

CHRONIC TOXICITY SUMMARY

SILICA (CRYSTALLINE, RESPIRABLE)*(silicon dioxide, quartz, tridymite, cristobalite)***CAS Registry Number: 7631-86-9****I. Chronic Toxicity Summary**

<i>Inhalation Reference Exposure Level</i>	3 µg/m³ [respirable, as defined occupationally by ACGIH (2004)/ISO (1995)]
<i>Critical effect(s)</i>	Silicosis in miners and other workers
<i>Hazard index target(s)</i>	Respiratory system

II. Physical and Chemical Properties (HSDB, 2001)

<i>Description</i>	Transparent crystals
<i>Molecular formula</i>	SiO ₂
<i>Molecular weight</i>	60.09 g/mol
<i>Density</i>	2.65 g/cm ³ @ 0 °C (quartz)
<i>Melting point</i>	1610 °C
<i>Boiling point</i>	2230 °C (2503.20 °K)
<i>Vapor pressure</i>	10 torr @ 1732 °C
<i>Solubility</i>	Practically insoluble in water or acids, except hydrofluoric acid; very slightly sol. in alkali.
<i>Conversion factor</i>	Not applicable

In crystalline silica, the silicon and oxygen atoms are arranged in a definite regular pattern throughout the crystal. The characteristic crystal faces of a crystalline form of silica are the outward expression of this regular arrangement of the atoms (HSDB, 2001). This REL is meant to be applied only to particles of crystalline silica (quartz, cristobalite, tridymite), of respirable size, as defined by the occupational hygiene methods described by ACGIH (2004)/ISO (1995) which has a 50% cut-point at 4 µm particle aerodynamic diameter. This occupational definition of respirable differs from the environmental definition of respirable, which is PM₁₀. (The occupational particle category “thoracic” has a 50% cut-point at 10 µm particle diameter (ACGIH, 2004) and the category “inhalable” has a 50% cut-point at 100 µm particle diameter (ACGIH, 2004).)

III. Major Uses and Sources

At least 11 chemically identical forms (polymorphs) have been described for crystalline silica. Alpha-quartz is the most abundant polymorph and constitutes 12% of the earth's crust (Elzea, 1997). Silica is also found in the amorphous (non-crystalline) state. The amorphous silica in diatomaceous earth (composed mainly of the cell walls of diatoms) can be converted to the crystalline form cristobalite by heating to 1000-1100 °C (calcining). Silica is often associated

with silicates, which, in addition to silicon and oxygen, contain other metals such as iron, magnesium, aluminum, calcium, potassium, and sodium.

The major uses of silica are in the manufacture of glass, abrasives, ceramics, and enamels, in scouring and grinding compounds, and in molds for castings. Silica is also used in decolorizing and purifying oils and petroleum products; as a clarifying agent; in filtering liquids; and in the manufacture of heat insulators, firebrick, and fire- and acid-proof packing materials. As diatomite (naturally occurring diatomaceous earth), silica is used as a filtration agent, as an abrasive, and as an industrial filler. Sources of ambient respirable crystalline silica in California include mines, quarries, diatomaceous earth calcining plants, sand blasting, and entrained fines (e.g., PM₁₀) from surface soil. The annual statewide industrial emissions from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 2,514,981 pounds of crystalline silica (CARB, 2001). The fraction, which is respirable as defined either occupationally or environmentally, is not known.

Measurement of crystalline silica has evolved. Instrumentation has varied by country. In South Africa since the 1930s, dust was collected with a konimeter (Le Roux, 1970; Cherrie and Aitken, 1999). A small volume of air (e.g., 5 cm³ captured in less than a second) was collected (impacted) onto a small area of a glass slide coated with adhesive. Total dust particles were counted and expressed as dust particles per cubic centimeter. Later, slides were heated to 500-550 °C (ignition) to remove carbonaceous materials and immersed in hot 50% hydrochloric acid followed by a second ignition to remove acid-soluble materials. The remainder was mostly silica particles, which could be counted. The konimeter was superseded by the thermal precipitator, which also deposited particles onto glass but could sample larger air volumes at high flow rates (> 1 L/minute) for several hours. With time, particle counting was replaced by estimation of a particle's surface area, initially by examining slides but more recently by an automated method (Kitto, 1960; 1970).

In the United States the impinger method was used from 1922 until 1984 (Lippmann, 2001). Air was drawn into a trap containing fluid, particles in an aliquot of the fluid were counted under magnification, and concentrations were expressed as million particles per cubic foot of air sampled. Later, gravimetric analysis was introduced. Gravimetric analysis is dominated by the larger particles in any given size range.

When it was realized that only a fraction of the dust was responsible for silicosis, respirable dust was collected onto filters using size-specific dust collectors, such as horizontal plate elutriators in South Africa and cyclones in the United States. The sizes of particles collected on the filter were a function of the apparatus used and the rate of airflow through the apparatus. Quartz dust was quantified by examining filters in an electron microscope with a specific X-ray diffraction beam absorbed by crystalline silica. The National Institute of Occupational Sciences and Health (NIOSH, 2003) has approved Method 7500, which uses one of three approved cyclones and a 5 µm PVC membrane filter to sample, and X-ray diffraction to measure crystalline silica. The ARB has used Method 7500 in research projects.

In order to harmonize respirable particulate sampling methodology in workers, an international agreement has been reached to use dust samplers that have a 50% cut point for particles of 4 µm aerodynamic diameter (ISO, 1995; ACGIH, 2004).

Various attempts have been made to estimate the changes in silica levels in workplaces over time (e.g., Seixas *et al.*, 1997 for diatomaceous earth facilities in California; Verma *et al.*, 1989 for Ontario hard rock miners). However, although some conversion factors have been proposed, correlation between dust particle number in earlier studies, when dust concentrations were higher, and dust particle weight in the later studies, when the dust concentrations have been lowered, is imprecise so it is difficult to compare the earlier silica measurements with the more recent ones.

IV. Effects of Human Exposures

Inhalation of crystalline silica initially causes respiratory irritation and an inflammatory reaction in the lungs (e.g., Vallyathan *et al.*, 1995). Acute exposures to high concentrations cause cough, shortness of breath, and pulmonary alveolar lipoproteinosis (acute silicosis). After chronic but lower workplace exposures to silica for six to sixteen years, the small airways become obstructed as measured by pulmonary function tests (e.g., decreased FEV₁) in granite quarry workers (no measurement of silica levels reported; Chia *et al.*, 1992). In a report on the hazards of exposure to crystalline silica, the American Thoracic Society (1997) stated: "Studies from many different work environments suggest that exposure to working environments contaminated by silica at dust levels that appear not to cause roentgenographically visible simple silicosis can cause chronic airflow limitation and/or mucus hypersecretion and/or pathologic emphysema." Hnizdo and Vallyathan (2003) also concluded that "chronic levels of silica dust that do not cause disabling silicosis may cause the development of chronic bronchitis, emphysema, and/or small airways disease that can lead to airflow obstruction, even in the absence of radiological silicosis." Fibrotic lesions associated with crystalline silica have also been found at autopsy in the lungs of granite workers who lacked radiological evidence of silicosis (Craighead and Vallyathan, 1980).

Silicosis results from chronic exposure; it is characterized by the presence of histologically unique silicotic nodules and by fibrotic scarring of the lung. The histological progression of silicosis has been described as: (1) granuloma composed of histiocytic cells, collagen, and lymphocytes; (2) cellular fibrotic nodule with irregular collagen at the center and circular collagen at the periphery; (3) more mature nodule with acellular and avascular center; and (4) late mature nodule composed of dust and collagen including a calcified center (Green and Vallyathan, 1996). Lung diseases other than cancer associated with silica exposure include silicosis, tuberculosis/silicotuberculosis, chronic bronchitis, small airways disease, and emphysema (Oxman *et al.*, 1993; Park *et al.*, 2002; Hnizdo and Vallyathan, 2003; Balmes *et al.*, 2003). Silica exposure has been implicated in autoimmune diseases (rheumatoid arthritis, scleroderma, systemic lupus erythematosus) in gold miners and granite workers (Steenland and Goldsmith, 1995; Parks *et al.*, 1999) and in the causation of kidney disease in some occupations (Goldsmith and Goldsmith, 1993; Stratta *et al.*, 2001), possibly by an immune mechanism.

At the cellular level, silica particles are engulfed in the lung by alveolar macrophages (AM). According to the generally assumed pathological model, the AM subsequently release various growth factors and reactive oxygen species (ROS; superoxide anion, hydrogen peroxide, hydroxyl radical) (Lapp and Castranova, 1993; Mossman and Churg, 1998; Ding *et al.*, 2002). ROS and some growth factors (e.g., activator protein-1, platelet activating factor) are inflammatory and attract neutrophils to the site of inflammation, while other factors (fibronectin,

alveolar macrophage-derived growth factor) stimulate fibroblasts to proliferate and to make collagen. Since silica particles cannot be digested by the macrophage, the inflammatory process becomes chronic (frustrated phagocytosis). An increased silica burden leads to more foci of inflammation, nodule formation, and fibrosis. The internal process can continue after external exposure ends. Silica particles also enter into alveolar Type I epithelial cells (Churg, 1996), which can lead to cell death of Type I cells and to hypertrophy and proliferation of Type II epithelial cells to replace the Type I cells. The epithelial repair process is associated with a subsequent increase in collagen formation.

The initial diagnosis of silicosis is often based on chest radiographs. Recent papers have used the 1980 classification by the International Labor Organization (ILO, 1980) to identify and classify silicosis into categories and subcategories of seriousness by comparison of patient radiographs with ILO-supplied reference radiographs taken at various stages of silicosis (Table 1):

Table 1. International Labor Organization categorization of silicosis (ILO, 1980).

<i>ILO Category</i>	<i>Qualitative Description</i>
0/0	No small (up to 1 cm) silicotic opacities (nodules) are present
0/1	Probably no nodules, but some areas of radiograph are suspect [possible silicosis]
1/0	Small silicotic nodules are most likely present, but not certainly [probable silicosis]
1/1	Small silicotic nodules are definitely present
1/2	Small silicotic nodules are definitely present; other areas of the radiograph may indicate more advanced lesions including large opacities (> 1 cm), pleural thickening, etc.
2/1, 2/2, 2/3, 3/2, 3/3	More advanced stages of silicosis/increasing certainty of the presence of lung abnormalities

Some reports (e.g., Kreiss and Zhen, 1996; Hughes *et al.*, 1998) use 1/0 (probable) as the basis of classification of silicosis, since many cases of silicosis are not detected by chest radiographs, yet silicotic nodules and other lesions are found at autopsy (Craighead and Vallayathan, 1980; Hnizdo *et al.*, 1993). Other reports (e.g., Hnizdo and Sluis-Cremer, 1993) use the definite 1/1 as the lowest category indicating silicosis. Some disease is missed by radiography and is determined only by autopsy (Hnizdo *et al.*, 1993). The ILO criteria are intended as an epidemiologic classification and comparison tool, not as a diagnostic classification on an individual basis. In occupational medicine practice, a group of tests is used to clinically diagnose silica-related lung disease including physical examination, X-rays, and high resolution computed tomography (CT) scans of the lung (e.g., Begin *et al.*, 1991; Olivetti *et al.*, 1993).

A. Environmental silicosis

Several studies have reported "environmental silicosis", cases where the silicosis occurs in the absence of an industry usually associated with the disease (reviewed by USEPA, 1996). In one of the stronger examples, Saiyed *et al.* (1991) investigated non-occupational pneumoconiosis in Ladakh, India, high in the western Himalayas where there are no mines or industries. Among

449 randomly selected inhabitants of three villages, there were many cases of pneumoconiosis associated with progressive massive fibrosis (nodules > 1 cm) and "egg shell" calcification of hilar glands. The prevalence of pneumoconiosis was 2.0% (3/150) in the village of Saboo, 20.1% (31/149) in Shey, and 45.3% (68/150) in Chushot, and corresponded with the severity of dust storms and the presence or absence of chimneys in the kitchens (i.e., ventilated cooking). Without chimneys (Chushot), dust concentrations in kitchens averaged 7.5 mg/m³ during cooking periods. The free silica content of the dust storms was 60-70%. The authors suggested that exposure to free silica from dust storms and to soot from cooking with domestic fuels caused the pneumoconiosis. Perhaps the interaction of silica and soot led to the disease. Such exposures in this and other studies, such as Bar-Ziv and Goldberg (1974), might be considered to be non-industrial but occupational, since the subjects studied by Saiyed *et al.* (1991) were involved in the domestic work of cleaning and cooking (USEPA, 1996). In any case, the exposures were very high and thus similar to some occupational exposures.

B. Occupational silicosis

Several relatively recent reports have presented data that allow a quantitative relationship between occupational dust exposure and the development of silicosis in workers to be calculated.

Hard rock miners in Ontario, Canada (Muir *et al.*, 1989)

Muir *et al.* (1989) examined the relationship between cumulative exposure to silica (free crystalline silica, specifically alpha-quartz) and the development of silicosis in 2109 male hard rock (uranium, gold, mixed metals) miners in Ontario, Canada. The miners began work between 1940 and 1959 and were followed either until they ended their dust exposure or until December 31, 1982 (whichever came first). Five X-ray readers examined chest radiographs; one or more readers identified 32 cases of silicosis, defined as ILO category 1/1 or greater with round opacities. All five readers agreed on only six cases, while 12 cases were identified by only one reader (Table 2). A Weibull model of the form

$$R(x) = 1 - \exp[-(\alpha x)^\beta] \quad (x \geq 0, \beta > 0)$$

gave the best fit to the data for cumulative risk R of silicosis as a function of cumulative exposure in units of (mg/m³)-yr. In this model x is the cumulative exposure (lagged five years), α is the Weibull scale parameter, and β is the Weibull shape parameter (Table 2). Estimates of α and β for each reader are given in Table II of Muir *et al.* (1989).

Table 2. Silicosis Risk vs. Cumulative Respirable Silica in (mg/m³)-y (Table IV of Muir *et al.*)

<i>Reader</i>	<i>Cases (n)</i>	<i>1% risk^a</i>	<i>2% risk</i>	<i>5% risk</i>	<i>10% risk</i>
1	14	3.5 (2.4-5.1)	5.7 (3.9-8.4)	11.2 (6.8-18.2)	18.6 (9.9-35.0)
2	24	2.7 (2.0-3.6)	4.1 (3.2-5.3)	7.1 (5.5-9.1)	10.9 (8.1-14.8)
3	24	3.0 (2.3-3.9)	4.3 (3.4-5.3)	6.9 (5.6-8.5)	9.9 (7.8-12.7)
4	14	3.7 (2.6-5.2)	5.6 (4.1-7.7)	9.8 (6.7-14.3)	15.1 (9.3-24.4)
5	7	5.7 (4.0-8.0)	7.8 (5.5-11.0)	11.9 (7.8-18.3)	16.5 (9.7-28.2)
Any reader	32	2.1 (1.6-2.9)	3.3 (2.6-4.2)	6.0 (4.8-7.5)	9.6 (7.3-12.5)
At least 3	15	3.5 (2.5-4.9)	5.4 (4.0-7.3)	9.5 (6.6-13.6)	14.6 (9.3-23.2)
All readers	6	6.1 (4.1-8.9)	8.5 (5.6-12.8)	13.2 (7.8-22.5)	18.7 (9.7-36.1)

^a In parentheses is the 95% confidence interval (CI) for each risk estimate.

