjusts for potential dose-rate effects, it may serve as a better model than the original study relied on by OSHA, the Miller et al. (1998) study. OSHA agrees and the revised draft presents risk estimates derived from the Buchanan et al study.

Reviewers believed that the uncertainty analysis conducted by Steenland and Bartow (Toxichemica, 2004) was well designed and convincing in showing that potential biases in exposure estimation are not likely to have a large effect on risk estimates derived from the Steenland et al. (2001a) pooled cohort lung cancer study. Several specific comments and suggestions were made. Mr. Allen remarked that Monte Carlo approaches typically require more than the 50 iterations that were used in the uncertainty analysis. In addition, he suggested that it might be informative to increase the amount of error above what was assumed in the analysis to determine how much error in the exposure estimates might have been required to effect a substantial change in the risk estimates, and whether it was plausible for the exposure estimates to reflect that much error.

Clearly, more than 50 iterations could have been performed. However, the inter-simulation variance of exposure-response coefficients did not appear to change much with an increased number of iterations. For the analysis of random measurement error, the inter-simulation standard error (.004) was only one-third of the average of the standard error (.014) that resulted from incorporating random error in the model across the 50 iterations. Thus, OSHA believes that the simulation would not have benefited substantially by running more simulations. On Mr. Allen's suggestion for additional analysis, OSHA agrees that it would be informative to increase the assumed amount of error to determine at what point risk estimates are significantly influenced. Steenland and Bartow (Toxichemica, Inc., 2004) assumed a level of uncertainty for two types of random error based on actual data describing variation around estimates of mean exposure level and mean percent silica content of dusts, and believes that this approach is sufficient for the purpose of OSHA's preliminary risk assessment.

Dr. Crump commented that the analysis could have assumed that silica concentrations differed randomly by work area rather than by job since random sampling of jobs in the same work area might tend to "average out variations by work area and underestimate uncertainty." In their analysis, Steenland and Bartow (Toxichemica, Inc., 2004) constructed job-exposure matrices that were combinations of tasks and work areas where there was sufficient detail in the original data for each study. OSHA has revised the text in the risk assessment to clarify this point. Dr. Crump also suggested that assuming that the average measure of exposure assigned to

a job is the true average could be a major source of error that is unaccounted for. Sources of such error include the possibility that measurements were taken at times when it was believed that a particular problem was causing higher exposures, or because historical (and presumably higher and more influential) exposures were not always measured but projected based on historical knowledge of operations or estimated from data obtained from different measurement methods (i.e., particle count data). The Toxichemica, Inc. analysis assumed that the average measurements for a given job were a fair reflection of the true average exposures of workers in that job, on the whole. While it is possible that some measurements were systematically biased above or below the true average for a job, there is no "gold standard" measurement available to determine this. The Toxichemica, Inc. analysis did include consideration of some of the kinds of error mentioned by Dr. Crump, in particular errors in the estimate of silica content of dust and systematic bias in exposure measurements.

Dr. Seixas commented that the simulation performed for the uncertainty analysis reflected modeling for classical, rather than Berkson, error:

> The typical Monte Carlo simulation, which is what appears to have been done, would introduce classical error. I don't think the report should repeatedly state that the simulation produces coefficients "adjusted for Berkson error" as I don't believe this is Berkson, nor that the simulation actually adjusts for it….In fact, the results [i.e., the resulting exposure-response coefficients after simulation]…almost all went down (toward the null), which is what is generally expected by adding random (classical) error into the exposure variable….There is no mention of measurement error generally reducing the effect of exposure response relationships, and that this principle indicates that the estimated risks are most likely to be underestimates….This is an important aspect of measurement error with significant implications for risk assessment and should not be overlooked.

The Toxichemica, Inc. report discusses the limitation of the simulation approach in more detail. For example, one limitation is that the simulation did not account for correlations between simulated Berkson errors and the disease outcomes that are implied by the specific model. The reviewer may be correct that, without proper accounting of such limitations the Toxichemica analysis can be viewed as an exercise in simulating the effect of additional classical error. OSHA notes that the adjusted exposure-response coefficients are not necessarily better estimates (which might have been implied by terming them "adjusted coefficients"), but they are informative regarding the potential effects of measurement error on the observed dose-response coefficients. OSHA also agrees with Dr. Seixas that classical measurement error structures typically do bias exposure-response coefficients towards the null; however, it has also been demonstrated that Berkson error can cause bias in either direction (Steenland and Deddens, 2000).

In the draft risk assessment document, OSHA presented lung cancer risk estimates based on a lung dosimetry model for crystalline silica developed by Kuempel et al. (2001). This modeling approach is a rat-based toxicokinetic/toxicodynamic modeling effort to predict human

lung cancer risk based on lung burden concentrations necessary to cause the precursor events that can lead to adverse physiological effects in the lung. The resulting relationship between cumulative exposure and human lung burden were used to estimate lung cancer risks as a function of lung burden from the diatomaceous earth and Vermont granite cohort studies. Reviewers' responses to the discussion were mixed, although most thought that OSHA had not explained the Kuempel et al. model in sufficient detail. Two reviewers (Drs. Finkelstein and Miller) thought that models such as the rat-based model would be useful in instances only when there are no or inadequate epidemiology data. For example, Dr. Miller suggested that lung burden …may be the correct target organ dose metric, but epidemiological data on it is very sparse; hence the normal focus on exposure experienced as a surrogate for dose. The extrapolation involved requires many more assumptions than assessing risk from epidemiological studies, and it may not be prudent to place the same degree of reliance on the model-based estimates as on those from epidemiological observation.

In contrast, Dr. Crump thought that lung burden metrics:

> …can provide a reasonable alternative to the more empirical metrics emphasized in the papers reviewed by OSHA….Without estimating risk using the metrics based on lung burden, the effect of these metrics upon the estimated risk will not be known. If workers in the epidemiological studies predominately were exposed for only a short time (e.g., a few months), different exposure metrics could predict significantly different risks from 45 years of exposure even if they provided equivalent fits to the epidemiological data.

OSHA has added new language to clarify the discussion of the Keumpel et al. (2001) analysis. After considering the comments of the expert reviewers, OSHA has chosen to not rely on the rat-based model, but instead to rely on the lung cancer risk estimates of the epidemiology studies themselves and the exposure metrics used in those studies. OSHA notes that the conversion by Kuempel et al. of the two epidemiology studies' metrics of cumulative exposure to equivalent lung burdens *after* the epidemiology exposure-response analysis had already been based on cumulative exposure adds little new information. Although a risk assessment based on silica lung burden data in humans whose mortality experience was evaluated would provide additional useful information on exposure-response relationships, the Kuempel et al. (2001) analysis does not provide that kind of information. OSHA believes that the available epidemiological data provide a strong basis for estimating lung cancer risks from cumulative exposure metrics.

The draft risk assessment summarized several published risk assessments that used a variety of exposure-response models and statistical methodologies to evaluate them. In general, reviewers believed the studies were adequately described but that the presentation would be improved by greater use of summary tables to facilitate comparing modeling approaches across studies. OSHA has expanded or added summary tables as appropriate.

Dr. Ginsberg thought the rationale for estimating risks at exposure levels above OSHA's current standard (of approximately 0.1 mg/m^3) was unclear, and both Dr. Ginsberg and Dr.

Salmon suggested that OSHA make an effort to estimate risks at lower exposures that were evaluated in the draft (i.e., below 0.05 mg/m^3). OSHA's risk assessment provided risk estimates for exposure to 0.25 and 0.5 mg/m^3 respirable crystalline silica over a working life to represent the range of risks to which workers are exposed under the current PEL for construction and maritime, which is a particle count formula rather than the gravimetric PEL that applies in general industry. OSHA has revised the draft to emphasize this point throughout. With respect to estimating risks at lower exposure levels, the revised draft provides risk estimates associated with exposure to the proposed action level of 0.025 mg/m^3. Given the Agency's preliminary findings with respect to technological feasibility of alternative PELs, OSHA believes that an effort to estimate risk at levels below the proposed action level would have little or no impact on the Agency's regulatory action, and has therefore chosen not to do so.

Dr. Ginsberg also questioned whether OSHA was giving proper weight to the South African miner study (Hnizdo et al., 1997), which, in the Steenland et al. (2001a) pooled cohort study, showed an approximate 10-fold higher potency for lung cancer than did the other nine cohorts included. He stated that:

> In toxicology and risk assessment, one should consider whether the most sensitive study and endpoint is of high enough quality to be the source of risk calculations[,]…whether the entire risk range should be presented...or whether some central tendency potency estimate should be used. It may be that the South African gold miner study is more potent for a good reason…and should be given serious consideration as a stand alone data point for potency estimation and risk calculations. Or perhaps that study is no better or even inferior or less relevant than the others.

OSHA believes that the excess lung cancer risk associated with exposure to crystalline silica is best characterized as a range of risks across the various industries studied rather than on a single study that reflects the highest potency, and that the estimates derived from the Steenland et al. (2001a) pooled cohort study (and updated analyses presented in the present assessment) reflect a reasonable approach to deriving a central tendency estimate. OSHA's choices on how to best characterize lung cancer risks reflects what the Agency believes is good evidence that crystalline silica exhibits varying toxic potency in different workplace settings, as explained in section I.F of the health effects review, and the revised risk assessment makes OSHA's position clear.

Dr. Ginsberg also commented that more attention could be devoted to the issue of a threshold, particularly where addressed by the individual studies examined. OSHA addresses this issue further in its revised assessment. Dr. Ginsberg also believed that OSHA did not adequately address potential confounding by smoking; he explained that

> [OSHA]…assumes that the only issue with smoking as an uncontrolled variable is the potential for smoking rate to correlate with silica exposure in such a manner to bias the disease risk high. The text goes on to assert that this is unlikely from the available evidence and study design. However, this rationale excludes the

> possibility that when smoking is an uncontrolled variable it will lead to elevate cancer risk in both the reference and silica-exposed population leading to a high and variable baseline [risk] that will tend to bias the results towards the null hypothesis and weaken associations between silica and lung cancer.

OSHA agrees that this is an important consideration and has revised the draft accordingly. Furthermore, OSHA has included risk analyses based on two studies that had individual worker data on smoking and adjusted for smoking in the risk model; these are the Hughes et al. (2001) study of North American industrial sand workers and a recent study of British coal miners (Miller et al., 2007; Miller and MacCalman, 2009).

Dr. Crump raised a number of points concerning the use of log-transformed exposure metrics and non-linear exposure-response models. He believed the reasons for using log-transformed cumulative exposure in the pooled cohort analysis are "faulty" given that (1) the model based on untransformed exposure and a 15-year lag gave a better fit than that using log-transformed cumulative exposure, and (2) that the lack of any improvement in fit of the model based on log-transformed cumulative exposure did not show improvement when interaction terms were added, which he viewed as a disadvantage. OSHA notes that the model using untransformed exposure, while providing a better fit nevertheless did not fit significantly better than the model based on log-transformed exposure (log-likelihood of 21.4 vs. 18.8). Although employing models that reduce heterogeneity in pooled cohort studies such as this is desirable, OSHA agrees that lack of heterogeneity is not an absolute requirement for accepting a single ("average") coefficient from across studies in a risk assessment, and notes that random effects models in meta-analysis routinely use such summary risk measures across heterogeneous studies. OSHA has explored this issue further in the preliminary risk assessment using linear relative risk models as suggested by Dr. Crump (see below) with the result that log transformation of cumulative exposure results in approximately the same fit to the data as linear models using untransformed exposure. However, the linear models based on use of log-transformed exposure better captures the initially steeper slope of the exposure-response curve that is evident from the pooled data set based on a categorical analysis, whereas the model with untransformed exposure fails to do so. In exploring this issue, OSHA also relied on a 2-piece linear spline model, which outperforms linear models based on either untransformed or log-transformed cumulative exposure.

Dr. Crump also addressed the issue of model selection, in particular the choice of log-linear (i.e., log relative risk) models vs. linear relative risk models, both of which were employed by various authors of the studies relied upon by OSHA. He stated that, "although log-linear models are relied upon extensively, such models are generally selected for convenience…rather than for biological plausibility." As Dr. Crump pointed out in his comments, use of log-relative-risk models result in a supralinear exposure-response curve and, when combined with use of log-transformed exposure (as was done in the pooled cohort study), results in a sublinear exposure-response.

In response to these comments, OSHA asked Drs. Steenland and Bartell to explore use of linear models with the pooled data set (Steenland, personal communication, 2010), with the

result that the revised assessment now presents results from analyses using linear relative risk models, with and without log-transformation of cumulative exposure. From this analysis, OSHA preliminarily concludes that a linear model with log-transformation of exposure and a linear 2-piece spline model with untransformed exposure provide reasonable fits to the pooled data set, and the revised analysis presents risk estimates based on use of these models.

OSHA's draft risk assessment was based on exposure-response models that used cumulative exposure to respirable crystalline silica. The draft did include a discussion of the possible dose-rate effects where, at high silica concentrations, a few studies (Hughes et al., 1998; Buchanan et al., 2003) found that risk increases at a rate greater than would be predicted from cumulative exposure alone (i.e., the rate of accumulation of dose influences risk). In general, the reviewers agreed that cumulative exposure was the proper metric for estimating silica-related health risks, and that the draft provided a good discussion of dose-rate effect. Reviewers also agreed that available data were not sufficiently robust to adequately characterize how the rate of exposure accumulation affects risk. However, Dr. Crump suggested that a dose-rate effect can be present *in addition* to a cumulative dose effect, and that OSHA should consider using available studies that attempted to account for a dose-rate effect. Accordingly, the revised assessment presents estimates of silicosis morbidity risks based on the Buchanan et al. (2003) study, which uses model parameters to account for possible dose-rate effects.

The draft risk assessment characterized excess lung cancer risks as a range of estimates represented on the low end by the estimate derived from the Steenland et al. (2001a) pooled cohort analysis, and by the upper end represented by estimates derived from the individual studies on diatomaceous earth (Rice et al., 2001) and Vermont granite (Attfield and Costello, 2004) workers. Overall, the reviewers stated that the pooled IARC analysis of 10 lung cancer mortality studies should be the basis of OSHA's "best" estimates of lung cancer risk. For example, Dr. Salmon stated that:

> The IARC multi-center study probably represents a reliable median estimate, but by its nature is likely to underestimate the upper bound on risk in a situation where individual cohorts show real variation in risks due to differences in the nature and intensity of the exposure and the effectiveness in determining health endpoints.

Dr. Crump, as described above, further argued that a linear risk model should be employed for the pooled cohort analysis rather than a log-linear model using log-transformed exposure metrics. Dr. Seixas questioned whether the U.S. diatomaceous earth and U.S. granite worker studies be considered plausible upper bounds, since risk estimates derived from these studies were based on maximum likelihood estimates (MLE) rather than on upper confidence interval estimates.

OSHA continues to believe that lung cancer risk estimates are best represented as range, with the estimates derived from the Steenland et al. (2001a) pooled cohort analysis providing a reasonable median estimate of risk across the cohorts included. In the revised risk assessment, the range of plausible lung cancer risk estimates are now derived from analysis of the Hughes et

al. (2001) industrial sand study and the Miller and MacCalman (2009) coal miner study, in addition to the diatomaceous earth and U.S. granite studies included before. The revised assessment also reports the range of lung cancer risk estimates that are derived from the linear relative risk model coefficients for each of the individual cohorts used in the IARC multi-center study.

One reviewer, Dr. Miller, questioned OSHA's assumption of length of lifetime in the analyses of both mortality and morbidity. In the draft assessment, OSHA analyzed mortality risks based on a life table method that summed age-specific risks to age 85. However, many of the underlying studies used age 75 to represent a lifetime, and OSHA's assessment of silicosis morbidity risks did not use a life table approach, but rather reflected the risk that accumulated up to the last follow up of each cohort (which included retirees). OSHA has made appropriate clarifications of assumptions regarding length of lifetime in its risk calculations and has included an appendix that describes the life table calculations used.

Most reviewers commented positively on OSHA's use of cohort studies that included retirees as the appropriate studies for OSHA's assessment of silicosis morbidity risk. Several pointed to the overall consistency in the estimates among the various studies used; however, some reviewers suggested that OSHA was not clear on precisely which studies were being ultimately relied upon. Other reviewers had some specific suggestions. Dr. Crump suggested that OSHA look for a dose-rate effect for silicosis morbidity. Dr. Salmon suggested that OSHA review its reasoning underlying its concerns with exposure measures used in the Hnizdo and Sluis-Cremer (1993) study of silicosis. He pointed out that the report by Churchyard et al (2004) would provide a useful comparison with earlier South African mining studies since exposure was measured using gravimetric methods in occupational situations similar to those from which particle count data were obtained. In response, OSHA has clarified its discussion of the results of the silicosis morbidity analysis, included the Buchanan et al. (2003) study of British coal miners to better address dose-rate effect for silicosis, and revised its discussion of the exposure data underlying the Hnizdo and Sluis-Cremer (1993) study.

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Supplemental Literature Review of Epidemiological Studies on Lung Cancer Associated with Exposure to Respirable Crystalline Silica

Occupational Safety and Health Administration
Docket OSHA-2010-0034

Table of Contents

This document reviews four papers on the risk of lung disease associated with exposure to respirable crystalline silica that have been published subsequent to completion of the comprehensive literature review included in the OSHA background document on Health Effects (OSHA, 2013). These papers were reviewed by the OSHA Directorate of Standards and Guidance to ensure that OSHA has evaluated the most current literature and to determine whether the information in these papers is consistent with or could potentially alter the analysis presented in OSHA's Preliminary Risk Assessment. The papers reviewed in this document include:

1) Vacek PM, Verma DK, Graham WG, Callas PW, and Gibbs GW. (2011). Mortality in Vermont granite workers and its association with silica exposure. Occup Environ Med. 68(5):312-8. Epub 2010 Sep 19.

2) Mundt KA, Birk T, Parsons W, Borsch-Galetke E, Siegmund K, Heavner K, and Guldner K. (2011). Respirable crystalline silica exposure-response evaluation of silicosis morbidity and lung cancer mortality in the German porcelain industry cohort. J Occup Environ Med. 53(3):282-9. [Including information from Birk et al., 2009; Birk et al., 2010, and Mundt et al., 2012 (erratum)].

3) Gamble JF. (2011). Crystalline silica and lung cancer: a critical review of the occupational epidemiology literature of exposure-response studies testing this hypothesis. Crit Rev Toxicol. 41(5):404-65.

4) Cox LA Jr. (2011) An exposure-response threshold for lung diseases and lung cancer caused by crystalline silica. Risk Anal.31(10):1543-60. Epub 2011 Apr 7.

Vacek et al., 2011 – Mortality in Vermont Granite Workers and its Association with Silica Exposure

Vacek et al. examined a group of 7,052 men who had worked in the Vermont granite industry at any time between January 1, 1947 and December 31, 1998 (total of 269,253 person-years of follow-up for calculation of Standardized Mortality Ratios (SMRs)). Cumulative silica exposures were estimated using a job exposure matrix created from measurements taken in the Vermont granite industry between 1924 and 2004, and worker mortality was ascertained by searching the National Death Index, Social Security Administration vital status records, Vermont State Records, commercially available data, and death records from Quebec in cases where a worker was known to have died in Canada. The study also relied on information from previous studies, pension records, and state surveillance data to characterize exposure/work histories. Health outcomes including overall mortality, silicosis mortality, and mortality from other respiratory diseases (diseases other than silicosis, influenza, pneumonia, bronchitis, emphysema, and asthma) were all explored by the study.