The Ontario cohort gives the shallowest dose-response relationship for silicosis of the several cohorts examined (see Summary Table 15 below) due in part to the lack of follow-up of members who left the mines (either for another type of work or for retirement). Silicosis often develops after leaving employment (Hnizdo and Sluis-Cremer, 1993; Chen *et al.*, 2001). In Hnizdo and Sluis-Cremer (1993), for more than half the cases of silicosis radiographic signs developed at an average of 7.4 years after mining exposure ended. In addition, some of the Ontario miners in the Muir *et al.* study may have changed to a less dusty job if their physician told them that their (annual) radiograph showed abnormalities. The lack of follow-up, leading to under-ascertainment of silicosis, is a serious limitation of this study.

Gray iron foundry workers (Rosenman *et al.*, 1996)

Rosenman *et al.* (1996) evaluated 1,072 (96.8% males) current and retired workers in a Mid-western gray iron foundry, which produces engine blocks for the automotive industry. Medical records and silica exposure data were analyzed for those with at least 5 years of employment as of June 1991. Nearly half had worked at the foundry for 20 years. Sixty had radiographic evidence of pneumoconiosis (ILO categories 1/0 and greater). Twenty-eight workers had radiographs consistent with silicosis; of these 25 had simple silicosis and three had progressive massive fibrosis. The prevalence of radiographic changes consistent with silicosis increased with years at the foundry, work area, quantitative silica exposure, and cigarette smoking. In regard to quantitative silica exposure, the authors stated that 0.3-2.7% of workers at the OSHA standard (90-100 $\mu\text{g}/\text{m}^3$) were silicotic, as were 4.9-9.9% of workers above 100 $\mu\text{g}/\text{m}^3$. After controlling for confounders, Rosenman *et al.* (1996) used a logistic regression analysis based on cumulative silica exposure to determine an odds ratio of 1.45 for developing a radiograph consistent with silicosis after 20 years of work at 100 $\mu\text{g}/\text{m}^3$ and an odds ratio of 2.10 after 40 years of work at 100 $\mu\text{g}/\text{m}^3$ (Tables 3 and 4). This study probably underestimates risk due to lack of follow-up of the current workers. Although silica is not the only toxic chemical in a foundry, the unique nature of the silicotic nodule diminishes the likelihood of confounding by other exposures.

Table 3. Silicosis risk based on Rosenman *et al.* data (Finkelstein, 2000)

<i>Cumulative silica exposure</i>	<i>Prevalence of silicosis</i>
< 2 (mg/m ³)-y	0.4%
2-6 (mg/m ³)-y	2.7%
> 6 (mg/m ³)-y	10%

Table 4. Odds ratios for silicosis (from Table 8 of Rosenman *et al.*)^a

<i>Time-weighted average silica exposure (mg/m³)</i>	<i>20-year cumulative exposure [(mg/m³)-y]</i>	<i>Odds ratio (95% C.I.)</i>	<i>40-year cumulative exposure [(mg/m³)-y]</i>	<i>Odds ratio (95% C.I.)</i>
0.010	0.2	1.04 (1.02-1.15)	0.4	1.08 (1.05-1.11)
0.025	0.5	1.10 (1.06-1.14)	1.0	1.20 (1.12-1.30)
0.050	1.0	1.20 (1.12-1.30)	2.0	1.45 (1.25-1.68)
0.075	1.5	1.32 (1.18-1.47)	3.0	1.74 (1.40-2.17)
0.100	2.0	1.45 (1.25-1.68)	4.0	2.10 (1.15-2.82)
0.150	3.0	1.74 (1.40-2.17)	6.0	3.04 (1.96-4.72)
0.200	4.0	2.10 (1.56-2.82)	8.0	4.40 (2.45-7.93)
0.300	6.0	3.04 (1.96-4.72)	12.0	9.24 (3.83-22.3)

^a Additional mean silica exposures, their calculated odds ratios, and 95% confidence intervals (C.I.) are given in the paper.

Diatomaceous earth workers in California (Hughes *et al.*, 1998; Park *et al.*, 2002)

Hughes *et al.* (1998) investigated 1,809 Caucasian male diatomaceous earth workers in Lompoc, California, who had at least one year of exposure to cristobalite between 1942 and 1987. The crystalline silica isomorph cristobalite is formed when the amorphous silica in diatomaceous earth is calcined at 1000-1100 °C. Quantitative estimates of dust exposure were made and published in the peer-reviewed literature by Seixas *et al.* (1997) based on 6395 air sampling records taken from 1948-1988. The average estimated respirable dust concentrations for 135 jobs were 3.55 ± 1.25 mg/m³ prior to 1949, 1.37 ± 0.48 mg/m³ from 1949-1953, 0.47 ± 0.16 mg/m³ from 1954-1973, and 0.29 ± 0.10 mg/m³ from 1974-1988. The workers had periodic chest radiographs. Based on the median of radiographic readings by three independent readers, 81 workers (4.5%) were judged to have opacities on chest radiographs (small opacities, ILO profusion $\geq 1/0$, and/or large opacities). Age-adjusted relative risk of opacities increased significantly with cumulative exposure to crystalline silica. The concentration of respirable crystalline silica was an important determinant of risk after accounting for cumulative exposure. The workers were split into two categories: those exposed to < 0.50 mg/m³ (or hired after 1950) and those exposed to > 0.50 mg/m³ (or hired before 1950). The risk of opacities for a cumulative exposure to crystalline silica of 2.0 mg/m³-yr is shown in Table 5.

Table 5. Silica exposure and silicosis based on data of Hughes *et al.* (1998)

<i>Average crystalline silica exposure</i>	<i>Cumulative risk of silicotic opacities</i>
< 0.50 mg/m ³ (or hired after 1950)	1.1%
> 0.50 mg/m ³ (or hired before 1950)	3.7%

The findings of Hughes *et al.* (1998) indicate an exposure-response relationship between cumulative exposure to crystalline silica as cristobalite and radiographic opacities. The relationship was substantially steeper among those exposed at the highest average concentrations of crystalline silica. The authors believe that the data do not support the regulatory assumption that cristobalite is more fibrogenic than quartz (i.e., prior to 2000 the occupational limit for cristobalite was half that for quartz), since at average silica levels comparable to other

epidemiologic studies quartz gave a higher incidence of silicosis than did cristobalite in this study. However, since radiography can under-diagnose silicosis, complete accounting for silicosis will require evaluation at autopsy. The ACGIH recently lowered the TLV for alpha-quartz from 100 to 50 $\mu\text{g}/\text{m}^3$, so that it has the same TLV as cristobalite (ACGIH, 2000).

Park *et al.* (2002) carried out a quantitative risk assessment, by Poisson regression methods, of the onset of silicosis among the diatomaceous earth workers in Lompoc. A linear relative risk model gave the best fit to the data. They estimated an excess lifetime risk for radiographic silicosis of 68-75 cases per thousand workers exposed to 50 $\mu\text{g}/\text{m}^3$ silica (cristobalite) for a 45 year work-life, then living to age 85. At 1 $\mu\text{g}/\text{m}^3$ silica the excess lifetime risk was estimated to be 1.6 cases of lung disease other than cancer per thousand workers exposed (Table 6).

Table 6. Excess lifetime risk of silicosis predicted by Park *et al.* (2002)

<i>Silica concentration (mg/m^3)</i>	<i>45 year cumulative exposure in $\text{mg}/\text{m}^3\text{-y}$</i>	<i>Radiographic silicosis - all workers</i>	<i>Radiographic silicosis in workers with < 10 $\text{mg}/\text{m}^3\text{-y}$</i>
0.001	0.045	6.2/1000*	1.6/1000
0.005	0.225	17/1000	7.8/1000
0.01	0.45	26/1000	16/1000
0.02	1.8	39/1000	31/1000
0.05	2.25	68/1000	75/1000
0.1	4.5	100/1000	140/1000
0.2	9	150/1000	260/1000

* Excess risk estimates assume that workers were exposed to a constant silica concentration for up to 45 years (ages 20-65). Annual risks are accumulated up to age 85.

White South African gold miners (Hnizdo and Sluis-Cremer, 1993)

Hnizdo and Sluis-Cremer (1993) investigated silicosis risk retrospectively in a cohort of 2,235 white male South African gold miners. Exposure estimates were made for nine separate occupational categories based on a special study of dust levels in these mines done by Beadle in the 1960s (Beadle, 1971). To compensate for the fact that the average hours working in dust ranged among the 9 categories from 4 hours for “other officials” to 8 hours for “shaft sinkers and developers,” exposure was “normalized” to 8-hour shifts. The workers had a minimum of 10 years and an average of 24 years service from 1940 until the early 1970s. Dust levels were fairly constant during this period (see, e.g., Table 2 in Gibbs and DuToit (2002)). The miners had an annual chest radiograph while mining; they were followed until 1991 for radiographic signs of the onset of silicosis. An ILO category 1/1 (definite silicosis) or greater was selected to designate silicosis. Two independent readers initially read the chest films, but only the reader whose interpretations correlated better with autopsy results was used for additional analysis; the use of one reader is a limitation of the study. There were 313 miners (14% of the cohort) who developed radiographic signs of silicosis at an average age of 55.9 years. The latency period was largely independent of the cumulative dust exposure (CDE). In 57% of the silicotics, the radiographic signs developed at an average of 7.4 years after mining exposure ceased. The risk of silicosis determined by chest radiographs increased exponentially with cumulative dust dose. At the highest level of 15- $(\text{mg}/\text{m}^3)\text{-years}$ CDE (approximately 37 years of gold mining at an

average respirable dust concentration of 0.4 mg/m^3), the cumulative risk for silicosis reached 77% as estimated by the accelerated failure time model using the log-logistic distribution (SAS Proc LIFEREG):

$$\text{CR}(t) = 1 - \{1/[1 + \exp(-\mu/\sigma) \times t^{(1/\sigma)}]\}$$

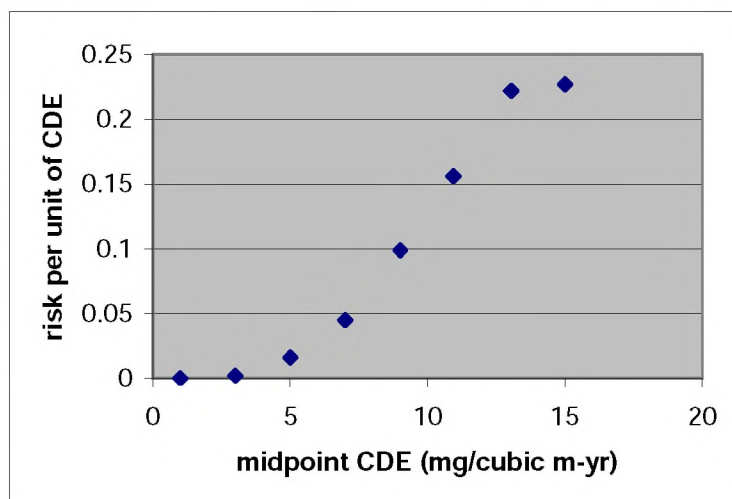
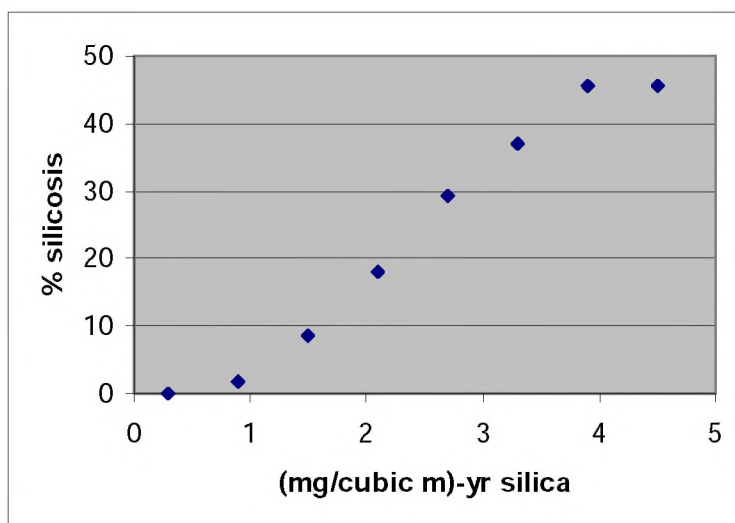
where $\text{CR}(t)$ = cumulative risk at time t , and μ (2.439) is the intercept and σ (0.2199) is the scale parameter estimated by SAS's LIFEREG procedure. The authors concluded that the risk of silicosis was strongly dose-dependent, but that the latency period was largely independent of dose. The life table analysis (SAS Proc LIFETEST) below (Table 7) shows the number of miners who developed silicosis ("cases"), the number of miners considered by the authors to be at risk, and the risk per unit of CDE (also as calculated by the authors). In the table in column 1 (in parentheses) are OEHHA's determination of the mg/m^3 -yr respirable silica exposure, based on Hnizdo and Sluis-Cremer's estimate of 30% silica in the dust, and in column 4 is the total number of miners actually at each midpoint level of CDE or silica. The values in column 4 of Table 7 are the number of workers in the group with the temporally integrated dust exposure in column 1.

Table 7. Life table results - Risk of silicosis per unit Cumulative Dust Exposure (CDE)
(from Table IV of Hnizdo and Sluis-Cremer, 1993)

<i>Midpoint in (mg/m^3)-y of CDE (silica)</i>	<i>Cases of silicosis</i>	<i>Number of workers at risk based on life table</i>	<i>Number of workers remaining at this CDE midpoint</i>	<i>"Risk/ unit CDE"</i>	<i>Mean years in dust</i>	<i>Mean dust conc. (mg/m^3)</i>
1 (0.3)	0	2218	204			
3 (0.9)	9	2014	474	0.002	20.5	0.17
5 (1.5)	48	1540	556	0.016	23.5	0.24
7 (2.1)	85	984	469	0.045	27.2	0.30
9 (2.7)	93	515	318	0.099	28.0	0.33
11 (3.3)	53	197	142	0.156	29.4	0.38
13 (3.9)	20	55	44	0.222	31.5	0.41
15 (4.5)	5	11	11	0.227	37.0	0.42

^a CDE = Σ number of dusty shifts x mean mass respirable dust conc. x average number of hours spent underground / (270 shifts/year x 8 h/shift)

A plot of risk of silicosis per unit of Cumulative Dust Exposure (CDE) versus the mid-point unit CDE, as given in Figure 1 of the Hnizdo and Sluis-Cremer report, and a plot of % silicosis among the workers actually exposed to a given level of silica (Figure 2), as determined by OEHHA staff, respectively, are given below.