The authors found that overall mortality, including mortality from unknown causes, was significantly increased compared to the comparison group of all U.S. white males (SMR 1.08, 95% confidence interval (CI) 1.05 to 1.12); this was mostly due to increased mortality from tuberculosis, malignant neoplasms, and non-malignant respiratory diseases. The study found that most deaths from tuberculosis and silicosis occurred in men who started working prior to 1940—the point at which dust controls were implemented in the granite industry. Only six of the 55 men who died of silicosis began work after 1940. Three of those started work after 1949 and worked less than 10 years in the industry (although one had 40 years of experience as a stone cutter in Canada). All of the 55 deaths from silicosis occurred in workers born before 1925.

The study used a nested case-control analysis to explore the exposure-response relationships between silica exposure and silicosis, other non-malignant respiratory disease, lung cancer, and various non-malignant and malignant renal diseases. The study did not show significant association between lung cancer risk and exposure measured in

several ways as continuous variables. However, silica exposure was significantly related to both silicosis and other non-malignant respiratory disease: for each 1 mg/m^3-year increase in cumulative exposure, the risk of silicosis mortality increased by 13% (OR 1.13, 95% CI 1.05 to 1.21); the risk of mortality from other non-malignant respiratory disease increased by 10% (OR 1.10, 95% CI 1.03 to 1.16). The study divided silica exposure into quintiles for silicosis, other non-malignant respiratory diseases, lung cancer, renal cancer, and non-malignant renal disease; and only showed a significant dose-response relationship between silica exposure and the silicosis outcome. Of note, the quintiles used in the Vacek et al. analysis were higher than typical values of cumulative exposure to silica used in many studies upon which OSHA based its risk assessment. In the ten studies explored by Steenland et al. (2001) and Mannetje et al. (2002a,b), for example, median cumulative exposures ranged from 0.13 to 11.37 mg/m^3-years, with some studies exploring silica exposures spanning only the lower end of the spectrum (e.g., Hnizdo and Sluis-Cremer, 1991; Hughes et al., 2001; and Steenland and Brown, 1995a,b). Attfield and Costello (2004), whose exposure groups are compared to Vacek's in Table 1, specifically found a positive exposure-response relationship among granite workers at the lower end of the exposure spectrum using a model that omitted the highest exposure group in their study, reflecting the authors' position that underlying exposure data for the high-exposure group was weaker than for the other groups and that competing causes of death or misdiagnoses of death may have clouded the exposure-response relationship at higher exposure levels. The regression models used in the Vacek study also exhibited signs of uncontrolled confounding. For instance, for every outcome (except silicosis), workers in the second lowest exposure stratum in the models exhibited a lower risk than those in the lowest stratum of cumulative silica exposure. In the highest exposure (fifth) stratum , all outcomes except non-malignant respiratory disease showed a decline in the likelihood of the outcome (calculated as odds ratio) compared to the next lower stratum. These two problems at the high and low ends of the quintile divisions would be more than sufficient to suppress a linear trend from being observed. Thus, OSHA believes the use by Vacek et al. of high cumulative exposures to define exposure groups fails to adequately explore the dose-effect relationship between silicosis and silica, especially at the low-dose cumulative exposures typically found in modern

operations where silica exposure is possible. OSHA believes the study offers insufficient evidence against lowering silica exposure limits.

Table 1. Exposure groups for Vacek et al. (2011) and Attfield & Costello (2004)

Vacek et al.		**Attfield & Costello**	
Cumulative exposure groups (mg-my/m^3)*	*Number of workers (cases + controls)*	*Cumulative exposure groups* (mg-my/m^3)*	*Number of workers*
<1.04	44	0 - <.25	1,748
1.05 - 3.64	43	.25 - <0.5	556
3.65 - 6.71	43	0.5 - <1.0	760
6.72 – 10.21	44	1.0 - <1.5	509
>10.21	43	1.5 - <2.0	375
		2.0 - <3.0	428
		3.0 - <5.0	374
		≥5.0	658

*Quintiles as used in Vacek's analysis of silicosis SMR. Attfield & Costello evaluated SMR respiratory tuberculosis, diseases of the respiratory system, pneumoconiosis, malignancy of the kidneys, and all causes using the same exposure groups for each outcome.

Vacek et al. also asserted that the cohort data used in their analysis, which extended follow-up by four years compared to Attfield and Costello (2004), provided no evidence of a relationship between lung cancer mortality and silica exposure. However, Attfield and Costello (2004) demonstrated that excluding the highest exposure group in the cohort from their Poisson regression model for exposure-response analysis revealed a stronger relationship between silica exposure and lung cancer mortality compared to what was observed when the highest exposure group was included. The Vacek et al. study's quintiles for lung cancer mortality analysis included 51 deaths in subjects whose cumulative respirable free silica exposure exceeded 4.10 mg-yr/m^3. Attfield and Costello's analysis, in contrast, excluded 30 deaths of subjects whose cumulative exposure levels were at or above 6.0 mg-yr/m^3, capping the seventh exposure group at 29 deaths among subjects whose cumulative exposure levels ranged from 3.0 to <6.0 mg-yr/m^3. Additionally, Vacek found a large excess of lung cancer (almost 100 excess lung cancer deaths, according to Table 3 of the study) that is understated by considering only a SMR and failing to account for the healthy worker effect (HWE). The HWE is the phenomenon that results in lower observations of morbidity and mortality among worker

populations compared to the general population because individuals with illnesses and disabilities or who are otherwise less robust are either excluded from employment or self-select out of higher-risk jobs. HWE is routinely and inappropriately ignored for cancer outcomes (Park et al., 1991). The actual excess could correspond to a SMR at least 0.10 higher than what Vacek et al. reported.

Several other key aspects of the Vacek et al. study also limit its utility in OSHA's risk analysis. The authors were unable to obtain information on smoking for a number of the workers in their cohort due to what were cited as "data confidentiality protections"; however they nonetheless suggest that the elevated SMR for lung cancer is due, at least in part, to differences between the smoking habits of the cohort and reference populations (Vacek et al., 2011). Examination of Vacek et al.'s reported SMRs for causes of death through 2004 among U.S. white males does not necessarily support this claim, however. Although the SMR for other non-malignant lung diseases, which is often associated with smoking, was elevated, there was no significant SMR elevation observed among deaths caused by other smoking-associated diseases (e.g., cancers of the digestive organs, larynx, or bladder; bronchitis, emphysema, and asthma). Elevated SMRs would be expected if there was a significant difference in smoking between the study and reference populations. In addition, lower mortality than expected was observed for bronchitis, heart disease, and leukemia. Further, the population smoking estimate (37%) could be confounded by social class (i.e., persons with higher socio-economic status tend to smoke less); and the granite worker smoking estimate (50%) may be overestimated since the source was a sample selected for a pulmonary function study. The comparison of the two groups—the aging granite cohort versus the general population—also was not adjusted for age.

Analysis of Mundt, et al (2011) German Porcelain Workers Cohort

The risks of silicosis morbidity and lung cancer mortality associated with exposure to silica were examined in a cohort of German porcelain manufacturing workers (Mundt et al., 2011). This cohort was the subject of two previous studies authored by Birk et al.: Birk et al. (2009) and Birk et al. (2010). The first study used SMRs without quantitative exposure estimates (Birk et al., 2009). The analysis presented in Mundt et al. (2011) uses the quantitative exposure estimates from the second study, Birk et al. (2010). This series of study methods was described as unique because it used data obtained from an industry-wide medical surveillance program, including radiographs; quantitative exposure data for creation of a job exposure matrix; and data that included female porcelain workers, who comprised approximately half of the cohort.

The original cohort described in Birk et al. (2009) and Birk et al. (2010) included 17,644 (8,288 male and 9,356 female) German porcelain workers who had participated in medical surveillance programs for silicosis between 1985 and 1987, had paper records of medical surveillance, and were employed in the industry for at least 6 months. Even though Mundt et al.'s (2011) methods reference the same 17,644 participants, Mundt describes results for 8,291 males and 9,322 females, which resulted in more males and less females, with 31 fewer participants than originally reported. Birk et al. (2009) and Mundt et al. (2011) determined vital status from health insurance and pension records and community and central population registries, for 94% of the cohort. Causes of death, including lung cancer, were determined from death certificates, which were available for 93% of the cohort.

To assess silicosis morbidity in Mundt et al. (2011), two radiologists separately reread and classified all radiographs according to International Labour Organization (ILO) methods. Radiographs that scored 1/1 or greater were considered positive evidence of silicosis, which is consistent with ASTM standard practice (ASTM, 2009). If the findings disagreed, the two readers discussed the films to obtain a consensus reading; a third reader was requested to resolve any remaining differences. During the first sampling phase of rereadings, considerably fewer films were classified as positive, and rereadings

produced a very low false negative rate compared to original readings. Therefore, during the second phase of rereadings, the authors decided not to read original films classified as 0/0 or 0/1 and ultimately reread 3.13% (n=552) of original participants' (n=17,644) films. In total, 40 cases of silicosis were observed.

Mundt et al. (2011)'s cohort was followed through the end of 2005, with an average of 19 years of follow-up per subject. From Table 1 in Birk et al. (2009), the mean employment duration for men was 22.5 years (range = 0.5–57.6 years) and mean age at start of follow-up was 35.2 years (range = 15.3–63.7 years). For women, mean employment duration was 20.6 years (range = 0.5–49.9 years) and mean age at start of follow-up was 34 years (range = 14.6–61.7 years). Median year of hire was 1975 (range = 1938–1991) for men and 1976 (range 1943–1996) for women. Follow-up ended at age 75 because records were not available for many cohort members older than 75 years; this excluded 22 male and 6 female deaths from the cohort. Nine percent (n = 1610) of cohort members had died by the end of the follow-up period, including 94 lung cancer deaths.

In contrast to the previous analysis of this cohort by Birk et al. (2009), which used SMRs as a metric, the potential relationships between silica exposure and silicosis morbidity or lung cancer mortality were assessed by Mundt et al. (2011) through internal comparisons and the use of hazard ratios, based on both average and cumulative exposure. A hazard ratio (HR) is a valid estimate of an incidence rate ratio that is calculated from Cox proportional hazard models and accounts for person-time, rather than only the odds or risk of an event occurring. This metric reflects the analysis of time survived to an event and assumes the hazard pertinent to the event (e.g., death) in one group is proportionate to the same hazard in another group, depending on the underlying risk factors. Since hazard ratios depend on the length of follow-up, caution should be taken when interpreting a single, average HR because this single estimate may ignore the distribution of events during follow-up (Hernán, 2010).

Lung cancer mortality and silicosis morbidity HRs were adjusted for smoking and employment duration, although smoking status was unknown for approximately 31% of

the cohort. Results were stratified by gender in the cancer mortality analysis, but adjusted for gender in the silicosis morbidity analysis. Separate person-time estimates were used for lung cancer mortality and silicosis morbidity. While men represented 47% of the cohort population, 79% of lung cancer deaths and 85% of silicosis cases were observed in men. No lung cancer deaths were observed among silicotics, so that a difference in lung cancer incidence between silicotics and non-silicotics could not be analyzed.

Quantitative exposure estimates were developed using the job exposure matrix (JEM) created for this study by Birk et al. (2010). The JEM was based on over 8,000 combined static (stationary area) and personal total dust, respirable dust, and respirable crystalline silica dust industrial hygiene measurements for approximately 100 production areas/job task code combinations during 1954 through the end of 2005. Average silica concentrations were derived for six primary similar exposure groups between 1938 and the end of 2005, using a historical estimation approach for the early years. Significant reductions in average annual exposure were seen over time, with an average annual exposure of 0.11 mg/m^3 for workers hired prior to 1960 compared with an average of 0.03 mg/m^3 for workers hired after 1960. The greatest average annual exposures were seen among workers in the materials preparation area (0.17 mg/m^3). Greater than 40% of the cohort accumulated less than 0.5 mg/m^3-years and nearly 70% of the cohort had average annual exposures less than 0.05 mg/m^3; these cutoff points determined the respective reference groups for cumulative exposure and average annual exposure (Birk et al., 2010; Mundt et al., 2011). Thus, the risks for average annual exposures below 0.05 mg/m^3 were not evaluated for either silicosis or lung cancer in Mundt et al. (2011). The silica exposure levels among porcelain workers in this study are lower than have been reported in other industry studies. For example, the median of the average annual exposure in a study of North American industrial sand workers was 0.15 mg/m^3 (Hughes et al, 2001) and among U.S. granite workers it was 0.05 mg/m^3 (Costello and Graham, 1988).

For average annual exposure, cut points were established at ≤ 0.05 (reference), > 0.05–0.1, > 0.1–0.15, > 0.15–0.2, and > 0.2 mg/m^3. Cut points used for categorizing

cumulative silica exposure were first set at ≤ 0.5 (reference), > 0.5–1.0, >1.0–1.5, and > 1.5–3.0 mg/m^3-years; however, because the authors observed no evidence of increased lung cancer mortality or silicosis morbidity risk in these categories, they then redefined the reference group as ≤ 3.0 mg/m^3-years and established exposure cut points at >3–4, >4–5, >5–6, and > 6 mg/m^3-years. Re-grouping the reference group and re-stratifying the exposure categories in this manner created a baseline with a greater exposure level, lessening the gap between reference and effect levels, and therefore diminishing effects that could have otherwise been elucidated if the reference group remained at ≤ 0.5.

Mundt et al. (2011) reported an exposure-response trend with radiographic silicosis hazard ratios of 5.3, 7.3, and 6.8 for cumulative exposures >4 to 5, >5 to 6, and >6 mg/m^3-year, respectively, adjusted for age, gender, and smoking. Silicosis hazard ratios were 1.1, 3.3, 13.6, and 23.2 for average annual exposures >0.05-0.1, >0.1-0.15, >0.15-0.2, and >0.2 mg/m^3, respectively; the hazard ratios increased with increased average annual exposure, adjusted for duration of employment.

After controlling for age and smoking, the HRs for lung cancer mortality associated with cumulative exposure were not statistically elevated for males or females. However, there was a fairly consistent trend of increasing risk among males, with likely attenuation above 6.0 mg/m^3-years. The female HR estimates are uninformative since four exposure strata, including the reference level, contained only one case. The relative HRs raise questions about individual smoking status, which was unknown for 31% of the population; smoking status was unknown for 11 of the 20 female cases. Observing lung cancer among non-smokers is unusual in most occupational cohorts, and it's unknown whether other exposures – such as glaze pigments or furnace emissions – could have influenced the study. Short-term employees are of particular concern because they may have been heavier smokers than long-term employees, or they may have been subjects of exposure misclassification (i.e., left employment because of high exposure conditions that were not accurately captured in this retrospective exposure assessment).

The lung cancer mortality HRs associated with average annual exposure were statistically significant in two of the four average annual exposure groups: 2.1 (95% CI 1.1-4.0) for average annual exposure group >0.05-0.1 mg/m^3 and 2.4 (95% CI 1.1-5.2) for average annual exposure group >0.15-0.2 mg/m^3, controlling for age, smoking, and duration of employment. The authors reported more than 99% statistical power to detect a relative risk for lung cancer of 1.5 at $\alpha = 0.05$. However, it was unclear whether enough workers were exposed above 3.0 mg/m^3-years to detect a trend when using exposure to < 3 mg/m^3-years as the reference group (Table 2 of Mundt et al.).

Mundt et al. (2011) notes that the validity of the exposure assessment was evidenced by the "strong and statistically significant association seen between respirable crystalline silica exposure and silicosis," but the study does not support exclusion of lung cancer mortality risk based on the exposure assessment alone. Silicosis morbidity could be a more sensitive endpoint than lung cancer mortality: Unlike lung cancer, silicosis is well-known as a signature disease – an outcome only associated with silica exposure and not in the general population – allowing for more definitive attribution of silicosis cases to crystalline silica exposure. Therefore, OSHA noted several limitations that might preclude the conclusion that there was no association between silica exposure and lung cancer.

The mean age of the cohort at the start of follow-up was 35 years (Birk et al., 2009); thus, this was a relatively young cohort in which to observe lung cancer, which typically has a long latency period. Birk et al. (2009) also acknowledged that workers who were 75 years of age or older were excluded from the analysis because records were missing for many of those workers. The authors claimed this would not have affected the results because there were very few person-years in this age group. However, OSHA noted that the absence of findings of an increased risk of lung cancer mortality might have been influenced by the relatively young age of this cohort and the short follow up period. The reported median age at silicosis determination was only 56 years old and only 9.2% of the cohort was deceased by the end of the follow up period. Mundt et al. (2011) acknowledges this limitation and the value of extended follow up, stating that the lack of

increased risk of lung cancer was a preliminary finding and that consistent associations could not be made. There was also a very strong healthy worker effect observed for lung cancer in this population (SMR = 0.71, 95% CI = 0.56-0.89 for men; SMR = 0.72, 95% CI = 0.44-1.12 for women) (Birk et al., 2009).

For the lung cancer analysis, the authors did not consider lagged exposures. The method of using the lagged exposure increased the exposure-response for silicosis, but it's unclear why the authors did not consider lagged exposure for cancer. Even though silicotics in other studies were reported to have subsequently died of lung cancer (even in studies that did not link silicosis with lung cancer), Mundt et al. (2011) did not observe any silicotics who developed lung cancer. The fact that 75% of cohort members with silicosis were still alive at the end of the follow-up period suggests that a longer follow-up period may have been a more adequate way to detect lung cancer among this population.

A separate analysis performed for silicosis (Table 3 in Mundt et al., 2011; erratum Table 3 in Mundt et al., 2012) determined HRs for only those workers who were hired since 1960, apparently when there was greater certainty about exposure estimates. This increased the HR for silicosis in the >4-5 mg/m^3-years and >6 mg/m^3-years group, but there were no silicosis cases in the >5-6 mg/m^3-years group. The study authors do acknowledge some possible exposure misclassification in the lower exposure groups because some silicosis cases were detected in those groups.

The authors suggest the possibility of a threshold for lung cancer mortality; however, no formal threshold analysis was conducted in this study. Elevated hazard ratios were observed among the lower exposure groups, a statistically significant finding, with no apparent trend associated with increasing exposure.

The inclusion of female workers in this study may have depressed the effects noticed in previous studies on male workers. Risks of silicosis were lower among females, possibly because they did not have job assignments with exposures as high as

males. The number of cancer cases in females appeared to be too small (i.e., n=20) to make conclusions; nonetheless, the authors conducted a separate analysis of lung cancer among women, and found no pattern in the HRs by exposure group. There is no explanation given why men and women were combined for the analysis of silicosis risk, but not combined for the analysis of lung cancer risk.

Comparison of Gamble and OSHA Reviews of Association between Respirable Crystalline Silica and Lung Cancer

In March of 2009, 27 scientists from eight countries participated in an International Agency for Research on Cancer (IARC) review to reassess carcinogenicity of silica, other dusts, fibers, metals, and arsenic, which were previously classified as Group 1 carcinogens (carcinogenic to humans) (IARC, 2009). The Working Group noted the increased risk of lung cancer observed in various silica studies and reaffirmed that crystalline silica dust is a Group 1 carcinogen (IARC, 2012).

Gamble (2011) reviewed the studies that IARC considered in reaching its conclusion that there is a causal link between crystalline silica and lung cancer as well as additional studies that were published after the IARC review. Gamble's overall conclusions were based on 19 exposure-response trends from 18 cohorts, and he determined whether there was evidence of causality and exposure-response relationships between respirable crystalline silica and lung cancer in each cohort. OSHA evaluated most of the studies that Gamble reviewed, and Table 2, organized into the cohorts identified by Gamble, compares Gamble's conclusions with OSHA conclusions reported in the OSHA background document for respirable crystalline silica (OSHA, 2013). The table also notes where OSHA and Gamble's conclusions were based on different studies of the same cohort.