Figure 1. Risk of silicosis per unit CDE vs. CDE mid-point**Figure 2. Percent silicosis among workers at each silica level**

Black South African gold miners (Churchyard *et al.*, 2004; Murray *et al.*, 1996)

Black migrant contract workers constitute a large majority (85 - 90%) of South African gold miners. In a cross sectional study, Churchyard *et al.* (2004) interviewed and took chest radiographs of 520 black gold miners (mean age = 46.7 years, range = 37.1 – 59.9) who were still mining (average service = 21.8 years, range 6.3-34.5). Two readers examined the radiographs. As in the Hnizdo and Sluis-Cremer study, silicosis was defined as an ILO (1980) profusion of $\geq 1/1$. The mean respirable dust concentration was 0.37 mg/m^3 (0 - 0.70); the mean

quartz concentration was 0.053 mg/m^3 (0 - 0.095). The prevalence of silicosis was determined to be 18.3% by one reader and 19.9% by the other (mean 19.1%) (Table 8). This included several workers with more serious silicosis as indicated by ILO profusions $\geq 2/1$ (see Table 1). Significant trends were found between the prevalence of silicosis and: (1) length of service (OR = 1.69 per 5 years), (2) mean intensity of exposure (OR = 1.18 per 0.01 mg/m^3), and (3) cumulative exposure to quartz (OR = 3.2). The study confirms the large burden of silicosis among older black workers in this industry (see next paragraph). The burden is likely to worsen with continuous employment in dusty jobs. For this cohort the prevalence of silicosis will increase even if the miners stop mining immediately. If, as assumed by the authors, the dust levels during the working life of these black miners were constant, silicosis developed while they were exposed to a quartz level below the workplace limit of 0.100 mg/m^3 .

Table 8. Silicosis in black gold miners (Churchyard *et al.*, 2003; 2004)

<i>Cumulative quartz exposure in $\text{mg/m}^3\text{-yr}$</i>	<i>Mid-point of cumulative quartz exposure</i>	<i>Number in quintile*</i>	<i>Cases of silicosis</i>	<i>Percent silicosis</i>
0 – 0.80	0.4	103	11	10.7
0.80 – 0.99	0.9	97	8	8.2
0.99 – 1.24	1.12	103	18	17.5
1.24 – 1.48	1.36	104	23	22.1
1.48 – 3.08	2.28	103	33	32.0
(Total)		(510)**	(93)	(18.2)

* Personal communication from Dr. J. teWaterNaude, December 2, 2004.

** Ten of the 520 films were unreadable.

Murray *et al.* (1996) analyzed data from 16,454 black South African gold miners dying from unnatural causes between 1975 and 1991 in order to study change in prevalence in silicosis and pulmonary tuberculosis (TB). TB prevalence increased from 0.9% in 1975 to 3.9% in 1991, while that for silicosis increased from 9.3% to 12.8%. The prevalence of both increased with age and duration of service. Silicosis was the most significant predictor of TB (OR = 1.78, CI = 1.27 - 2.30, $p = 0.0001$). A highly significant trend for TB, for year of autopsy, remained after adjustment for other variables, such as age and duration of service (OR = 1.04, CI = 1.01 – 1.06, $p = 0.0046$). (Another 21,202 black gold miners died of natural causes during the study period.)

Hong Kong granite workers (Ng and Chan, 1994)

Ng and Chan (1994) investigated silicosis among 338 male workers, who had worked at least one year between 1967 and 1985 in two granite quarries in Hong Kong. Three readers examined the chest radiographs. Silicosis was defined as an ILO classification of at least 1/1 (for small rounded opacities) or greater, assigned by at least two of the three readers. Exposure was estimated for each worker based on job category and particle counts. Thirty-six workers (10.6%) were designated silicotic. Both a logistic and a linear model fit the data well. The study suffered because only about half of the previously employed granite workers were studied, which

probably led to an underestimate of silicosis risk in at least the highest exposure category and maybe in others. The data are summarized in Table 9.

Table 9. Silica exposure and silicosis in Ng and Chan (Finkelstein, 2000)

<i>Mean cumulative exposure (mg/m³)-y</i>	<i>Prevalence of silicosis ^a</i>
< 1	0%
3.1	13%
7.1	25%
22	22%

^a rounded opacities determined by at least 2 of 3 readers (Table 3 of Ng and Chan)

Gold miners in South Dakota (Steenland and Brown, 1995)

Steenland and Brown (1995) studied a very large cohort (3330) of white male gold miners in South Dakota, who had worked at least 1 year underground between 1940 and 1965 (average = 9 years underground). The mine dust contained on average 13% silica (range = 1-48%). A job-exposure matrix was created for full-time underground workers grouped into five categories. The authors estimated that most miners were exposed to a median silica level of 0.05 mg/m^3 , but that those hired before 1930 were exposed to a median level of 0.15 mg/m^3 . A total of 170 cases of silicosis (5.1% of the cohort) was determined from death certificates only ($n = 128$ cases), from two cross-sectional radiographic surveys in 1960 and 1976 ($n = 29$ cases; ILO category 1/1 or greater), or from both ($n = 13$ cases). Unfortunately, only 25% of living cohort members were surveyed radiographically. The life-time risk of silicosis was less than 1% with a cumulative exposure under 0.5 mg/m^3 -years and increased to 68% to 84% for the highest cumulative exposure category (more than $4 \text{ (mg/m}^3\text{)-years}$) (Table 10).

Table 10. Risk of silicosis for cohort by cumulative exposure (Table 3, Steenland and Brown)

<i>Silica exposure in (mg/m^3)-yrs: range (midpoint)</i>	<i>Miners with silicosis</i>	<i>Number entering exposure category (from life table)</i>	<i>Number remaining at this exposure level</i>	<i>Cumulative^a Risk</i>	<i>Mean years of exposure</i>	<i>Mean year first exposed</i>
0-0.2 (0.10)	5	3330	1530	0.002	2.9	1953
0.2-0.5 (0.35)	5	1800	740	0.005	9.7	1948
0.5-1.0 (0.75)	15	1060	376	0.017-0.022 ^b	15.4	1942
1.0-2.0 (1.50)	33	684	353	0.060-0.084 ^b	13.2	1931
2.0-3.0 (2.50)	44	331	206	0.167-0.245 ^b	18.8	1926
3.0-4.0 (3.50)	42	125	73	0.403-0.534 ^b	25.5	1921
>4.0	26	52	52	0.678-0.844 ^b	30.6	1914

^a Cumulative risk = $1 - \exp[-\text{sum of (hazards * interval width)}]$, where the hazards for each category of cumulative exposure are:

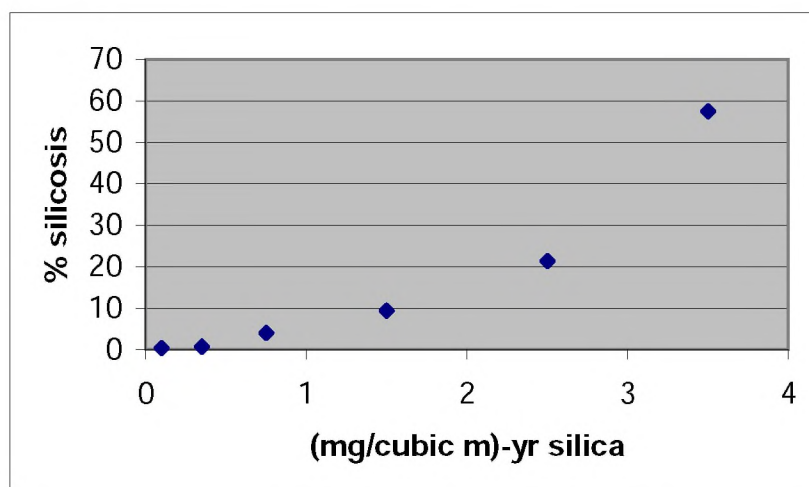
no. cases/(width*(no. entering category - 0.5*no. cases - 0.5*no. withdrawals))

^b Cumulative risk adjusted for age and calendar time (Steenland and Brown, 1995)

The best predictor of disease was cumulative exposure ($(\text{mg/m}^3) - \text{years}$), followed by duration of exposure (years), and then by average exposure (mg/m^3). Figure 1 of Steenland and Brown indicates that a plot of their data for silicosis risk versus cumulative silica exposure was similar to a plot of the data of Hnizdo and Sluis-Cremer (1993). After adjustment for competing risks of death, Steenland and Brown estimate that a 45-year exposure to $90 - 100 \mu\text{g/m}^3$ silica would lead to a lifetime risk of silicosis for gold miners of 35% to 47%. A limitation of this study is the reliance on death certificates rather than on ILO interpretation of radiographs. In addition, no mention was made of validating the data on the death certificates. It was also not clear what, if any, autopsy data were available. A plot of silicosis incidence among the workers (as determined by OEHHA staff) actually exposed to the estimated level of silica is given in Figure 3 below. An accompanying editorial (Wagner, 1995) commended the article for estimating both

the risk of silicosis while working and the lifetime risk of silicosis resulting from exposure during work.

Figure 3. % Silicosis vs. silica exposure in Steenland and Brown (see Table 10)



Miners in Leadville, Colorado (Kreiss and Zhen, 1996)

Kreiss and Zhen (1996) investigated the exposure-response relationships for silicosis among 134 male miners over 40 years old in Leadville, Colorado. The men had been studied three years earlier in a random sample of respiratory disease in their community (Kreiss *et al.*, 1989). Of 100 dust-exposed miners, 32 had radiological profusions of small opacities of ILO category 1/0 or greater at a mean of 36.1 years since their first silica exposure. Of miners with cumulative silica, exposures of 2 (mg/m³)-years or less, 20% had silicosis while 63% of miners accumulating greater than 2 (mg/m³)-years had silicosis. Average silica exposure was also strongly associated with silicosis prevalence rates (Table 11).

Table 11. Miners studied by Kreiss and Zhen (1996)

<i>Average silica exposure</i>	<i>% silicotics</i>
0.025-0.05 mg/m ³	13% (5/38)
> 0.05-0.1 mg/m ³	34% (15/44)
> 0.1 mg/m ³	75% (9/12)
<i>Cumulative silica exposure</i>	<i>% silicotics</i>
≤ 2 (mg/m ³)-y	20% (14/70)
2 – 4 (mg/m ³)-y	63% (15/24)

Based on logistic regression models of the form $R(x) = [1 + \exp(-\alpha - B'x)]^{-1}$, Kreiss and Zhen concluded that the risk of silicosis was best predicted by elapsed time since last silica exposure

together with either (1) cumulative silica exposure or (2) a combination of average silica exposure and duration of exposure. Exposure-response relationships were substantially higher using measured silica exposures (compared to using estimated silica exposures based on measured total dust exposures and assuming a constant silica proportion of dust). The risk of silicosis in this study is higher than in workforce studies having no follow-up of those leaving the mining industry (e.g., Muir *et al.*, 1989) and in studies without job title-specific silica measurements (e.g., Hnizdo and Sluis-Cremer, 1993). However, the risk is comparable to several recent studies of exposure-response relationships for mining dust (e.g., Ng and Chan, 1994; Steenland and Brown, 1995) (see Summary Table 15 below). A limitation relative to other studies is the small number of subjects (100) in the group.

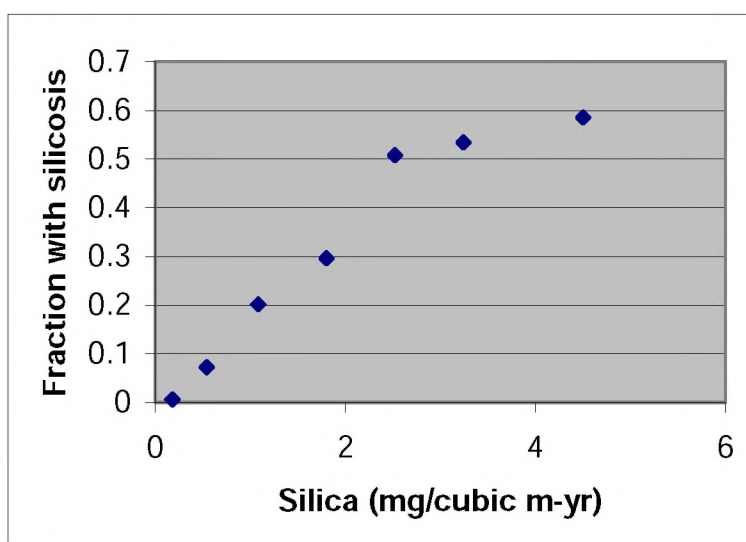
Chinese tin miners (Chen *et al.*, 2001)

Chen *et al.* (2001) found a clear exposure-response relationship between silica dust exposure and silicosis in a cohort of 3010 (2795 male and 215 female) miners employed for at least 1 year during the period 1960-1965 in any of four Chinese tin mines. No other diseases due to silica or tin were mentioned. Each cohort member was followed through 1994. Historical Chinese total dust (CTD) data were used to create a job exposure matrix for each facility, job title, and calendar year. The CTD data were converted to estimates of respirable crystalline silica for comparison with findings from other epidemiological studies of silicosis (including some of those above). Each miner's work history was abstracted from employment records. The diagnosis of silicosis was based on 1986 Chinese Roentgen diagnostic criteria for pneumoconiosis. The criteria classified silicosis as stages I-III, similar to an ILO classification of 1/1 or greater. Of the 3010 miners, 1015 (33.7%) were identified as silicotic (mean age = 48.3 years, with a mean of 21.3 years after first exposure) (Table 12). Among the silicotics, 684 (67.4%) developed silicosis after their tin mine exposure had ended (mean = 3.7 years after). The risk of silicosis was strongly related to cumulative exposure to silica. The Weibull distribution gave a very good fit to the data. The risk of silicosis was less than 0.1% when CTD was less than 10 (mg/m³)-yr (= 0.36 (mg/m³)-yr of respirable crystalline silica). The risk of silicosis increased to 68.7% when CTD exposure was equal to 150 (mg/m³)-yr (= 5.4 (mg/m³)-yr of respirable crystalline silica). Latency period was not correlated to the risk of silicosis or to cumulative dose. From their data, the authors predicted a 55% risk of silicosis for 45 years exposure to 0.1 mg/m³ respirable crystalline silica, the workplace exposure limit (4.5-(mg/m³)-years silica). Figure 4 plots the fraction of the workers in Chen *et al.* with silicosis (column 2 in Table 12 divided by column 4) exposed to a given level of silica (mid-point – in parentheses in column 1 of Table 12), as calculated by OEHHA staff.

Table 12. Cumulative silicosis risk based on cumulative total dust (CTD)
(Table 5, Chen *et al.*, 2001)

<i>Range of CTD exposure in (mg/m³)-y/ (silica mid-point)</i>	<i>Cases of silicosis (n)</i>	<i>Workers entering category</i>	<i>Workers at this level of CTD/silica</i>	<i>Cumulative risk based on Weibull model</i>	<i>Mean net exposure (years)</i>	<i>Mean latency (years)</i>
<10 (0.18)	2	3010	333	0.001	2.2	14.7
10-19.99 (0.54)	24	2677	334	0.010	5.3	21.3
20-39.99 (1.08)	126	2343	626	0.070	9.3	22.0
40-59.99 (1.80)	127	1717	429	0.145	11.9	21.5
60-79.99 (2.52)	196	1288	386	0.285	9.9	20.3
80-99.99 (3.24)	141	902	264	0.405	10.8	19.0
100-149.99 (4.50)	244	638	417	0.663	13.1	20.4
≥ 150 (≥ 5.4)	155	221	221	0.917	15.7	25.4

Figure 4. Percent silicosis vs. silica level from Chen *et al.*



Industrial sand workers (McDonald *et al.*, 2001; Hughes *et al.*, 2001; Rando *et al.*, 2001)

McDonald *et al.* (2001) studied a cohort of 2670 men employed before 1980 for 3 years or more and followed through 1994 in one of nine North American sand-producing plants and in a large associated office complex (since most of the office employees had previously worked in the mines). They found 37 deaths due to silicosis and silicotuberculosis. The mean exposure of the cohort was 42 $\mu\text{g}/\text{m}^3$ silica (Rando *et al.*, 2001). Odds ratios for silicosis mortality, determined using conditional multiple logistic regression (SAS software), were significantly related to cumulative silica exposure (Hughes *et al.*, 2001) (Table 13). The odds ratios are in general agreement with those in the gray foundry workers of Rosenman *et al.* (1996) (Table 4).

Table 13. Median cumulative silica exposure and odds ratio (Table 3 in Hughes *et al.*, 2001)

<i>No lagging</i>			<i>Lagged 15 yr</i>		
<i>Median exposure in (mg/m³)-y</i>	<i>Silicotics (n)</i>	<i>Odds ratio^a for mortality</i>	<i>Median exposure in (mg/m³)-y</i>	<i>Silicotics (n)</i>	<i>Odds ratio^{a,b} for mortality</i>
0.832	7	1.00	0.142	7	1.00
2.744	7	1.27	1.229	7	2.54
6.916	8	2.62	2.583	7	4.55
12.084	7	2.13	7.990	8	5.16

^a Matched odds ratio relative to lowest cumulative exposure category. Although labeled a cohort study, the data analysis compared cases of silicosis with non-silicotic controls.

^b Significant increasing trend across exposure categories (see Hughes *et al.* for more details)

Ceramic workers (Cavariani *et al.*, 1995; Legrand-Cattan *et al.* (1998))

Cavariani *et al.* (1995) investigated the incidence of silicosis among 2,480 men in the ceramics industry in central Italy. The workers were surveyed during the period 1974-1987 and followed through 1991 with annual chest radiographs. The cumulative risk of silicosis (ILO category 1/1 or greater) was 48% after 30 years of employment. A multivariate Cox's proportional hazards model indicated that silicosis increased linearly up to the period of 25-29 years employment. A hazard risk of 14.6 was found comparing those with ≥ 30 years exposure to those employed 10 years. Smoking significantly contributed to the model, but its role was unclear.

Legrand-Cattan *et al.* (1998) examined the dose-response relationship in two French ceramic plants. A 1992 cross-sectional study included more than 200 silica-exposed workers. Three ILO certified B readers read chest radiographs. Silica was sampled in the airborne dust. The results are tabulated below (Table 14).

Table 14. Silicosis in two French ceramic plants (Legrand-Cattan *et al.*, 1998)

<i>Cumulative exposure to silica in (mg/m³ – years)</i>	<i>Number of workers at this level</i>	<i>Number with small opacities with ILO profusion $\geq 1/0$</i>	<i>Percent</i>
< 0.35	50	2	4
0.35 – 1.08	57	8	14
1.09 – 1.77	55	11	20
> 1.77	55	17	31
Total	217	38	(18)

A dose response relationship is clear; the authors reported a p value of 0.002. However, the study is limited by the lack of follow-up of the workers.

Slate workers (Glover *et al.*, 1980; Saiyed *et al.*, 1985; Saiyed and Bannerjee, 1985)

Slate contains calcium carbonate, iron oxides, silicates, amorphous silica, and crystalline silica. Glover *et al.* (1980) studied slate workers in North Wales. The respirable slate dust contained 13-32% crystalline silica. In the study group were 725 current and former workers exposed only to slate dust, while the controls were 530 men from the same area who had never been exposed to dust. Pneumoconiosis was found in 239 slate workers (33 %), and 10% had degrees of pneumoconiosis (category 2 or higher using the 1971 ILO scheme) that would bring worker's compensation. The prevalence of respiratory symptoms (cough, phlegm, dyspnea) was high. There was evidence of an effect of both simple and complicated pneumoconiosis on lung function (declines in FVC and FEV₁) additional to the effect of age. The high prevalence (40-50%) of radiological lesions suggested the presence of healed tubercular lesions in men over 55. Either pneumoconiosis or old tubercular lesions (or both) could account for the symptomatology and disability of the men.

Saiyed *et al.* (1985) surveyed the slate-pencil industry in India. An industrial hygiene survey revealed very high levels of free silica (2-10 mg/m³), while a medical survey showed that 324 of 593 workers (54.6%) had silicosis. Of these, 105 had "conglomerate" silicosis (progressive massive fibrosis, PMF). Some lung lesions were detectable after less than five years of exposure to slate dust. Saiyed and Bannerjee (1985) conducted a follow-up examination 16 months later. The progression of silicosis was very rapid, and a total of 23 workers had died during this period (mean age = 34.7 years; mean exposure = 11.9 years). The authors attributed the high mortality to high levels of silica leading to early onset of PMF. The progression of silicosis was related to the intensity and duration of dust exposure, and to the severity of silicosis found initially.

Silicosis has been reported in other groups of slate workers in Norway (Bang and Suhr, 1998; Suhr *et al.*, 2003) and in Germany (Mehnert *et al.*, 1990).

Silica particle size

Data on silica particle size in the various workplaces are limited. According to Witschi and Last (2001), silica particles with a diameter of 1 µm (range = 0.5 - 3 µm) appear to be the most fibrotic in humans. NIOSH (1974) reviewed the existing literature and found that in five diatomite plants the mean silica diameter was 1.1 µm (range = 0.5 - 2 µm). For nine potteries, the particle size was 1.2 µm. For 18 foundries, more than 90% of the particles were less than 3 µm. The majority of particles to which shipyard sandblasters were exposed was also less than 3 µm. In the Vermont granite sheds, 10 mppcf (million particles per cubic foot) granite dust were initially estimated to be equal to 0.1 mg/m³ respirable quartz. Steenland and Brown (1995) used this estimate for silica in South Dakota gold mines. Assuming that the density of quartz is 2.65 g/cm³ and that the quartz particles are spherical, the data indicate that the particles have a diameter of 0.59 µm. NIOSH (1974) listed 0.94 µm as the median particle size in metal mines. No indication was given of the dispersion of the particle sizes around the average value. Davis *et al.* (1983) used the value of 10 mppcf in granite sheds as equal to 0.075 mg/m³ silica. For that estimation, OEHHA staff calculated the particle diameter to be 0.53 µm. Thus, existing data indicate that the majority of silica in the workplace is respirable. In most of the occupational studies examined, the exposures were measured using a calibrated cyclone sampler similar to that recommended in the current NIOSH (2003) method. This allows collection of particles

primarily in the 0.5 – 5 μm range, with a collection efficiency profile intended to match the penetration of particles into the alveolar region of the human lung. In the case of the South African gold mine studies (Beadle, 1971; Page-Shipp and Harris, 1972; Hnizdo and Sluis-Cremer, 1993), particle number was determined by an optical method selecting respirable particles (range of 0.5 to 5 μm). Thus, the risk estimates obtained from these studies refer to particles in the size range where penetration occurs into the respiratory region of the lung. This corresponds to the size range of particles thought to be responsible for silicosis. It differs from the definition of “respirable” particles (*i.e.* PM_{10}) commonly used in environmental measurements, which refers to particles capable of penetrating anywhere in the lower respiratory tract (described as “thoracic” particles in occupational studies).

Risk estimation for silicosis from epidemiologic studies

The data from the above studies have been used by a number of investigators (Finkelstein, 2000; Chen *et al.*, 2001; Hughes, 1995) and by OEHHA staff to estimate percent silicosis based on cumulative silica exposure in units of $(\text{mg}/\text{m}^3)\text{-yr}$. The results are summarized in Table 15.

Table 15. Summary - Estimates of % silicosis based on cumulative silica exposure in (mg/m³)-y

<i>Study</i>	<i>Population (number with silicosis)</i>	<i>Exposure of 2 (mg/m³)-y</i>	<i>Exposure of 4 (mg/m³)-y</i>	<i>Exposure of 4.5 (mg/m³)-y</i>
Muir <i>et al.</i> , 1989	2109 male Ontario hard rock miners ("15")	0.4 ^{a,c}	1.2 ^{a,c}	2 ^b
Rosenman <i>et al.</i> , 1996	1072 Midwestern foundry workers (28)	2 ^a	10 ^a	3 ^b
Graham <i>et al.</i> , 1991	408 Vermont granite workers (35)	~3 ^c	—	—
Hughes <i>et al.</i> , 1998	1809 white male diatomaceous earth workers (81)	1.1 (low intensity) 3.7 (high intens.) ^a	4 (low) 12 (high) ^a	—
Park <i>et al.</i> , 2002	2342 white male diatomaceous earth workers (80)	~7 ^c	13 ^c	14 ^c
Hnizdo & Sluis-Cremer 1993	2235 white male South African gold miners (313)	5 ^a 10 ^c	52 ^a 60 ^c	77 ^b
Ng & Chan, 1994	338 male Hong Kong granite workers (36)	6 ^a	15 ^a	15-20 ^b
Steenland & Brown, 1995	3330 male S. Dakota gold miners (170)	8 ^a	53 ^a	70 ^b
Kreiss & Zhen, 1996	100 miners in Leadville, CO (32)	11 ^a	53 ^a	92 ^b
Chen <i>et al.</i> , 2001	3010 Chinese tin miners (1015)	14 ^d	47 ^d	55 ^b
Churchyard <i>et al.</i> , 2004	510 black gold miners (93)	~28	-	-

^a From Table II of Finkelstein (2000)

^b From Table 6 of Chen *et al.* (2001)

^c From Tables 3 and 4 of Hughes (1995)

^d Interpolated by OEHHA staff from Fig. 2 of Chen *et al.* (2001).

^e Estimated by OEHHA staff from Table 4 of Park *et al.* (2002)

^f 158 had an ILO reading $\geq 1/0$, while 103 had an ILO reading $\geq 1/1$.

In Table 15, more than 14,000 workers were studied, of whom approximately 12% were classified as silicotic. The 12% is likely an underestimate of the incidence of silicosis due to lack of follow-up by chest radiographs during life in some cohorts and to the lack of an autopsy after death.

Determination of LOAEL and NOAEL for silicosis (Rice and Stayner, 1995)

In another approach to the data, Rice and Stayner (1995) identified the NOAEL and LOAEL for silicosis in several studies (Table 16). The study of Hnizdo and Sluis-Cremer (1993) yielded both a LOAEL and a NOAEL.

Table 16. Estimates of NOAELs and LOAELs for silicosis (Rice and Stayner, 1995)

<i>Study</i>	<i>Subjects</i>	<i>NOAEL in $\mu\text{g}/\text{m}^3$</i>	<i>LOAEL in $\mu\text{g}/\text{m}^3$</i>
Davis <i>et al.</i> , 1983	969 granite workers	67.5	
Hnizdo and Sluis-Cremer, 1993	2235 gold miners	7	20
McDonald and Oakes, 1984	1321 gold miners	-	8 ^a
	64 gypsum miners	35	49
Muir <i>et al.</i> , 1989	2109 gold miners	Could not determine	Could not determine
Rice <i>et al.</i> , 1986	888 dusty trade workers	80-100	200-252

^a McDonald and Oakes (1984) considered this value to be only an approximation.

Proposals to change the occupational exposure limit

Silicosis is still being diagnosed at death in workers who were supposed to be exposed to occupational levels of 50-100 $\mu\text{g}/\text{m}^3$. Thus, there have been recommendations that the occupational exposure limit for respirable, crystalline silica (specifically alpha-quartz) be lowered from the current level of 100 $\mu\text{g}/\text{m}^3$ to 50 $\mu\text{g}/\text{m}^3$ (NIOSH, 1974; Rosenman *et al.*, 1996; ACGIH, 1999; Finkelstein, 2000). In 2000, the ACGIH lowered its TLV for quartz from 100 to 50 $\mu\text{g}/\text{m}^3$. In 1986, WHO recommended that the occupational level be set at 40 $\mu\text{g}/\text{m}^3$ (WHO, 1986). Greaves (2000) recommended that the TLV be lowered to 10 $\mu\text{g}/\text{m}^3$. Based on existing data Greaves (2000) estimated that at 10 $\mu\text{g}/\text{m}^3$ the incidence rate for ILO grade 1/0 silicosis would be less than 5%, while for grade 1/1 it would be less than 2%. Chen *et al.* (2001) recommended that the TLV be lowered to 5 $\mu\text{g}/\text{m}^3$. "If the lifetime risk of silicosis is to be under 1 in 1000 (a criterion used by OSHA) for a lifetime exposure of 45 years, then the mean Chinese total dust concentration must be lower than 0.14 mg/m^3 (or lower than 0.005 mg/m^3 respirable crystalline silica)" (Chen *et al.*, 2001). Mannetje *et al.* (2002) pooled data from six occupational cohorts. These included four groups discussed above: diatomaceous earth workers, Vermont granite workers, U.S. industrial sand workers, and South Dakota gold miners. Among them 170 deaths from silicosis were reported. The estimated mortality risk from silicosis to age 65 after 45 years of exposure at 100 $\mu\text{g}/\text{m}^3$ silica was 13 per 1000, while the risk of death at 50 $\mu\text{g}/\text{m}^3$ was estimated at 6 per 1000. Both estimates are above the 1 per 1000 risk acceptable to OSHA. Mannetje *et al.* also concluded that the occupational standards for silica should be lowered, but they did not specify a level. They further state that their estimates of silicosis mortality are probably underestimates due to exposure misclassification and to outcome misclassification, since deaths due to silicosis might have been coded to tuberculosis or chronic obstructive pulmonary disease.

C. Silica exposure and lung cancer in workers

In 1997, IARC classified respirable crystalline silica in Class 1, a Known Human Carcinogen, based on occupational epidemiologic studies. However, chronic RELs are not based on cancer endpoints. Further, there is no approved cancer potency factor for silica.