Gamble concluded that the weight of the evidence from occupational epidemiology studies does not support a causal association between lung cancer and crystalline silica exposure. In contrast OSHA preliminarily concluded that the human studies the Agency reviewed provided ample evidence that exposure to respirable crystalline silica increased the risk of lung cancer among exposed workers.

Table 2. Comparison of Gamble and OSHA Interpretations for Respirable Crystalline Silica Studies

Cohort and Reference[a]	Evidence of Causality?		Evidence of Exposure Response?		Comments
	Gamble	OSHA	Gamble	OSHA	
U.S. Gold Mining Steenland and Brown (1995a) Steenland and Brown (1995b)	No	No	No	No	
Vermont Granite Attfield and Costello (2004) Graham et al. (2004) **Gamble:** Vacek et al. (2009; 2011 [2010 Epub])	No, based on Vacek et al. (2009 and 2011)	Yes, based on Attfield and Costello	No, based on Vacek et al. (2009 and 2011)	Yes, based on Attfield and Costello.	The Graham et al. study and an apparently unpublished study by Vacek et al. (2009) found no difference in mortality rate between workers hired before and after dust controls were implemented, suggesting no association between silica exposure and lung cancer. However, **OSHA** believed that results of the Attfield and Costello (2004) study, based on a quantitative exposure assessment for each cohort member, provided evidence of a causal relationship. The background document offered possible explanations for the reduced standardized rate ratio (SRR) in the highest exposure group in the Attfield and Costello study (e.g., exposure misclassification, survivor effect). OSHA used the Attfield and Costello study in its risk assessment. **Gamble** placed greater importance than OSHA on the

Cohort and Reference[a]	Evidence of Causality?		Evidence of Exposure Response?		Comments
	Gamble	OSHA	Gamble	OSHA	
					"intervention design" studies by Graham et al. and Vacek et al. (2009), noting that the intervention study design is the most powerful design. Gamble described an intervention design study as comparing mortality before and after installation of dust controls (i.e., in pre- versus post-1940 hires). **Gamble** disputed the explanations for why excluding the high exposure group in the Attfield and Costello study was appropriate, and stated that the findings from the Vacek et al. (2011) exposure-response studies supported the findings of the intervention studies. Gamble concluded that the more recent studies by Vacek et al. should supersede the Attfield and Costello and the Graham et al. studies, apparently because the Vacek et al. studies had increased numbers of cohort members, improved exposure estimates, and an extended follow-up period. As explained in more detail above, **OSHA** noted the following limitations in the Vacek et al. (2011) study: the exposure-response analysis included workers from the highest exposure groups which were the most uncertain and disproportionally affected the exposure-response trend, therefore failing to explore exposure-response relationships at lower exposures found in modern operations; author's conclusions that increased lung cancer is related to smoking is not supported by findings

Cohort and Reference[a]	Evidence of Causality?		Evidence of Exposure Response?		Comments
	Gamble	OSHA	Gamble	OSHA	
					for other smoking-related diseases; evidence of confounding in regression models; failure to account for healthy worker effect; likely overestimate of smokers; and lack of age adjustment for granite cohort versus general population.
Diatomaceous Earth Checkoway et al. (1997) Rice et al. (2001)	No	Yes	No	Yes	**OSHA** noted that the authors found a positive but not monotonic dose-response trend and the increased risk ratio was statistically significant in the highest exposure group. The Rice analysis was used in OSHA's risk assessment. **Gamble** concluded that the studies were unreliable because of bias, confounding and exposure misclassification in pre 1930 hires, who may have been exposed to asbestos and to lower levels of silica than estimated. After conducting his own analysis to reduce exposure misclassification and confounding by eliminating pre 1930 hires and adjusting for smoking, Gamble found no significant associations. **OSHA** discussed analyses conducted to determine possible confounding by asbestos exposure or smoking and those analyses demonstrated that the Checkoway et al. findings were not likely confounded by either smoking or asbestos. In addition, in their analyses, Checkoway included only workers whose exposure to silica and asbestos could be quantified.

Cohort and Reference[a]	Evidence of Causality?		Evidence of Exposure Response?		Comments
	Gamble	OSHA	Gamble	OSHA	
UK Pottery Cherry et al. (1998)	No	Yes	No	Yes	**OSHA** noted that mean exposure was related to cancer, and silica exposures were higher in cases than controls. **Gamble** noted numerous limitations including lack of effect with cumulative exposure, questionable adjustment for confounding, possible contribution of polycyclic aromatic hydrocarbons, and possible bias because of destroyed records for many cases.
Chinese Pottery **Gamble:** Chen et al. (2007) **OSHA:** McLaughlin et al. (1992)	No, based on Chen et al.	Yes (weak), based on McLaughlin et al.	No, based on Chen et al.	Yes (weak), based on McLaughlin et al.	The McLaughlin et al. study provided some evidence of an association between silica and lung cancer but the dose-response relationship did not show a strong trend. **Gamble** noted that the updated study by Chen et al. did not show a causal relationship between silica and lung cancer. However, IARC (2012) noted the high correlation between silica and polycyclic aromatic hydrocarbon (PAH) exposures in this cohort and that adjustments for PAHs by McLaughlin et al. increased relative risks. **Gamble** stated that the Chen et al. (2007) study was an improvement over the original study because it better separated out confounding effects. The **OSHA** review of the Chen et al. (2007) paper is discussed below. OSHA concluded that because of the high correlation between silica and PAHs, the lack of effect on lung cancer after adjustment for PAHs simply

Cohort and Reference[a]	Evidence of Causality?		Evidence of Exposure Response?		Comments
	Gamble	OSHA	Gamble	OSHA	
					means that the effects of the two compounds cannot be separated.
Sardinia, Silicotic Miners Carta et al. (2001)	No	No	No	No	
South African Gold Mining Hnizdo et al. (1997)	Yes	Yes	Yes	Yes	**OSHA** concluded that of the South African mining studies, this study used the most detailed exposure estimates, thus reducing the possibility of exposure misclassification. Although not conclusive in isolation, OSHA believed the body of evidence from the South African studies is suggestive of an exposure-related association with lung cancer. Although **Gamble's** conclusions about this study were consistent with OSHA's, he concluded that the body of evidence from mining studies did not support an association between lung cancer and silica exposure. He also noted the authors' observation that results of this study are inconsistent from other mining studies and discussed possible confounding by radon.
South African Gold Mining Reid and Sluis-Cremer	Equivocal	Yes (Apparent causality if the database	Equivocal	Non-applicable (N/A)	Although study authors attributed increased lung cancer mortality to lifestyle choices, **OSHA** noted associations with other health endpoints related to silica, such as renal failure and chronic

Cohort and Reference[a]	Evidence of Causality?		Evidence of Exposure Response?		Comments
	Gamble	OSHA	Gamble	OSHA	
(1996)		as a whole is considered.)			obstructive pulmonary disease**.** In addition, the elevated odds ratio (OR) was nearly statistically significant. Therefore, OSHA did not consider this study to be inconsistent with Hnizdo et al. (1997).
South African Gold Mining[b] Hessel et al. (1986) Hessel et al. (1990)	No	Unreliable	No	Unreliable	Hnizdo et al. (1991, 1997) have suggested that these studies might have been biased towards the null by overmatching for exposure and including smoking as a matching criterion (Hessel et al., 1986), or by not matching on date of birth (Hessel et al., 1990). **Gamble** also expressed bias from overmatching as a possible limitation.
Australia Gold Mining de Klerk and Musk (1998)	No	No in non-silicotics Yes, in silicotics	No	N/A	Regarding the observation that lung cancer was increased in silicotics, **Gamble** stated "This suggests that silicosis is an intermediary, and therefore the usual statistical methods of adjusting for confounders do not provide interpretable results."
Chinese Tungsten **Gamble:** Chen et al. (2007) **OSHA:** McLaughlin et al. (1992)	No, based on Chen et al.	No, based on McLaughlin et al.	No, based on Chen et al.	No, based on McLaughlin et al.	
Chinese Tin-Limu	Equivocal	Unreliable	Equivocal	Unreliable	**OSHA** concluded that because silica and arsenic were highly correlated, quantifying the effect of

Cohort and Reference[a]	Evidence of Causality?		Evidence of Exposure Response?		Comments
	Gamble	OSHA	Gamble	OSHA	
Chen and Chen (2002)					silica was not possible. **Gamble** noted the small number of cases at Limu but noted that results did not support an exposure response relationship. Despite the non-monotonic exposure-response trend and instability, Gamble classified the results as equivocal because of the high OR in the high exposure category.
Chinese Fe/Cu Mining **Gamble:** Chen et al. (2007) **OSHA:** McLaughlin et al. (1992)	No, based on Chen et al.	No, based on McLaughlin et al.	No, based on Chen et al.	No, based on McLaughlin et al.	
Finnish Granite Koskela et al. (1994)	No	No	No	No	
German Stone/Pottery Ulm et al. (1999)	No	Unreliable	No	Unreliable	**OSHA** discounted this study because of low exposures, limited cohort size, and imprecise methods of exposure classification. Exclusion of silicotics would have tended to over select workers with lowest exposures, and exposures were likely below the current silica PEL. Both OSHA and IARC (2012) noted low power of the study. **Gamble** presented the following arguments against low power of the study: (1) Loss in power by excluding silicotics is not known; (2) the

Cohort and Reference[a]	Evidence of Causality?		Evidence of Exposure Response?		Comments
	Gamble	OSHA	Gamble	OSHA	
					number of cases (114) is similar to the Chinese pottery study (n=120) and higher than the UK pottery study (n=52); (3) cumulative exposures seem to be comparable to the UK pottery study.
U.S. Industrial Sand Steenland and Sanderson (2001)	Yes	Yes	Yes	Yes	
U.S. Industrial Sand McDonald et al. (2001) Hughes et al. (2001) McDonald et al. (2005)	Yes	Yes	Yes	Yes	**OSHA** believed the studies of this cohort were the most thorough and complete of the industrial sand studies because of exposure data for individual cohort members based on modern methods of collection, availability of smoking histories, long-term work experience, and use of a nested case-control design. Data from the Hughes et al. (2001) study were used in the OSHA risk assessment.
UK Industrial Sand Brown and Rushton (2005a) Brown and Rushton (2005b)	No	Unreliable	No	Unreliable	**OSHA** believed that these findings should be discounted due to low cumulative exposures, unusual distribution of lung cancer deaths among short-tenured workers, the young cohort with inadequate accumulation of exposure years, possible confounding or misclassification, and lack of nested case-control study design. IARC (2012) also noted limitations such as low silica exposures, unusual lung cancer distribution, and low power.