V. Effects of Animal Exposures

Several papers have reported that freshly fractured quartz, which has increased surface activity, causes greater inflammation than "aged" quartz. Vallyathan *et al.* (1991) reported that "fresh" silica was 4.2-fold more potent than silica aged for 1-2 days in decreasing the membrane integrity of male rat macrophages; 50% more potent in activating hydrogen peroxide secretion by macrophages; and 4.6-fold more potent in stimulating cellular chemiluminescence. Vallyathan *et al.* (1995) reported that inhalation of 19.3 mg/m³ aged (for 2 months) quartz for five hours/day for 10 days by male Fischer 344 rats increased the number of cells recoverable by bronchoalveolar lavage (BAL) (Table 17). Aged quartz also gave histopathological evidence of increased pulmonary infiltrates, showed higher levels of biochemical markers of lung injury, increased lipid peroxidation, and increased the ability of pulmonary phagocytes to produce more oxygen radicals than air-exposed controls. These pulmonary responses were significantly more pronounced after inhalation of 22.4 mg/m³ freshly fractured quartz.

Table 17. Cells recovered in bronchoalveolar lavage from rats (Vallyathan *et al.*, 1995)

<i>Cell type</i>	<i>Room air</i>	<i>Aged quartz</i>	<i>Freshly fractured</i>	<i>Fresh/aged</i>
Total cells	7.1±0.78*	9.3±1.2	20.4±2.2	2.2
Macrophages	6.7±0.69	4.7±0.79	5.4±0.78	1.1
Neutrophils	≥ 0.038	5.3±0.66	10.4±1.44	2.0
Lymphocytes	≥ 0.038	1.7±0.25	3.6±0.27	2.1
Red blood cells	≥ 0.038	1.7±0.26	6.0±0.57	3.5

* Cell counts are in millions. Each value is the mean ± standard error of 5 rats.

Burns *et al.* (1980) exposed female Balb/c mice for up to 39 weeks to 4.9 mg/m³ Min-U-Sil brand crystalline silica. By 24 weeks, silica-laden macrophages were present in the lungs. After 39 weeks of exposure, silicotic lesions were seen in the lungs and adjacent lymph nodes (Table 18).

Davis *et al.* (1998) exposed mice to an aerosol of cristobalite silica (mass median aerodynamic diameter (MMAD) = 1.7 µm) for five hours/day in order to examine (1) the effects of exposure dose, (2) the evolution of disease over time, and (3) the variation in responses among strains. In C3H/HeN mice, incremental, cumulative exposure doses of cristobalite (10 mg/m³ for 8 days, 43 mg/m³ for 9 days, and 70 mg/m³ for 12 days) caused (1) increased initial lung dust burden at 12 to 16 weeks post-exposure, (2) progressively intense pathological responses, and (3) increased total lung collagen (as measured by hydroxyproline).

The histopathological changes and total lung collagen increased with time after exposure. Silicosis was compared in four inbred strains of mice (BALB/c, C3H/HeN, MRL/MpJ, New

Zealand Black) 16 weeks after aerosol inhalation exposure to cristobalite (70 mg/m^3 , 5 hours/day, 12 days). C3H/HeN mice had histopathological silicotic lesions, enlarged intrapulmonary lymphoid tissue, and increased lung wet weight, increased bronchoalveolar lavage (BAL) recoverable macrophages, lymphocytes, and neutrophils, and increased total lung collagen (hydroxyproline analyses). BALB/c mice developed slight pulmonary lesions. MRL/MpJ mice showed prominent pulmonary infiltrates with lymphocytes. New Zealand Black (NZB) mice developed extensive alveolar proteinaceous deposits, inflammation, and fibrosis. The authors found both dose-time-response relationships and a substantial variation of responses among mouse strains to the high level, short duration exposure.

At Brookhaven National Laboratory, groups of Fischer 344 rats were exposed to 0, 2, 10, and 20 mg/m^3 Min-U-Sil brand silica (alpha-quartz) for six months (Kutzman, 1984a; as summarized by USEPA, 1996). Other groups of rats had the same exposure, but were allowed to "recover" in air for an additional 6 months (Kutzman, 1984b; as summarized by USEPA, 1996). Significant alterations in total lung weight, total lung collagen, total elastin per unit lung dry weight, and total protein per unit lung dry weight at 2 mg/m^3 silica and microscopic evidence of silicotic lesions at the higher silica levels indicated that 2 mg/m^3 was a LOAEL for silica effects. After six months in clean air, the silica-induced lesions appeared to worsen.

Muhle *et al.* (1989) exposed groups of 50 male and 50 female rats to 1 mg/m^3 DQ12 quartz six hours/day, five days/week for 24 months. DQ12 contains 87% crystalline alpha-quartz, has a mass median aerodynamic diameter (MMAD) of $1.3 \mu\text{m}$, and is 74% respirable. Moderate fibrosis was seen in 85 animals, slight fibrosis in 13, and very slight fibrosis in 1 (total rats with fibrosis = 99/100). Varying amounts of peribronchial granulomatous foci were noted in 95 rats.

Muhle *et al.* (1998) reported lung fibrosis in hamsters exposed to 3 mg/m^3 DQ12 silica. After 18 months of exposure to DQ12 for 6 h/day, 5 days/week, all hamsters in the group of 15-19 animals necropsied had very slight fibrosis. Approximately 100 silica-exposed animals were exposed for five more months to air only. Afterward 22.2% had very slight fibrosis, 68.7 % had slight fibrosis, and 1% had moderate fibrosis (i.e., more than 90/100 hamsters had lung fibrosis). No collagen measurements were reported. Thus, rats, mice, and hamsters show pulmonary fibrosis after crystalline silica exposure at and above 1 mg/m^3 .

Wagner *et al.* (1968) exposed dogs up to 2.5 years, guinea pigs up to 18 months, and rats up to 2 years for 6 hours/day, 5 days/week to 61% cristobalite (in calcined diatomaceous earth). Dust exposures were 2 and 5 million particles per cubic foot (mppcf), equivalent to 0.2 and 0.5 mg/m^3 cristobalite (USEPA, 1996), with occasional excursions to 50 mppcf. No lung fibrosis was detected at these levels but all levels caused accumulation of inflammatory cells in the lung parenchyma. However, in dogs fibrotic nodules developed in the hilar lymph nodes with more nodules at 5 mppcf than at 2 mppcf.

Scheuchenzuber *et al.* (1985) examined immunologic responses in Balb/c mice following inhalation of 1.954 mg/m^3 silica for 150, 300, or 570 days. Mice exposed for 570 days were tested immediately post-exposure. Those exposed for 150 or 300 days were tested immediately or were rested for 30 or 150 days to allow for possible recovery from effects of dust inhalation. Silica inhalation suppressed the number of specific plaque-forming cells (PFC) in the spleen produced in response to aerosolized *E. coli*. After 570 days of inhalation, silica also reduced the

ability of alveolar macrophages to phagocytize *Staphylococcus aureus in vitro* and impaired the ability to lyse allogeneic tumor cells (from mice other than Balb/c) *in vitro*. Silica inhalation did not affect antibody-dependent cell-mediated cytotoxic and mitogenic responses by splenic lymphocytes. (Fibrosis was not an endpoint measured, but the effect level is similar to the LOAELs in other animal studies.)

Table 18. Animal studies of silica inhalation analyzed by USEPA (1996)

<i>Study</i>	<i>Species</i>	<i>Duration^a</i>	<i>LOAEL</i>
Muhle <i>et al.</i> , 1989	Rat	24 mo	1.0 mg/m ³
Scheuchenzuber <i>et al.</i> , 1985	Mice	150-570 d	2.0
Burns <i>et al.</i> , 1980	Mice	3-39 wk	4.9
Kutzman, 1984a	Rat	6 mo	2.0
Kutzman, 1984b	Rat	6 mo + 6 mo recovery	2.0
Wagner <i>et al.</i> , 1986	Dog	Up to 2.5 yr	0.2

^a Inhalation exposure was generally for 6 h/day, 5 d/wk.

Quartz has the ability to induce the generation of free radicals and to cause oxidative stress in tissues. Many substances that affect the quartz surface can modify this ability. Some of these modifiers could originate from other minerals, which exist together with quartz in nature. Donaldson and Borm (1998) proposed that the hazard posed by quartz may vary widely depending on the origin of the silica sample or on its contact with other chemicals/minerals. Such mechanistic data could assist in the interpretation of epidemiological studies such as those above. Experimentally their group found that DQ12 quartz, a European quartz standard which is often used in experimental studies of silica effects, is much more inflammatory in rat lung than respirable silica collected from two workplaces (Clouter *et al.*, 2001).

Humans appear to show adverse effects of silica exposure at lower levels than animals (compare LOAELs in Table 18 to LOAELs/NOAELs in Table 16). Rodents tend to be obligate nose-breathers and to have extensive nasal turbinates, which may result in less silica reaching the lower lung. For silica, results in animals may not be a good predictor of human effect levels.

VI. Derivation of Chronic Reference Exposure Level (REL)

<i>Key study</i>	Hnizdo and Sluis-Cremer, 1993
<i>Study population</i>	2235 white South African gold miners
<i>Exposure method</i>	Workplace inhalation
<i>Critical effects</i>	Silicosis (313 miners) (14 %)
<i>LOAEL</i>	3 mg/m ³ -years CDE (9 miners with silicosis)
<i>NOAEL</i>	2 mg/m ³ -years CDE (0 miners with silicosis) or 600 µg/m ³ -years silica (dust = 30% silica)
<i>BMCL₀₁</i>	2.12 (mg/m ³)-yr CDE or 0.636 (mg/m ³)-yr silica
<i>Exposure continuity</i>	8 h/day, 5 d/wk
<i>Exposure duration</i>	Average of 24 years dust exposure (10-39 years)
<i>Average experimental exposure</i>	235 µg/m ³ -yr silica at BMC ₀₁ (636 x 10 m ³ /20 m ³ x 270 shifts/365 days) 235 µg/m ³ -yr/24 yr = 9.8 µg/m ³
<i>Human Equivalent Concentration (HEC)</i>	9.8 µg/m ³
<i>LOAEL uncertainty factor</i>	Not needed in BMC approach
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	3
<i>Cumulative uncertainty factor</i>	3
<i>Inhalation Reference Exposure Level</i>	3 µg/m ³ (based on 30% silica in mine dust) [respirable, as defined occupationally by ACGIH/ISO]
<i>First supportive study</i>	Steenland and Brown, 1995
<i>Study population</i>	3330 S. Dakota gold miners
<i>Exposure method</i>	Workplace inhalation
<i>Critical effects</i>	Silicosis (170 miners) (5.1%)
<i>LOAEL</i>	0-0.2 mg/m ³ -years (5 miners with silicosis)
<i>NOAEL</i>	Not found
<i>BMCL₀₁</i>	0.34 (mg/m ³)-yr (see text below)
<i>Exposure continuity</i>	8 h/day, 5 d/wk
<i>Exposure duration</i>	3-36 years (average 9 years underground)
<i>Average experimental exposure</i>	112 µg/m ³ -y (340 x 10 m ³ /20 m ³ x 5 d/7 d x 48 wk/52 wk) 112 µg/m ³ -y/9 y = 12.4 µg/m ³
<i>Human Equivalent Concentration (HEC)</i>	12.4 µg/m ³
<i>LOAEL uncertainty factor</i>	Not needed in BMC approach
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	3
<i>Cumulative uncertainty factor</i>	3
<i>Inhalation Reference Exposure Level</i>	4 µg/m ³ [respirable, as defined occupationally]

<i>Second supportive study</i>	Hughes <i>et al.</i> , 1998
<i>Study population</i>	1809 California diatomaceous earth workers
<i>Exposure method</i>	Workplace inhalation
<i>Critical effects</i>	Silicosis (81 workers) (4.5%)
<i>LOAEL</i>	$> 1, \leq 3 \text{ mg/m}^3\text{-years}$ (17 workers with silicosis)
<i>NOAEL</i>	$\leq 1 \text{ mg/m}^3\text{-years}$ (6 cases). (Six cases were observed, but Hughes <i>et al.</i> assigned the group a Relative Risk = 1 for silicosis.)
<i>Exposure continuity</i>	8 h/day, 5 d/wk
<i>Exposure duration</i>	1-45 years (mean = 11.5 years)
<i>Average experimental exposure</i>	$\leq 330 \text{ }\mu\text{g/m}^3\text{-y}$ ($1000 \times 10/20 \times 5/7 \times 48/52$) $\leq 330 \text{ }\mu\text{g/m}^3\text{-y} / 11.5\text{years} = \leq 29 \text{ }\mu\text{g/m}^3$
<i>Human Equivalent Concentration (HEC)</i>	$29 \text{ }\mu\text{g/m}^3$
<i>LOAEL uncertainty factor</i>	3 (authors' NOAEL actually is a LOAEL)
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	3
<i>Cumulative uncertainty factor</i>	10
<i>Inhalation Reference Exposure Level</i>	$3 \text{ }\mu\text{g/m}^3$ [respirable, as defined occupationally]
<i>Third supportive study</i>	Chen <i>et al.</i> (2001)
<i>Study population</i>	3010 Chinese tin miners
<i>Exposure method</i>	Workplace inhalation
<i>Critical effects</i>	Silicosis (1015 workers) (33.7 %)
<i>LOAEL</i>	$10\text{-}19.99 \text{ mg CTD/m}^3\text{-years}$ (24 cases)
<i>NOAEL</i>	$\leq 10 \text{ mg CTD/m}^3\text{-years}$ (2 cases) $\leq 360 \text{ }\mu\text{g silica/m}^3\text{-years}$
<i>BMCL₀₁</i>	$132 \text{ }\mu\text{g silica/m}^3\text{-years}$
<i>Exposure continuity</i>	8 h/day, 5 d/wk
<i>Exposure duration</i>	2.2 years for NOAEL group
<i>Average experimental exposure</i>	$40 \text{ }\mu\text{g/m}^3\text{-y}$ ($132 \times 10/20 \times 5/7 \times 48/52$) $40 \text{ }\mu\text{g/m}^3\text{-y} / 2.2 \text{ years} = 18 \text{ }\mu\text{g/m}^3$
<i>Human Equivalent Concentration (HEC)</i>	$18 \text{ }\mu\text{g/m}^3$
<i>LOAEL uncertainty factor</i>	Not needed in BMC approach
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	3
<i>Cumulative uncertainty factor</i>	3
<i>Inhalation Reference Exposure Level</i>	$6 \text{ }\mu\text{g/m}^3$ [respirable, as defined occupationally]

<i>Fourth supportive study</i>	Churchyard <i>et al.</i> , 2004
<i>Study population</i>	510-520 black South African gold miners
<i>Exposure method</i>	Workplace inhalation
<i>Critical effects</i>	Silicosis (93 cases)
<i>LOAEL</i>	0-0.80 mg/m ³ -yr (11 cases)
<i>NOAEL</i>	Not identified
<i>BMCL₀₅</i>	0.673 (mg/m ³)-yr
<i>Exposure continuity</i>	270 shifts/year
<i>Exposure duration</i>	21.8 yr (6.3-34.5)
<i>Average experimental exposure</i>	249 (µg/m ³)-yr (673 x 10/20 x 270shifts/365)
	249 (µg/m ³)-yr/21.8 yr= 11.4 µg/m ³
<i>Human equivalent concentration (HEC)</i>	11.4 µg/m ³
<i>LOAEL uncertainty factor</i>	Not needed in BMC approach
<i>Subchronic uncertainty factor</i>	1
<i>Interspecies uncertainty factor</i>	1
<i>Intraspecies uncertainty factor</i>	3
<i>Cumulative uncertainty factor</i>	3
<i>Inhalation Reference Exposure Level</i>	4 µg/m ³ [respirable, as defined occupationally]

The study of 2235 white South African gold miners by Hnizdo and Sluis-Cremer (1993) not only determined a NOAEL of 2 (mg/m³)-yr CDE (600 µg/m³-yr silica), but also had sufficient dose-response data for a BMC derivation. This study was powerful enough to detect a 1.9% incidence of silicosis (9 cases out of 474 exposed) at 0.9 mg/m³-yr silica (0/204 vs. 9/474, $p = 0.064$ by Fisher exact test, two-tailed). Because this incidence represents approximately the sensitivity limit of the data, and silicosis is a severe irreversible endpoint, the BMCL₀₁ (*i.e.*, the lower bound estimate of the concentration at which 1% of the population develops silicosis) was selected as the basis of the chronic REL. In benchmark analysis of chronic animal studies, BMCL₀₅ is typically regarded by OEHHHA as equivalent to a NOAEL. However, the power of this large-scale study is sufficient to demonstrate measurable responses below the 5% incidence level (which cannot then be logically considered a no-effect level). Furthermore, the endpoint measured in this epidemiological study is considered to be severe, since it represents the occurrence of clinically recognizable and irreversible disease, rather than an adverse physiological or biochemical response or a histopathological result seen at autopsy.