Cohort and Reference[a]	Evidence of Causality?		Evidence of Exposure Response?		Comments
	Gamble	OSHA	Gamble	OSHA	
					Gamble concluded this was clearly a negative study and refuted many criticisms of the study (i.e., exposures were also low in the U.S. studies; and average follow-up time of 28 years was adequate). **OSHA** did verify in the background document that exposures were lower in the Brown and Rushton cohort than in the ten cohorts examined in the pooled analysis by Steenland et al. (2001). The background document also noted that for the Brown and Rushton cohort, over one-half of the deaths and almost three-fourths of the lung cancer mortalities had less than 10 years of service.
German Porcelain Mundt et al. (2011)	No	Preliminary results, inconclusive	No	Preliminary results, inconclusive	As described in more detail in the review of this study above, **OSHA** noted these limitations: findings are preliminary due to deaths in only 9.2% of the cohort; the cohort was young (mean age 35) and workers 75 years or older were excluded; regrouping of the reference group into a cumulative exposure category of < 3.0 mg/m^3-year and restratification of exposure categories resulted in a baseline with greater exposures and therefore diminished ability to see effects; it was unclear if enough workers were exposed to levels above 3.0 mg/m^3-year to detect a trend; results were uninformative for women due to the low number of cases among women; the cancer analysis was not lagged; and there was evidence

Cohort and Reference[a]	Evidence of Causality?		Evidence of Exposure Response?		Comments
	Gamble	OSHA	Gamble	OSHA	
					of exposure misclassification.

[a]The cohorts listed in this table were those identified by Gamble in Table 1 of his review. Most of the studies referenced in this table were part of a series of studies of the same cohort. For simplicity, only the most recent or key studies referenced by Gamble or OSHA are included.

[b]These South African gold mining studies were not identified as a cohort by Gamble, possibly because they overlapped with the other South African gold mining studies listed in the table. However, this study is listed in the Table on page 460 of the Gamble review, and was listed consistently in this table here. It appears to be the basis of Gamble's statements about his review of 19 exposure-response analyses from 18 cohorts.

In addition to the studies discussed by Gamble and summarized in Table 2, above, the OSHA background document discussed a study of British Coal miners by Miller and MacCalman (2009). Gamble did not discuss the Miller and MacCalman study. OSHA found it to be a credible study that provided convincing evidence of the carcinogenicity of respirable crystalline silica, and the study was used in OSHA's risk assessment. That study further adds to the weight of evidence that respirable silica exposure is associated with lung cancer.

For cohorts addressed in Table 2, the section below presents Gamble's major points as well as the basis for the differing findings by Gamble and OSHA, where relevant.

1. Gamble noted that studies reported discordant findings and the majority showed no association between crystalline silica and lung cancer.

For the studies of cohorts summarized in Table 2, Gamble indicated that five (two of which he classified as equivocal) provided evidence of a causal relationship, while 14 provided no evidence of a causal association between respirable crystalline silica exposure and lung cancer. In contrast, OSHA preliminarily concluded that nine of the studies in Table 2 provided evidence of an association, five did not provide evidence of an association, and five of the studies should be discounted because of limitations.

In contrast to Gamble, OSHA interpreted the majority of reliable studies (i.e., studies that it did not discount because of study design limitations) in Table 2 as showing evidence of an association between respirable silica exposure and lung cancer. Apparent reasons for the differing conclusions of Gamble and OSHA were:

- The conclusion was based on different studies of the same cohort because OSHA and Gamble had differing opinions on which study was most appropriate (e.g., Attfield and Costello, 2004 versus Graham et al., 2004 and Vacek et al., 2009, 2011 for the Vermont

granite worker cohort). Interpretation of the Vermont granite studies is discussed in greater detail below.

- Gamble's decision was influenced by studies that OSHA had not reviewed in the background document (e.g., Vacek et al., 2011 study for Vermont Granite workers; Chen et al., 2007 study for Chinese pottery workers). (Subsequent reviews of these studies did not change OSHA's conclusions.)
- Studies considered to be reliable by OSHA were found to be limited by Gamble (e.g., Checkoway et al., 1997 study for diatomaceous earth workers; Cherry et al., 1998 study for UK pottery workers). In his reanalysis of the Checkoway et al. (1997) study, Gamble found no association between respirable crystalline silica exposure and lung cancer. Gamble's reanalysis is discussed in greater detail below.
- Studies that Gamble based his conclusion on were found to be unreliable by OSHA because of limitations (e.g., Chen and Chen, 2002 study of Chinese Tin-Limu workers; Ulm et al., 1999 study of German stone/pottery workers; Brown and Rushton, 2005a,b study of UK Industrial sand workers).
- When Gamble found studies to be limited, he apparently interpreted them as showing no evidence of an association (e.g., Cherry et al., 1998; Hessel et al., 1986, 1990), whereas the most appropriate conclusion would likely be that the study is inconclusive or unreliable.

Differences between Gamble's and OSHA's conclusions about the Vermont granite and diatomaceous earth cohorts warrant further discussion.

Vermont Granite Studies

In interpreting the Vermont Granite studies, OSHA placed greater weight on quantitative exposure studies, such as the study by Attfield and Costello (2004), than on non-quantitative studies. Both OSHA and IARC considered the lack of quantitative exposure information in the Graham et al. (2004) study to be a limitation. As noted in the OSHA background document, dust

levels decreased gradually from the time controls were introduced in 1940 through the time they were fully implemented in 1955. Although most workers were likely exposed to lower levels of dust as controls were being implemented, the levels were likely higher compared to levels after controls were fully implemented.

However, Gamble stated that "intervention design" studies, such as those by Graham et al. (2004) and apparently an unpublished study by Vacek et al. (2009) are the most powerful for assessing causal associations or dust control effectiveness. Gamble described an intervention study as comparing mortality in workers hired before and after installation of dust controls (i.e., in pre- and post-1940 hires). Gamble stated that the intervention studies have comparable weight to the exposure-response analyses and stated that findings from the Vacek et al. (2011) quantitative exposure response study supported the findings from the intervention design studies. Gamble concluded that the most recent studies by Vacek et al (2009, 2011), which had the largest cohort numbers, improved exposure estimates, and longest follow-up period, should supersede the earlier studies by Attfield and Costello (2004) and Graham et al. (2004). However, OSHA found numerous limitations for the Vacek et al. (2011) study, as described in the detailed summary above and in Table 2, and did not consider it to be the key study for the Vermont granite cohort.

One notable, possible limitation of the Vacek et al. (2011) study is that the exposure estimates they used (from Verma et al., 2011) may not actually be an improvement over those used by Attfield and Costello (2004). A major difference between the two exposure estimates is that exposures for channel bar operators were estimated to be much lower by Verma et al. than by Attfield and Costello. Verma et al. state that their estimates for channel bar operators were much lower because those workers were doing wet drilling, while Attfield and Costello's estimates are based on dry drilling. However, such an assumption about wet drilling would fail to account for dust generated from other activities conducted in the same area or that water may not have always been used during channel bar drilling. Actual conditions in Vermont quarries in the 1940s can be viewed at http://quarriesandbeyond.org/.

The differences between the Verma et al. (2011) and Attfield and Costello (2004) estimates for wet channel operators could result in those workers being assigned from a higher to a lower or reference group category. If the channel bar operators were incorrectly placed in the reference group, the exposure-response relationship would be attenuated.

Diatomaceous Earth Studies

OSHA found the Checkoway et al. (1997) study of diatomaceous earth workers to be one of the key studies for assessing associations between respirable crystalline silica and lung cancer. However, Gamble concluded that the study was unreliable because of bias, confounding, and exposure misclassification before 1930, resulting from uncertain exposure estimates and possible co-exposure to asbestos. Gamble also claimed that, before 1930, uncalcined products, consisting mainly of amorphous silica and less than 5% quartz, were the primary products at the plant and therefore silica exposures may have been overestimated in the pre-1930 hires. However, Checkoway et al. (1998) stated that their exposure estimates were based on company records reporting crystalline silica concentrations in different products and annual production of natural, calcined, or flux-calcined diatomaceous earth.

Gamble conducted his own analysis to reduce exposure misclassification and address confounders by eliminating pre-1930 hires and adjusting for smoking; Gamble's reanalysis found no significant associations between lung cancer and silica exposure. However, OSHA previously examined possible confounding by asbestos and smoking in the Checkoway et al. (1997) study and continues to maintain that confounding likely did not influence the outcomes of the study (OSHA, 2013).

Checkoway et al. (1996) was able to quantitatively characterize asbestos exposures in workers hired after 1930 and determined that asbestos did not likely confound the association between silica exposure and lung cancer. The Checkoway et al. (1997) study, which included pre

1930 hires, updated the cohort from the Checkoway et al. (1993) study by excluding 317 workers whose exposures could not be adequately quantified and including 89 previously excluded workers whose asbestos exposures could be quantified. No confounding by asbestos was observed in this study which included only workers with the best exposure estimates.

Gamble demonstrated that adjustment for smoking resulted in reduced relative risks for the Checkoway et al. (1997) study. Checkoway et al. (1997) also demonstrated a decrease in relative risk from 2.15 to 1.67 in the highest exposure category by applying a worst case estimate of 20 times greater lung cancer risk in smokers compared to nonsmokers. Rice et al. (2001) noted that although the two highest exposure groups had comparable smoking prevalence, they had substantially different rate ratios (1.26 versus 2.15). They also noted that smoking prevalence was not related to cumulative crystalline silica exposure. Therefore, the evidence suggested that smoking did not likely confound the result in the Checkoway et al. (1997) study.

Weight of Evidence Approaches

In general, OSHA and Gamble had fundamentally different approaches for weighing the evidence. OSHA emphasized that the findings of the best designed studies are more important than the total numbers of studies showing or not showing associations between respirable crystalline silica exposure and lung cancer. While Gamble tended to add up the total of positive and negative studies, OSHA placed the greatest weight on the best designed studies. An example of the different approaches for weighing the evidence was demonstrated by the evaluation of the Hessel et al. (1986, 1990) studies on South African gold miners. While both OSHA and Gamble noted bias from overmatching, OSHA considered the Hessel et al. studies to be unreliable; Gamble, however, counted the studies as showing no association between silica and lung cancer and included them as part of the weight of the evidence. Another example was the Cherry et al. (1998) on British pottery workers. Although the study showed that lung cancer was related to average silica exposure and was considered to be a key study by OSHA, Gamble felt the study was limited by confounding and bias. Instead of labeling it as unreliable or inconclusive, though,

Gamble weighed it as showing no evidence of an association. As noted above, OSHA did not consider studies it judged to be unreliable in assessing the weight of evidence for carcinogenic potential of silica.

OSHA gave studies greater weight and consideration if they (1) included a robust number of workers; (2) had adequate length of follow-up; (3) had sufficient power to detect modest increases in lung cancer incidence and mortality; (4) used quantitative exposure data of sufficient quality to avoid exposure misclassification; (5) evaluated exposure-response relationships between exposure to silica and lung cancer; and (6) considered confounding factors including smoking and exposure to other carcinogens.

OSHA noted that the following studies from five industry sectors met the Agency's criteria for the best designed studies:

- Diatomaceous earth (Checkoway et al., 1997)
- British pottery (Cherry et al., 1998)
- Vermont granite (Attfield and Costello, 2004)
- North American industrial sand (Hughes et al., 2001; McDonald et al., 2001, 2005; Steenland and Sanderson, 2001)
- British coal mining (Miller and MacCalman, 2009)

Collectively the studies of the cohorts listed above, in addition to the pooled analysis (Steenland et al., 2001), provided evidence of an association between exposure to respirable crystalline silica and lung cancer.

Studies Not Included in the Background Document (OSHA 2013)

Since the background document was written, two new studies examining possible associations between exposure to respirable crystalline silica and lung cancer were published,

one examining the Vermont granite cohort (Vacek et al., 2011) and one of German porcelain workers (Mundt et al., 2011). Both of these studies are reviewed above, and OSHA did not consider either of them to be key studies.

In addition, a study by Chen et al. (2007), examining the same cohorts of Chinese pottery workers, iron/copper miners, and tungsten miners that were examined by McLaughlin et al. (1992), was discussed by Gamble but was not reviewed in the OSHA background document. Therefore we review the study at this time. Our review of the Chen et al. (2007) study is limited to the Chinese pottery workers cohort because that was the only result that differed from that reported by McLaughlin et al. (1992). Whereas McLaughlin et al. (1992) reported a weak association between exposure to respirable crystalline silica and lung cancer, Chen et al. (2007) reported no association for pottery workers.

The nested case-control study of Chinese pottery workers by Chen et al. (2007) included 120 cases and 459 controls, a greater number than the 62 cases and 238 controls in the McLaughlin et al. (1992) study. Whereas McLaughlin et al. (1992) reported estimated percentages of respirable dust and silica content of total dust only for facilities, Chen et al. (2007) estimated average values for each facility, job title, and calendar year. Chen et al. (2007) also estimated cumulative exposures by using a conversion factor for total dust and respirable silica. They estimated exposure to polycyclic aromatic hydrocarbons (PAHs) based on monitoring conducted between 1987 and 1988. Possible association between respirable silica exposure and lung cancer mortality was determined by conditional logistic regression analysis, a matched-regression method. Chen et al. (2007) reported that the method allowed for control of residual confounding by smoking and occupational confounders such as PAH.

Chen et al. (2007) stratified cumulative respirable crystalline silica exposure into the following quintiles: 0.1–1.1, 1.1–2.6, 2.6–5.4, 5.4–10.1, and 10.1–72.4 mg/m^3-year. Exposure to PAHs and respirable crystalline silica were highly correlated (Pearson's correlation coefficient = 0.57–0.80). In pottery workers, odds ratios (95% CI) for lung cancer mortality, lagged for 15

years and adjusted for smoking, in each respective silica exposure category were 0.8 (0.29, 2.19), 1.3 (0.63, 2.64), 1.7 (0.82, 3.58), 1.5 (0.71, 3.21), and 3.5 (1.45, 8.66). When the values were adjusted for both smoking and PAH exposure, respective odds ratios (95% CI) were 0.7 (0.25, 1.98), 0.7 (0.29, 1.81), 0.7 (0.25, 2.19), 0.5 (0.15, 1.84), and 0.9 (0.19-4.32). Therefore, Chen et al. concluded that risk of lung cancer in Chinese pottery workers was related to PAH exposure and not to respirable crystalline silica exposure.

However, as was noted above, exposures to respirable silica and PAHs were highly correlated in Chinese miners and pottery workers (r = 0.057–0.80). OSHA notes that if respirable crystalline silica and PAHs exposures are correlated, the fact that the association between respirable crystalline silica and lung cancer becomes nonsignificant after adjustment for PAHs does not mean that respirable crystalline silica is not a risk factor. It means that the effects of the two exposures cannot be separated and that PAHs are adjusting out the real effect of respirable crystalline silica. A pooled analysis of the mining and pottery cohorts also showed no association between respirable crystalline silica exposure and lung cancer.

McLaughlin et al. (1992) did adjust for PAH exposure in their analysis, but Gamble (2011) claimed that the Chen et al. (2007) study better separated out confounders. The IARC working group noted the high correlation (r = 0.56) between silica and PAH exposure in this cohort and that the original adjustment for PAHs in the analysis by McLaughlin et al. raised rather than lowered relative risks (IARC, 2012). The 2012 monograph from the IARC working group does not express preference for either the McLaughlin et al. or Chen et al. study Section 2.3 “Synthesis” of the IARC (2012) monograph states “in another (Chinese pottery workers), adjustment for PAHs removed a significant crystalline silica exposure effect. . .” That statement from the IARC working group implies that confounding could not be resolved in the cohort of Chinese pottery workers.

Regardless, the Chinese pottery cohort was not one of the key ones that influenced OSHA’s decision. The Chinese pottery cohort, represented by hundreds of workers, was much

smaller than the Vermont granite, U.S. industrial sand, UK pottery, diatomaceous earth, and UK coal mining cohorts, which were comprised of thousands of workers. Although the Chinese pottery cohort was included in the IARC pooled analysis, removal of the Chinese study from the pooled analysis did not appreciably change the exposure coefficient (Steenland et al., 2001). Therefore, the findings from the Chen et al. (2007) pottery workers cohort are unlikely to affect the weight of evidence for determining an association between respirable crystalline silica exposure and lung cancer.

2. Gamble noted a tendency for studies with higher cumulative exposures to have weak or non-existent associations.

As indicated above, OSHA found that studies in diatomaceous earth workers, British pottery workers, Vermont granite workers, North American sand workers, and British coal mining workers were well designed and provided evidence of an association between respirable crystalline silica exposure and lung cancer. Studies in those cohorts demonstrated exposure-response relationships between exposure to respirable crystalline silica and lung cancer mortality. With the exception of the British pottery worker study that demonstrated exposure-response relationships only with average exposures (Cherry et al., 1998), the studies reported associations with cumulative exposures (Checkoway et al., 1997; Attfield and Costello, 2004; Graham et al., 2004; Hughes et al., 2001; McDonald et al., 2001, 2005; Steenland and Sanderson, 2001; Miller and MacCalman, 2009). Table 3 summarizes unit risks per exposure category of cumulative exposure for the key studies that provided that information.

As noted in Table 3, most studies demonstrated positive exposure-response trends, especially at higher exposures. An exception was the study by Attfield and Costello (2004) that demonstrated a negative exposure-response trend at the highest exposure category. As noted in the OSHA background document, Attfield and Costello (2004) stated that underlying exposure data for the highest exposure group was more likely to include unreliable exposure estimates because 83 percent of the workers in that group had 20 or more years of exposure before the

introduction of controls, when exposure measurements were most uncertain. They also noted possibilities of “a highly selected healthy worker” effect and that lung cancer may have been obscured by competing high rates of silicosis and tuberculosis deaths. The “highly selected healthy worker effect” describes a situation where short term workers might leave the workplace because of disease, resulting in lower cumulative exposures or depletion of susceptible workers (Stayner et al., 2003). Medical surveillance leading to removal of affected workers from the exposure can also complicate exposure estimates (Park and Chen, 2012). Therefore, even given the negative exposure-response trend in Attfield and Costello’s highest exposure category, the key studies overall support an exposure-related trend.