Benchmark Concentration (BMC) models, developed by the USEPA (BMDS versions 1.3, 1.3.1, and 1.3.2), were fit to the human data in Hnizdo and Sluis-Cremer (1993) (Table 7 and Figure 2 above). Fitting the probit model to the log dose of the Hnizdo and Sluis-Cremer (1993) data yielded an MLE₀₁ of 2.45 (mg/m³)-yr CDE and a BMCL₀₁ of 2.12 (mg/m³)-yr CDE ($\chi^2 = 0.64$; p value for fit = 0.9957) (Figure 5, Table 19). (For comparison the BMCL₀₅ was 3.73 (mg/m³)-yr CDE.) Fitting the logistic model to the same data yielded a BMCL₀₁ of 1.73 (mg/m³)-yr CDE ($\chi^2 = 2.71$; p value for fit = 0.8446) (Table 19). The BMCL₀₁ from these data is about the same as the apparent NOAEL. In general, a BMC is preferred to a NOAEL because the BMC takes into account all the dose response data in a study. The apparent NOAEL may be either above or below an actual effect level, depending on the study design and distribution of the data.

Figure 5. Probit model fit to the log dose of the Hnizdo and Sluis-Cremer data.

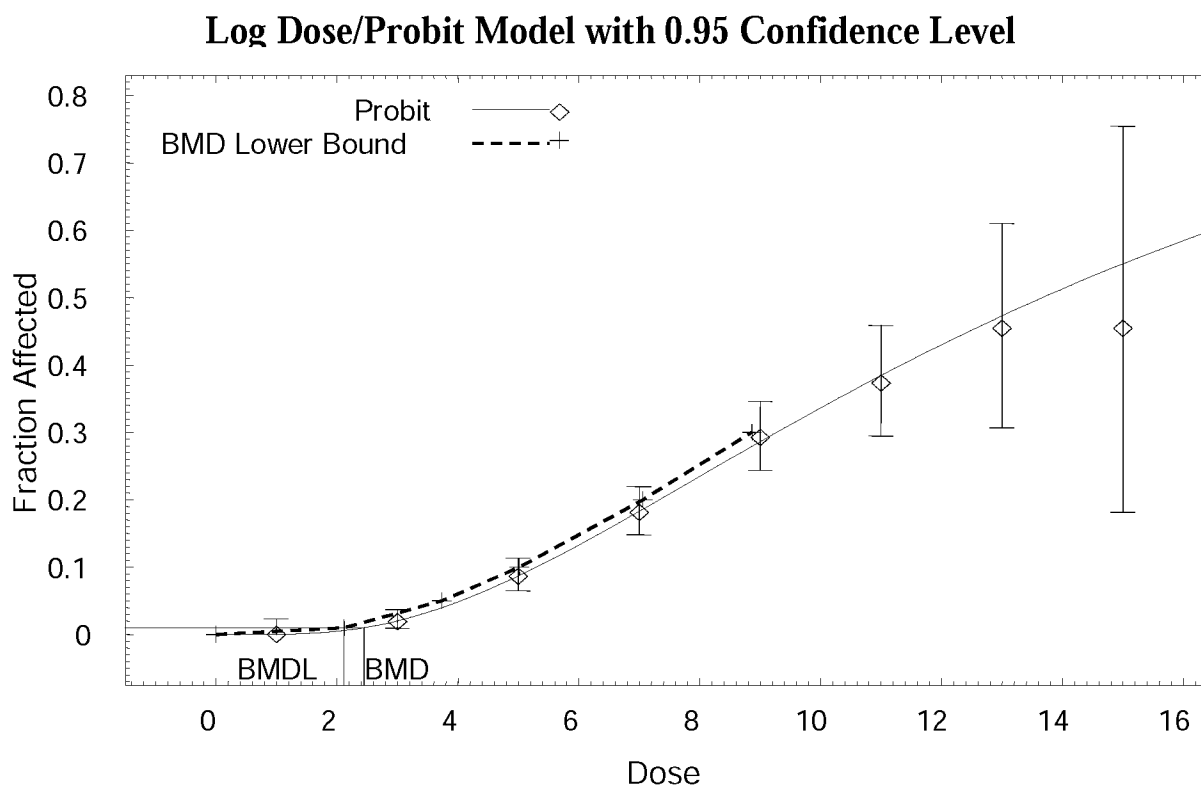


Table 19. Fits of benchmark models to the Hnizdo and Sluis-Cremer (1993) data

<i>BMDS Model</i>	<i>MLE₀₁</i>	<i>BMCL₀₁</i>	<i>p value for fit</i>
Probit-log-dose	2.45 (mg/m ³)-yr CDE	2.12 (mg/m ³)-yr CDE	0.9957
Logistic-log-dose	2.07	1.73	0.8446
Multistage (n=2)	2.47	1.89	0.7213
Quantal-quadratic	1.62	1.54	0.5017
Probit	1.56	1.32	0.0079
Logistic	1.48	1.28	0.0003
Quantal-linear	0.37	0.34	0.0000

For the estimate of 30% silica in the South African gold mine dust, Hnizdo and Sluis-Cremer (1993) relied on estimates for the years 1956-1960 by Beadle (Beadle and Bradley, 1970; Beadle, 1971). The original data, obtained by Corner House Laboratories for the South African Bureau of Mines, are partly presented by Beadle and Bradley (1970), but a more detailed presentation of exposures for various classes of workers is given by Page-Shipp and Harris

(1972). The latter paper also describes in some detail the methodology used to obtain the particle counts, and to convert those data into either respirable surface area or respirable mass values. Gibbs and Du Toit (2002) reviewed the data and methodology used by Hnizdo and Sluis-Cremer (1993) to estimate silica exposures of workers, which apparently depended on an unpublished analysis of the Corner House Laboratories' data done by Du Toit in 1991. Gibbs and Du Toit state that the exact relationship between the observed particle counts and theoretically derived mass concentrations cannot be determined, but that the uncertainties in this conversion do not appear to be severe for the dust characteristics observed in the South African mines. They accept the estimates by Beadle and Bradley (1970) of the quartz percentages in the dust, *i.e.* 54% for incinerated and acid-washed dust and 30% for unmodified dust.

However, Gibbs and Du Toit (2002) assert that Hnizdo and Sluis-Cremer (1993) incorrectly applied the 30% (total dust) silica content to figures for acid-treated dust in calculating the silica exposures of each occupational group. This contention is supported by the footnote to Table II in Hnizdo and Sluis-Cremer (1993) where the respirable dust concentration is described as "After heat and acid treatment". In order to clarify this point, OEHHA reviewed the independent reporting of the underlying data by Page-Shipp and Harris (1972). For most occupational groups, the silica exposures (shown in Table 20) calculated from Appendix I of Page-Shipp and Harris (1972), using the 54% silica content appropriate for acid-washed dust, correspond more closely to those calculated by Hnizdo and Sluis-Cremer (1993) (applying the 30% quartz content to their reported "respirable dust concentrations," *i.e.*, the untreated dust), than to the modified, and higher, quartz exposures proposed by Gibbs and Du Toit (2002). For example, 113 exposure samples were taken for stopers.

Table 20. Estimates of silica exposures in mg/m³ for different occupational groups in South African gold mines.

<i>Occupation</i>	<i>Shaft Sinkers</i>	<i>Developers</i>	<i>Stoppers</i>	<i>Assistant miners/ Trammers</i>	<i>Shift Bosses</i>	<i>Other Officials</i>	<i>Banks/ Skips</i>	<i>Workers Near shafts</i>	<i>Boiler-makers</i>	<i>Other Artisans</i>	<i>Miscellaneous</i>
Page-Shipp and Harris (1972) (Table III and Appendix I)											
Hours/shift (t)	7.70	8.00	7.80	7.70	5.20	4.00	7.50	6.50	6.30	5.70	7.20
Number of samples	10	37	113	157	43	106	33	34	41	61	11
RM x t	4.44	1.96	1.57	1.20	0.87	0.77	1.31	0.56	1.00	0.64	1.01
s.d.	3.94	1.59	1.00	0.93	0.71	0.53	1.38	0.57	0.71	0.51	0.79
Respirable Mass (RM)	0.58	0.25	0.20	0.16	0.17	0.19	0.17	0.09	0.16	0.11	0.14
Silica (54%)	0.31	0.13	0.11	0.08	0.09	0.10	0.09	0.05	0.09	0.06	0.08
(after acid treatment)											
Hnizdo and Sluis-Cremer (1993) (Table II)											
RM		0.48	0.37	0.27	0.30	0.30	0.13	0.10	0.19	0.19	
Silica (30%)		0.14*	0.11*	0.08*	0.09*	0.09*	0.04	0.03	0.06	0.06*	
(before acid treatment)											
Gibbs and Du Toit (2002) (Table 4)											
RM		0.48	0.37	0.27	0.30	0.30	0.13	0.10	0.19	0.19	
Silica (54%)		0.26	0.20	0.15	0.16	0.16	0.07*	0.05*	0.10*	0.10	
(after acid treatment)											

* denotes that value is equal to or closer to the value based on Page-Shipp and Harris

The last line of Appendix I of Page-Shipp and Harris (1972) gives a mean value for stopers of $1.57 \text{ (mg/m}^3\text{)-hours}$ respirable dust mass after acid treatment. Since the average work shift for stopers was 7.8 hours (Page-Shipp and Harris, 1972, Table III, last row), the average exposure level was 0.20 mg/m^3 . If 54% of this were quartz, the quartz level would be 0.11 mg/m^3 . Table II of Hnizdo and Sluis-Cremer (1993) lists 0.37 mg/m^3 respirable dust for stopers. Thirty % of 0.37 mg/m^3 equals 0.11 mg/m^3 , the same value reported by Page-Shipp and Harris. In Table 4 of Gibbs and Du Toit (2002) stopers are also reported to be exposed to 0.37 mg/m^3 respirable dust. If 54% were quartz, as Gibbs and Du Toit contend, the quartz level would be 0.2 mg/m^3 . For 6 of the 9 categories of workers comprising 83% of the samples taken the silica levels correspond more closely to values used by Hnizdo and Sluis-Cremer than to those suggested by Gibbs and Du Toit.

Several more recent analyses of quartz content of South African mining rock have been reported (Table 21). Kielblock *et al.* (1997) give the overall silica content of the dust as 15% for the late 1980s to early 1990s. Dr. Eva Hnizdo (personal communication, 2003), now with the U.S. National Institute of Occupational Safety and Health (NIOSH), provided a summary of various other estimates that have been made. “Past surveys indicate that the amount of airborne respirable dust in SA gold mines in 1980's and in 1970's was on average around 0.4 mg/m^3 with average quartz concentration of 0.08 mg/m^3 ” (about 20%). In a Ph.D. thesis submitted by the late R.E.G. Rendall (1999) on dust in the air of gold mines, the silica percentage averaged 22% during the period from 1964 to 1988. In summary,

- (1) Notwithstanding some apparent contradictions in the various accounts, the silica concentrations in air proposed by Hnizdo and Sluis-Cremer, based on the Corner House Laboratory data, are a reasonable contemporary estimate of the exposures experienced by the workers examined in the study by Hnizdo and Sluis-Cremer (1993).
- (2) Other, more recent estimates of percent silica in the mine dust were lower than the value of 30% used by Hnizdo and Sluis-Cremer (1993). Newer studies, which using more sophisticated methods to measure silica in the dust, indicate lower silica concentrations in the various occupational settings. Since dust levels in the mines were fairly constant for decades and quantification of silica was improving, 30% is more likely to be an overestimate than an underestimate of silica levels.
- (3) Analysis of the data of Page-Shipp and Harris (1972) by OEHHA staff indicated that Hnizdo and Sluis-Cremer (1993) used the correct silica content, despite an erroneous statement in a footnote to Table II of their paper¹.