Table 3. Unit Risks for Categories of Exposure in Key Respirable Crystalline Silica Studies

Cohort and Reference	**Unit Risk for Increasing Categories of Exposure**
Diatomaceous Earth (Checkoway et al., 1997)	SRR (95% CI) for lung cancer for cumulative exposure lagged 15 years: 1.00, 0.96 (0.47–1.98), 0.77 (0.35–1.72), 1.26 (0.62–2.57) and 2.15 (1.08–4.28); trend slope (adjusted) = 1.05 (95% CI 0.99-1.11)
Vermont Granite (Attfield and Costello, 2004)	SMRs for lung cancer mortality, for untransformed cumulative exposure lagged 15 years: 77, 98, 126, 125, 133, 147, 170, and 116 (trend not significant with high exposure group; $p<0.005$ without high exposure group)
U.S. Industrial Sand (McDonald et al., 2005)	For cumulative exposure lagged 15 years, lung cancer odds ratios were: 1.00, 0.94, 2.24, and 2.66 (p for trend = 0.006).
U.S. Industrial Sand (Hughes et al,. 2001)	Lung cancer mortality odds ratios lagged 15 years for cumulative exposures: 1.00, 0.84, 2.02 and 2.07 (p for trend = 0.04).
U.S. Industrial Sand (Steenland and Sanderson, 2001)	Lung cancer mortality odds ratio lagged 15 years for cumulative exposure: 1.0, 1.35, 1.63 , 2.00 (p for trend = 0.08)

Consistent with Gamble, OSHA acknowledged that the associations between exposure to respirable crystalline silica and lung cancer are not strong. OSHA further noted that the weak

effect makes it more difficult to detect association because errors in exposure estimates or outcomes tend to bias results toward the null. Because it is more difficult to detect an increased cancer risk for low-potency carcinogens, inconsistent findings are expected and do not preclude concluding that a compound is carcinogenic. Furthermore, a study that does not show a statistically significant increase in carcinogenicity may not necessarily be inconsistent with a study that does show a statistically significant increase. A closer examination of the study with the nonsignificant findings may reveal trends that are consistent with the study showing a significant association. An example is the Hnizdo et al. (1997) and Reid and Sluis-Cremer (1996) studies in miners.

To address the inconsistent study results, OSHA considered pooled exposure-response analyses looking at larger numbers of subjects. IARC sponsored a pooled exposure-response and risk assessment for lung cancer in 10 cohorts of silica-exposed workers, with 65,980 workers and 1,072 lung cancer deaths (Steenland et al., 2001). Steenland et al. (2001) found a monotonic increase in lung cancer odds ratios with quintiles of cumulative exposure, cumulative exposure lagged 15 years, and average respirable silica concentration. For the pooled categorical analysis with cumulative exposure lagged 15 years, the odds ratios (95% CI) for ascending quintiles of exposure were 1.0 (0.83-1.3), 1.3 (1.0-1.6), 1.5 (1.2-1.8), and 1.5 (1.2-1.9).

OSHA had Steenland and Bartell conduct a quantitative uncertainty analysis (Toxichemica, 2004). The analysis resulted in a mean pooled exposure coefficient, which was only slightly lower than the coefficient originally reported by Steenland et al. (2001), with a variance around the estimate of the mean comparable to the level of statistical uncertainty associated with the use of the log-linear model in the original analysis. This suggested that uncertainties in exposure estimates were not likely so great that the finding from the original pooled analysis should be questioned.

Gamble (2011) criticized the pooled analysis by Steenland et al. (2001) because: (1) it included the tin miner cohort which he felt should have been excluded because of confounding from arsenic; (2) only four of nine cohorts had statistically significant exposure-response trends;

and (3) five studies were excluded from the analysis. OSHA disagrees with Gamble's criticism because the purpose of the pooled analysis was to see if there was an overall relationship across all studies conducted up to that time for which quantitative exposure data were available . The OSHA background document noted that (1) analysis performed with and without the three Chinese studies, which were possibly confounded, did not result in an appreciable change in the pooled exposure coefficient; (2) the purpose of the pooled analysis was to address inconsistency in study findings and would therefore include studies with no statistically significant findings; and (3) three cohorts that had adequate quantitative exposure data were excluded from the pooled analysis because data were unavailable or because data were incompatible with a case-control study design. In closing, the pooled analysis conducted with large numbers of cases provided additional evidence of an association between exposure to respirable crystalline silica and lung cancer.

Conclusion

The main reason for the discordant conclusion regarding associations between crystalline silica exposure and lung cancer reached by OSHA and Gamble were (1) different opinions regarding the reliability and usefulness of individual studies in the data set and (2) different methods for assessing weight of evidence. In the background document on respirable crystalline silica, OSHA thoroughly evaluated the strengths and limitations of each study; the Agency stands by its interpretations of study reliability. In weighing the evidence, OSHA considered only the best designed studies, and believes that approach is more appropriate than simply summing up the number of positive and negative studies. Based on substantial evidence of an effect in the best designed studies, OSHA maintains that the weight of the evidence supports an association between exposure to respirable crystalline silica and lung cancer.

Review of Cox (2011): An Exposure-Response Threshold for Lung Diseases and Lung Cancer Caused by Crystalline Silica.

An exposure-response threshold for lung diseases in humans caused by exposure to respirable crystalline silica has been theorized, but not conclusively demonstrated. The extrapolation of risk observed in humans exposed to much lower levels remains problematic, including the use of exposure-response models to extrapolate risks observed at higher exposure levels to estimate risks at the lower end of the exposure-response curve. The paper by Cox reviews the evidence for a quantifiable exposure-response threshold in animals based primarily on a biological mode of action through which the inhalation of silica particles induces changes in the lung that lead to the development of lung disease only when a critical lung burden, or threshold, is exceeded. A mode of action is described through which exposure to poorly soluble particles in general, and crystalline silica in particular, can lead to a variety of lung diseases, including silicosis, chronic inflammation, fibrosis, lung cancer, and chronic obstructive pulmonary disease. The paper reviews evidence from animal studies that suggest a threshold exists for a lung burden that triggers inflammation that could lead to a variety of diseases, including both silicosis and lung cancer. However, the conclusion stated in the article that the current PEL for crystalline silica is "probably" below a threshold for lung disease in humans, including cancer, is not supported by the evidence presented.

The paper also asserts that exposure misclassification in human epidemiological studies leads to underestimation of exposure-response thresholds. A mathematical simulation is presented to demonstrate the theoretical effect of exposure measurement error on the ability of an epidemiological study to observe a hypothetical exposure-response threshold. In the simulation, the "true" response threshold is assumed to be 15 mg/m^3-years, such that the risk of disease below the threshold is 0, and the risk above the threshold is 1. A hypothetical population of 10,000 workers is assumed to be uniformly exposed to between 0 and 20 mg/m^3, so that any employee exposed above the threshold of 15 mg/m^3 would be a "case", and employees below the threshold remain disease free. Simulated exposure measurement error is introduced by multiplying the assigned exposure by a random value, k, that is uniformly distributed between 0

and 2, with a mean of 1 (i.e. no error). The randomization results in some individuals who were assigned exposures above the threshold (risk=1) to below the threshold (risk=0), and conversely moves other subjects from below the threshold to above the threshold. The introduction of random measurement error changes the slope of the hypothetical exposure response curve from a step function to a smooth curve, with an "observed" threshold now lower than the assumed value of 15 mg/m^3-years. However, the simulation is based entirely on the unrealistic assumption that a distinct threshold exists below which risk is zero and above which the risk is one, and therefore, provides no empirical evidence of systematic bias in the determination of an actual exposure-response threshold in epidemiologic studies. The author then cites a study that observed diminished lung function at estimated exposures to respirable silica dust in excess of 0.1-0.2 mg/m^3 for 30 to 40 years (Rushton, 2007), and asserts that based on the simulation model, the "true" threshold is likely to be as high as 0.4 mg/m^3, but acknowledges that this estimate is based on unproved assumptions.

OSHA believes that Kuempel et al. (2001) developed a more credible estimate of an exposure threshold for excess risk of lung cancer in humans from exposure to respirable crystalline silica based on biological mechanisms and statistical models. (Kuempel et al., 2001). In this analysis, an evaluation of both linear and nonlinear (threshold) models determined that the average minimum critical quartz lung burden (Mcrit) in rats associated with reduced pulmonary clearance and increased neutrophil inflammation was 0.39 mg quartz/g lung tissue. Mcrit is based on the lowest observed adverse effect level in a study in rats (Porter et al., 2002). A human lung dosimetry model, developed from respirable coal mine dust and quartz exposure and lung burden data in UK coal miners (Tran and Buchanan, 2000), was then used to estimate the human-equivalent working lifetime exposure concentrations associated with lung doses such as Mcrit. An 8-hour time-weighted average (TWA) concentration of 0.036 mg/m^3 over a 45-year working lifetime was estimated to result in a human-equivalent lung burden to the average Mcrit in rats. The human lung burdens associated with working lifetime exposure concentrations (8-hour TWA) of 0.05 and 0.1 mg/m^3 – the current NIOSH REL and OSHA PEL, respectively – were estimated to be 0.54 and 1.08 mg quartz / g lung, respectively. In addition, the 45-year

working lifetime 8-hour TWA concentration associated with the 95% lower confidence limit of Mcrit in the rat was estimated to be 0.005 mg/m^3. This value is consistent with the no observed adverse effect levels for silicosis estimated in human studies (Rice and Stayner, 1995). Kuempel, et al.'s estimates of excess lung cancer risk in humans exposed to crystalline silica, which was based on lung burdens in rats, are similar to those based on the human occupational epidemiology studies. It also suggests that workers exposed for a full working lifetime at current exposure limits have an excess risk of developing lung cancer, whether these risk estimates are derived using models that assume a biological mechanism of direct genotoxicity (low-dose linear) or indirect genotoxicity (non-linear) acting through chronic pulmonary inflammation.

A review of epidemiologic studies has also attempted to answer the question of whether silicosis is a necessary precursor to lung cancer in silica-exposed individuals. Checkoway and Franzblau (2000) reviewed 17 studies of lung cancer mortality among silicotics. They concluded that the question of whether silicosis is required for elevated lung cancer risk in silica-exposed individuals cannot be answered from currently available epidemiologic literature, and that risk assessments should consider silicosis and lung cancer in silica-exposed individuals as separate entities whose cause/effect relations are not necessarily linked.

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