¹ Dr. Eva Hnizdo reviewed this analysis of the silica content of the dust and agrees with the assessment. (“I am very pleased that you studied carefully all the reports and came to the conclusion that our study was after all reasonably correct. Based on the Churchyard study and the measurements data I have seen in SA during the 1990s, I am also convinced that our results are reasonable estimates of the exposure of the cohort.” (Hnizdo, personal communication October 2004))

Table 21. Estimates of respirable silica fraction of South African gold mine dust

<i>Authors</i>	<i>Time frame</i>	<i>% silica</i>		<i>Number of samples</i>	<i>Methods</i>
Beadle and Bradley, 1970	1958-1967	total dust: 25.7%; gravimetric: 28.5%; microscopy. acid-washed: 54%		142 grav; 143 elect ppt	gravimetric; precipitator + microscopy
Hnizdo and Sluis-Cremer (1993)	1956-1960	30%			precipitator + microscopy
Rendall (unpublished thesis)					
Survey 1	1987-8	17%		588	gravimetric
Survey 2	1977	20%		166	gravimetric
Survey 3	1977	17%		90	gravimetric
Survey 4a	1964-7	22%		112	gravimetric
Hnizdo (personal communication)	1970-1989	20%			
Kielblock (1997)	~1990	15.08%			Not stated
Churchyard (2004)	2000-1	14.3%			Gravimetric + X-ray diffraction

In the first supportive study Steenland and Brown (1995) found five cases of silicosis in the lowest dose group of 0 – 0.2 (mg/m³)-yr and considered the group to be a LOAEL (Table 10 above). None of the BMDS models gave an acceptable fit at the $p \geq 0.05$ level using six or seven silica levels. The closest was the quantal quadratic model ($\chi^2 = 9.62$; $p = 0.0473$), which resulted in a BMC₀₁ for silica of 0.43 (mg/m³)-yr using the six lowest levels of silica. In risk assessment, the highest dose or doses are often dropped in order to obtain an acceptable fit of the model to the data. This is reasonable with the benchmark approach since the highest doses should be least informative and the doses in the low dose region near the benchmark should be most informative for the benchmark concentration (USEPA, 1995; Filipsson *et al.*, 2003). Fitting the probit model to the log dose of the five lowest silica levels from Steenland and Brown yielded a BMCL₀₁ of 0.34 (mg/m³)-yr CDE ($\chi^2 = 1.32$; p value for fit = 0.5177). [For comparison, BMCL₀₅ = 0.85 (mg/m³)-yr CDE.] Fitting the quantal quadratic model gave a BMCL₀₁ of 0.45 (mg/m³)-yr ($\chi^2 = 3.36$; $p = 0.3395$). Use of the BMC₀₁ value of 0.34 (mg/m³)-yr CDE from the log dose probit model resulted in a chronic REL estimate for crystalline silica of 4 µg/m³. Steenland and Brown stated that “silicosis has no background rate for non-exposed populations that changes with age or calendar time” and thus they assumed that the five silicotics in the 0 – 0.2 (mg/m³)-yr were exposed to silica in the mines.

In a second supportive study, Hughes *et al.* (1998) found six cases of silicosis in the lowest exposure group of ≤ 1 mg/m³-yr but considered that group to be a NOAEL, not a LOAEL. If the lowest exposure group is used as a NOAEL, a chronic REL of 10 µg/m³ is calculated from the

data. Hughes *et al.* (1998) cite examples of possible non-occupational chest radiograph opacities (due, for example, to age or smoking) to explain the six cases in the lowest exposure group. However, due to the rarity of silicosis the six cases are biologically significant. OEHHA considers that the six cases may be work related, not cases of environmental or background silicosis. When a LOAEL to NOAEL UF of 3 is applied to the data of Hughes *et al.* (1998), the estimated REL is $3 \mu\text{g}/\text{m}^3$.

In a third supportive study, Chen *et al.* (2001) found two cases of silicosis in the lowest exposure group of $\leq 10 \text{ mg CTD}/\text{m}^3\text{-years}$ and considered that exposure level to be a NOAEL. One of the advantages of the benchmark dose analysis is that a NOAEL/LOAEL controversy, such as the one above with the Hughes *et al.* (1998) data, does not impact the procedure. The chart of the Chen *et al.* data above (Figure 4) indicates that the dose response is linear at low doses. Fitting the probit model to the log dose of the four lowest data points yielded a BMC_{01} of $0.132 (\text{mg}/\text{m}^3) \text{-yr CDE}$ ($\chi^2 = 2.19$; p value for fit = 0.335). Use of five, six, or seven data points gave BMC_{01} s of 0.14 to 0.17, but the p values were less than 0.1. For comparison, fitting the logistic model to the log dose of the four lowest data points yielded a BMCL_{01} of $0.093 (\text{mg}/\text{m}^3) \text{-yr CDE}$ ($\chi^2 = 4.86$; p value for fit = 0.0879). An inhalation chronic Reference Exposure Level for crystalline silica of $6 \mu\text{g}/\text{m}^3$ was estimated from the Chen *et al.* data.

The fourth supportive study is that of black South African gold miners by Churchyard *et al.* (2003, 2004). A problem with this data set is the statistical “noise” in the lower exposure groups; e.g., the lowest exposure group has a higher incidence of silicosis (11/103) than the next group (8/97). This noise causes problems in estimating a low benchmark such as the BMCL_{01} used with the Hnizdo and Sluis-Cremer (1993) data and with data from Steenland and Brown (1995) and Chen *et al.* (2001). The calculation therefore uses a 5% BMCL of $0.673 (\text{mg}/\text{m}^3)\text{-yr}$ from the probit log dose model as the benchmark, which is reasonably well within the range of the reliably observed data and which does not differ too widely from the MLE_{05} estimate of $0.955 (\text{mg}/\text{m}^3)\text{-yr}$ for that parameter. This BMCL_{05} is not strictly comparable to the BMCL_{01} calculated from the data of Hnizdo and Sluis-Cremer, but the concerns about the severity of the effect noted in the discussion of that derivation apply with equal or greater force here.

On the other hand, the variability in the low-dose data in this study implies that an unobserved factor is affecting the data. All the models predict that the “background” is substantially (as much as 5 – 10%) above zero, which is intrinsically implausible for silicosis unless there is an unrecorded additional source of silica exposure. Possibly, there were occasional excursions in the exposure of the workers in less exposed jobs, which were not captured by the systematic assessments for these job classifications. Alternatively, perhaps the assignment of an assumed zero exposure value to “non-dusty” job classifications noted in the paper was in fact inaccurate for some individuals. There may also be some distortion of the curve resulting from the “binning” of the exposure categories; certainly, the bin widths hinder the attempt to calculate a BMDL_{01} in this case. In relation to the model fit, other models (including the quantal linear model, which emphasizes the likely more reliable incidences at higher dose levels) are consistent with the BMCL_{05} results from the log probit model used here. Finally, the total number of cases and controls examined is fewer than in Hnizdo and Sluis-Cremer’s study, which reduces the precision.

None of these issues can be resolved without recourse to the individual data, which were not available for this analysis, and may not be resolved even then. However, the derivation of an HEC of $11.2 \mu\text{g}/\text{m}^3$ (and thus a comparison REL of $4 \mu\text{g}/\text{m}^3$) indicates at least that the results of the earlier analysis are unlikely to have underestimated the proper value of the REL. Although the uncertainties in the Churchyard *et al.* data prevent us from being more precise, we cannot eliminate the possibility that the REL should be set lower. However, the California ambient monitoring data, although subject to considerable uncertainty as to the relevant particle size distributions, suggest a plausible lower bound on the REL, which is consistent with our analysis of Hnizdo and Sluis-Cremer's data.

Other investigators have approached the possibility that some opacities on radiographs may be due to background influences such as age and smoking. In regard to smoking, Blanc and Gamsu (1988) reviewed the literature and concluded that smoking would not interfere with the determination of silicosis by the ILO system. Based on reading 1422 films of unexposed blue-collar workers, Castellan *et al.* (1985) stated that the use of the median result of 3 readers (the same number used by Hughes *et al.*) rarely results in interpreting a chest radiograph as ILO category $\geq 1/0$ in workers who were not exposed to dust (and regardless of smoking status).

The USEPA (1996) did a benchmark analysis with the Hnizdo and Sluis-Cremer (1993) data. They estimated that the lower bound for a 1% risk for silicosis (BMCL_{01}) was $1.31 (\text{mg}/\text{m}^3)\text{-yr}$, which by their methods is equivalent to a continuous, 70-year exposure to $6.7 \mu\text{g}/\text{m}^3$ silica. However, USEPA did not do a formal Reference Concentration (RfC) derivation for silica by either the BMC/UF or NOAEL/UF approach.

The key (Hnizdo and Sluis-Cremer, 1993) and supporting (Steenland and Brown, 1995; Hughes *et al.*, 1998; Chen *et al.*, 2001) studies were of human adults, nearly all males, who were presumably healthy, at least initially, since they were able to work. Thus there is need to protect the sensitive members of the population, especially children, in whose airways penetration of silica particles will be greater (Phalen *et al.*, 1985; Schiller-Scotland *et al.*, 1994; Oldham *et al.*, 1997; Bennett and Zeman, 1998). In addition, women may be more sensitive than men to the development of silicosis (Gerhardsson and Ahlmark, 1985; Katsnelson *et al.*, 1986). The selection of three as the intraspecies uncertainty factor (UF_H) was based on several considerations.

- (1) The workers who developed silicosis at low silica concentrations are by definition the most sensitive workers to silica-induced silicosis. Because of the large population of workers examined in these studies (more than 14,000), the sensitive individuals represent at least part of the range of sensitivity to be expected in the general population. This may justify reducing the UF_H from the default value of 10. Since these workers did not include children, the elderly, or females (except for the 215 females in Chen *et al.*), some uncertainty related to inter-individual variability remains. Therefore, a UF_H of 3 rather than 1 is chosen.
- (2) Mukherji *et al.* (1993) reported mean ambient silica levels (in PM_{10}) at three locations in the northern part of Santa Barbara County, California (see the Appendix to this report). At Santa Maria (an urban site) the level was $2.3 \mu\text{g}/\text{m}^3$; in Santa Ynez (a rural site) $0.6 \mu\text{g}/\text{m}^3$; and in Buellton (a remote background site) $0.2 \mu\text{g}/\text{m}^3$ crystalline silica. Thus, use

of a human intraspecies uncertainty factor (UF_H) of 10 with the data from the key study would result in an estimated chronic REL of $0.9 \mu\text{g}/\text{m}^3$ (ACGIH method), a level in the range of ambient levels in California. Although the reported levels at the urban site may (according to the authors) have reflected some anthropogenic contributions such as disturbance and tracking of siliceous road dust, the rural and remote site values are apparently (perhaps conservatively) reflective of the natural background to which all California residents are exposed. (U.S. EPA (1996) found slightly higher average ambient levels of silica in PM_{10} ; this average may include some sites affected by disturbance and emissions.) There is no evidence that these background levels of silica are causing silicosis. On the other hand, silicosis in the general population is not a target for medical attention, and autopsy rates are very low, so the possibility of a low frequency of response at these levels cannot be entirely dismissed. On balance, it appears plausible that a REL of $3 \mu\text{g}/\text{m}^3$ (benchmark + $UF_H = 3$) would be protective of the general population.

- (3) The dose-response curve for silicosis due to inhalation of crystalline silica is steep, and an upward curvature of this dose response was seen in some studies (Figure 7-1 in USEPA, 1996). It is notable that, whereas exposures in the $1\text{--}3 \mu\text{g}/\text{m}^3$ range are apparently without effect (based on the benchmark calculations and the California ambient background data), Rice and Stayner (1995) described a LOAEL for silicosis of $8 \mu\text{g}/\text{m}^3$ in gold miners (Table 16; based on data from McDonald and Oakes [1984]). This finding may partly reflect differences in physical state of the silica, and co-exposures, but it might indicate that, although the chronic REL should be protective of public health, chronic exposures only moderately exceeding the REL may lead to clinically observable disease.

The animal studies gave LOAELs for silica of $0.2 \text{ mg}/\text{m}^3$ in dogs and from 1 to $4.9 \text{ mg}/\text{m}^3$ in rodents. After extrapolation to equivalent continuous time and application of LOAEL to NOAEL, interspecies, and intraspecies UFs, the estimated chronic RELs from animal data are all less than $1 \mu\text{g}/\text{m}^3$. This reflects in part the greater uncertainty in extrapolating from animal studies to predicted human health effects.

The silica particles of concern in the causation of silicosis are those of respirable size. California EPA defines ‘respirable’ as particles $10 \mu\text{m}$ or less MMAD. This reflects one usual type of sampler (for “ PM_{10} ”) used for ambient air sampling in the general environment. The other usual type of environmental sampler, $\text{PM}_{2.5}$, collects even smaller particles. There are differences in the size range distribution between a typical PM_{10} measuring device and the NIOSH type personal samplers, or other devices with similar size selection properties, used by the investigators in the epidemiological studies. The NIOSH-type samplers capture 50% of particles with a MMAD of $4 \mu\text{m}$, and higher percentages of smaller particles. A smaller proportion of larger particles between 4 and $10 \mu\text{m}$ in aerodynamic diameter will also be collected. Figure 5, from Volume I of U.S. EPA’s Third External Review Draft of Air Quality Criteria for Particulate Matter (April 2002), includes particle penetration curves for PM_{10} , $\text{PM}_{2.5}$, and occupational samplers.

Figure 5. Size cut curves of particle penetration

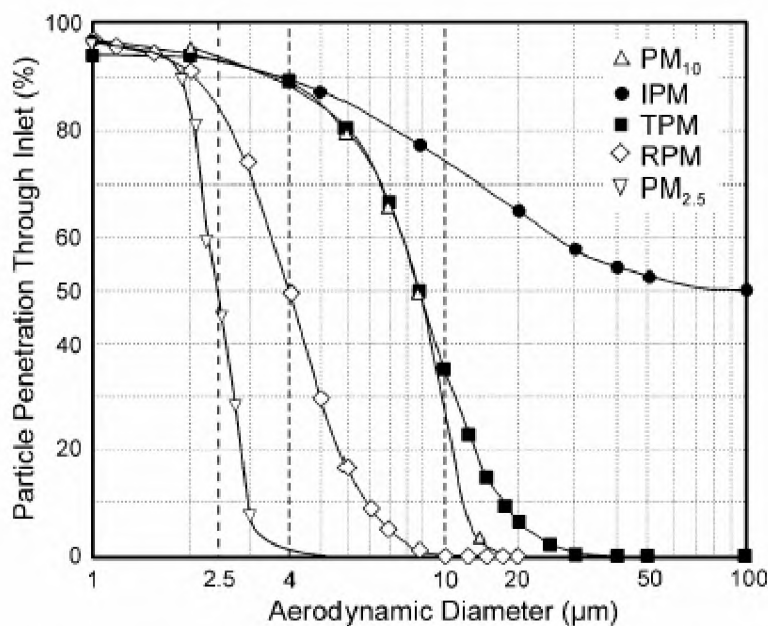


Figure 2-6. Specified particle penetration (size-cut curves) through an ideal (no-particle-loss) inlet for five different size-selective sampling criteria. Regulatory size cuts are defined in the Code of Federal Regulations; PM_{2.5} (2001c), PM₁₀ (2001a). PM_{2.5} is also defined in the Federal Register (1997). Size-cut curves for inhalable particulate matter (IPM), thoracic particulate matter (TPM) and respirable particulate matter (RPM) size cuts are computed from definitions given by American Conference of Governmental and Industrial Hygienists (1994).

The NIOSH samplers are designed to mimic the size range of particles that reach into the bronchiolar and alveolar spaces (what the occupational community calls respirable). PM₁₀ samplers are meant to capture particles that penetrate the entire length of the lower respiratory tree, including those that penetrate to the tracheobronchial and alveolar regions. Penetration (and therefore presumably deposition) by particle size is complex, and is dependent on the aerodynamic diameter, hygroscopicity, and electrostatic charge of the particles, and on a number of host factors including airway structure and geometry, as well as depth, rate, and mode of breathing (nasal vs. oronasal). The fractional penetration in the various regions of the respiratory tract is not linear with respect to size. Generally, though, larger particles impact higher in the respiratory tree (the extrathoracic and tracheobronchial regions), while smaller particles show greater penetration to the lower tracheobronchial and alveolar regions. There are a number of models of regional penetration and deposition in the respiratory tract, as well as some measurements. Chan and Lippmann (1980) showed peak alveolar deposition for particles about 3 μm MMAD with deposition dropping above and below that. Their data and model indicate

that tracheobronchial deposition rises rapidly above about 3 μm MMAD. Available data also indicate significant inter-individual variability in fractional deposition. The ICRP (1994) model used in evaluating risk from radioactive particles indicates that total deposition in the respiratory tract for particles 3 μm in activity median thermodynamic diameter (AMTD) is about 0.78 with a regional deposition fraction of 0.077 for the alveolar region for a reference male worker during nasal breathing. The same model predicts a total deposition in the respiratory tract of 0.77 for 10 μm AMTD particles and a deposition fraction of 0.024 in the alveolar region. Thus, many particles with a 10 μm MMAD get into the alveolar space. A smaller difference in regional penetration and deposition is predicted for mouth breathers. Therefore, if only the size range measured by the samplers used in the studies were considered, the measurement might underestimate the amount of silica that reaches the gas exchange regions of the lung, depending on the actual particle size distributions in the occupational studies and in the environments in which the REL is to be applied. Unfortunately, neither the occupational nor the environmental silica particle size distributions are known in detail; measurements have been reported only in terms of NIOSH sampler results or PM_{10} cutoff values.

It is generally assumed that the silicosis is induced by that fraction of the silica that reaches the alveoli. Nevertheless, no actual data exonerate the coarser particles in the 4 - 10 μm range. A fraction of these particles can enter the bronchioles and alveoli. However, some data from South African gold mines indicate that more than 99% of the crystalline silica dust can be in the $\text{PM}_{2.5}$ fraction (Sichel, 1957). Thus, the samplers used in the key study appear to be collecting the biologically relevant range of particles in that situation.

In the absence of comprehensive data on the silicosis-inducing activity of different particle sizes, it is not possible to adjust the REL for different particle size distributions, which might be found in the general environment, or for different measurement methods. The REL is therefore specified as applicable to concentrations of particles having a size range (and reactivity) similar to those measured in the occupational studies [respirable as defined occupationally (ISO, 1995; NIOSH, 2003; ACGIH, 2004)]. Results obtained by other sampling methods would need to be corrected for any difference in size selectivity of the method used. Such a correction factor would be specific to the particle size distribution present at the site studied, so no general correction factors can be proposed. A more inclusive sampling procedure, such as that used for PM_{10} , would overestimate the relevant exposure in any situation, and so would be inappropriate for precise risk quantification. However, PM_{10} would be useful as a screening method to establish that a particular situation is unlikely to present a hazard. For example, if the silica concentration in PM_{10} modeled at a receptor is less than the REL (3 $\mu\text{g}/\text{m}^3$), occupationally respirable silica will also be less than 3 $\mu\text{g}/\text{m}^3$, so a facility would not pose a risk due to silica at that receptor. If the silica concentration in $\text{PM}_{2.5}$ modeled at a receptor is less than 3 $\mu\text{g}/\text{m}^3$ but PM_{10} is greater than 3 $\mu\text{g}/\text{m}^3$, further testing would be needed. If both $\text{PM}_{2.5}$ and PM_{10} exceeded the REL, the chronic Hazard Index would exceed 1 to an undetermined extent, suggesting a need for risk management. More precise determination of the amount of material in the respirable size fraction for environmental samples may require further work on measurement methodology, since ISO (1995) and similar occupational methods have not been validated for the lower levels encountered in environmental samples.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the inhalation REL for silica include:

- (1) The availability of several long-term studies of inhalation in workers at varying exposure concentrations (see Summary Table 15 above), with adequate histopathological and radiological analysis, and with adequate follow-up.
- (2) The finding of a dose-response effect for silicosis in several of the studies (e.g., Hnizdo and Sluis-Cremer, 1993; Steenland and Brown, 1995; Chen *et al.*, 2001).
- (3) The observation of a NOAEL in some studies including the key study (summarized by Rice and Stayner, 1995).
- (4) The power of the Hnizdo and Sluis-Cremer (1993) data to detect a small effect.

Major areas of uncertainty are:

- (1) The limited follow-up of the cohort members in some studies (e.g., Muir *et al.*, 1989; Rosenman *et al.*, 1996) with consequent under-ascertainment of silicosis (even to the extent that such studies are useless for determining exposure-response).
- (2) The general underestimation of silicosis by radiography alone (Hnizdo *et al.*, 1993), which results in higher, less health-protective chronic REL estimates.
- (3) The possible underreporting of silicosis where complete radiographic data and autopsy data are not available (Steenland and Brown, 1995).
- (4) The uncertainties in exposure estimation, especially when reconstructing historical levels of silica exposure (Seixas *et al.*, 1997; Gibbs and Du Toit, 2002) including the variability in the estimates of percent quartz in the South African mine dust (Beadle, 1971; Hnizdo and Sluis-Cremer, 1993; Kielblock *et al.*, 1997; Gibbs and Du Toit, 2002; Hnizdo, personal communication) and when converting particle counts to mass.
- (5) The differences in percent silicosis in different studies at what were considered similar silica levels and similar exposure duration (see Summary Table 15 above).
- (6) The variability in toxicity of various forms of silica (e.g., freshly fractured vs. aged quartz; cristobalite vs. quartz) although all forms have toxicity (Table 17).
- (7) The limited information on silica particle size (including its variability) in the epidemiological studies, other than that the silica was respirable, and the variability in particle penetration and deposition as a function of particle size in the respiratory tract in the human population (e.g., Heyder *et al.*, 1982; ICRP, 1994; Hattis *et al.*, 2001).
- (8) The use of area samplers rather than personal samplers to estimate exposure, which usually results in an underestimation of silica exposure (Cherrie, 1999).

VIII. Potential for Differential Impacts on Children's Health

Silica is a respiratory irritant and a modifier of immune function. Since the key study involved over 2000 men, some were likely to be more sensitive to silica than others. In addition, we used a benchmark of 1% adverse effect, rather than the usual 5 %. Thus, use of the human intraspecies uncertainty factor (UF_H) of 3 should result in a REL that adequately protects most members of the general population. Exacerbation of asthma, which has a more severe impact on children than on adults, is a known response to some respiratory irritants. However, there is no

data on such a response to silica in infants or children. The epidemiological studies used in the derivation of the REL did not include children. If children's susceptibility were much greater than that of adults, it would be expected that clinical disease would be evident in children following exposures in the upper range of the respirable silica levels measured in ambient air in California. No such reports have been identified in the literature. There are no data on silica's effects on the immune system of children.

OEHHA is currently evaluating its risk assessment methodology, in particular the UF_H , for its adequacy in protecting infants and children. Since children have smaller airways than adults and breathe more air on a body weight basis, penetration and deposition of particles in the airways and alveoli in children is likely greater than that in adults exposed to the same concentration (Phalen *et al.*, 1985; Schiller-Scotland *et al.*, 1994; Oldham *et al.*, 1997; Bennett and Zeman, 1998).

IX. References

ACGIH. 1999. American Conference of Governmental Industrial Hygienists. 1999 TLVs and BEIs. Threshold Limit Values for chemical substances and physical agents and Biological Exposure Indices. Cincinnati: ACGIH.

ACGIH. 2000. American Conference of Governmental Industrial Hygienists. 2000 TLVs and BEIs. Threshold Limit Values for chemical substances and physical agents and Biological Exposure Indices. Cincinnati: ACGIH.

ACGIH. 2004. American Conference of Governmental Industrial Hygienists. 2004 TLVs and BEIs. Threshold Limit Values for chemical substances and physical agents and Biological Exposure Indices. Cincinnati: ACGIH. pp. 73-6.

American Thoracic Society. 1997. Adverse effects of crystalline silica exposure. *Am Respir Crit Care Med.* 155:761-5.

Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, Milton D, Schwartz D, Toren K, Viegi G. Environmental and Occupational Health Assembly, American Thoracic Society. 2003. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med.* 167(5):787-97.

Bar-Ziv J, Goldberg JM. 1974. Simple siliceous pneumoconiosis in Negev Bedouins. *Arch Environ Health.* 29:121-6.

Beadle DG. 1971. The relationship between the amount of dust breathed and the development of radiological signs of silicosis: an epidemiologic study of South African gold miners. In: Walton WH (ed). *Inhaled particles III*. Oxford: Pergamon Press, pp. 953-64.

Beadle DG, Bradley AA. 1970. The composition of airborne dust in South African gold mines. In: Shapiro HA (ed). *Pneumoconiosis. Proceedings of the International Conference*. Johannesburg 1969. Cape Town: Oxford University Press. pp. 462-6.

- Begin R, Ostiguy G, Fillion R, Colman N. 1991. Computed tomography scan in the early detection of silicosis. *Am Rev Respir Dis.* 144(3 Pt 1):697-705.
- Bennett WD, Zeman KL. 1998. Deposition of fine particles in children spontaneously breathing at rest. *Inhal Toxicol.* 10:831-42.
- Blanc PD, Gamsu G. 1988. The effect of cigarette smoking on the detection of small radiographic opacities in inorganic dust diseases. *J Thorac Imaging.* 3(4):51-6.
- Burns CA, Zarkower A, Ferguson FG. 1980. Murine immunological and histological changes in response to chronic silica exposure. *Environ Res.* 21(2):298-307.
- CARB. 2001. California Air Resources Board. California Emissions Inventory Development and Reporting System (CEIDARS). Data from Data Base Year 2001.
- Castellan RM, Sanderson WT, Petersen MR. 1985. Prevalence of radiographic appearance of pneumoconiosis in an unexposed blue collar population. *Am Rev Respir Dis.* 131(5):684-6.
- Cavariani F, Di Pietro A, Miceli M, Forastiere F, Biggeri A, Scavalli P, Petti A, Borgia P. 1995. Incidence of silicosis among ceramic workers in central Italy. *Scand J Work Environ Health.* 21 (Suppl 2):58-62
- Chan TL, Lippmann M. 1980. Experimental measurements and empirical modeling of the regional deposition of inhaled particles in humans. *Am Ind Hyg Assoc J.* 41:399-409.
- Chen W, Zhuang Z, Attfield MD, Chen BT, Gao P, Harrison JC, Fu C, Chen JQ, Wallace WE. 2001. Exposure to silica and silicosis among tin miners in China: exposure-response analyses and risk assessment. *Occup Environ Med.* 58(1):31-7.
- Chia KS, Ng TP, Jeyaratnam J. 1992. Small airways function of silica-exposed workers. *Am J Ind Med.* 22(2):155-62.
- Cherrie JW. 1999. The effect of room size and general ventilation on the relationship between near and far-field concentrations. *Appl Occup Environ Hyg.* 14(8):539-46.
- Cherrie JW, Aitken RJ. 1999. Measurement of human exposure to biologically relevant fractions of inhaled aerosols. *Occup Environ Med.* 56(11):747-52.
- Churchyard GJ, Ehrlich R, teWaterNaude JM, Pemba L, Dekker K, Vermeijs M, White N, Myers J (2004). Silicosis prevalence and exposure-response relations in South African goldminers. *Occup Environ Med.* 61(10):811-6.
- Churchyard G, Pembe L, Magadla B, Dekker K, Vermeijs M, Ehrlich R, teWaterNaude J, Myers J (2003). Silicosis prevalence and exposure response relationships in older black miners on a South African goldmine. Final report. Safety in Mines Research Advisory Committee. Simhealth 606. March 7, 2003.

- Churg A. 1996. The uptake of mineral particles by pulmonary epithelial cells. *Am J Respir Crit Care Med.* 154(4 Pt 1):1124-40.
- Clouter A, Brown D, Hohr D, Borm P, Donaldson K. 2001. Inflammatory effects of respirable quartz collected in workplaces versus standard DQ12 quartz: particle surface correlates. *Toxicol Sci.* 63(1):90-8.
- Craighead JE, Vallyathan NV. 1980. Cryptic pulmonary lesions in workers occupationally exposed to dust containing silica. *JAMA.* 244(17):1939-41.
- Davis GS, Leslie KO, Hemenway DR. 1998. Silicosis in mice: effects of dose, time, and genetic strain. *J Environ Pathol Toxicol Oncol.* 17(2):81-97.
- Davis LK, Wegman DH, Monson RR, Froines J. 1983. Mortality experience of Vermont granite workers. *Am J Ind Med.* 4(6):705-23.
- Ding M, Chen F, Shi X, Yucesoy B, Mossman B, Vallyathan V. 2002. Diseases caused by silica: mechanisms of injury and disease development. *Int Immunopharmacol.* 2(2-3):173-82.
- Donaldson K, Borm PJ. 1998. The quartz hazard: a variable entity. *Ann Occup Hyg.* 42(5):287-94.
- Elzea JM. 1997. The regulation of crystalline silica: an industry perspective. *J Expo Anal Environ Epidemiol.* 7(3):377-84.
- Filipsson AF, Sand S, Nilsson J, Victorin K. 2003. The benchmark dose method--review of available models, and recommendations for application in health risk assessment. *Crit Rev Toxicol.* 33(5):505-42.
- Finkelstein MM. 2000. Silica, silicosis, and lung cancer: a risk assessment. *Am. J. Ind. Med.* 38(1):8-18.
- Gerhardsson L, Ahlmark A. 1985. Silicosis in women. Experience from the Swedish Pneumoconiosis Register. *J Occup Med.* 27(5):347-50.
- Gibbs GW, Du Toit RS. 2002. Estimating the quartz exposure of South African gold miners. *Ann Occup Hyg.* 46(7):597-607.
- Glover JR, Bevan C, Cotes JE, Elwood PC, Hodges NG, Kell RL, Lowe CR, McDermott M, Oldham PD. 1980. Effects of exposure to slate dust in North Wales. *Br J Ind Med.* 37(2):152-62.
- Goldsmith JR, Goldsmith DF. 1993. Fiberglass or silica exposure and increased nephritis or ESRD (end-stage renal disease). *Am J Ind Med.* 23(6):873-81.
- Graham WG, Ashikaga T, Hemenway D, Weaver S, O'Grady RV. 1991. Radiographic abnormalities in Vermont granite workers exposed to low levels of granite dust. *Chest.* 100(6):1507-14.

Greaves IA. 2000. Not-so-simple silicosis: a case for public health action. *Am J Ind Med.* 37(3):245-51.

Green FHY, Vallyathan V. 1996. Pathologic responses to inhaled silica. In: Castranova V, Vallyathan V, Wallace WE (eds.). *Silica and Silica-Induced Lung Diseases*. Boca Raton: CRC Press, 1996, pp. 39-59.

Hattis D, Russ A, Goble R, Banati P, Chu M. 2001. Human interindividual variability in susceptibility to airborne particles. *Risk Anal.* 21(4):585-99.

HSDB. 2001. Hazardous Substances Data Bank. National Library of Medicine, Bethesda, MD. Available at: <http://toxnet.nlm.nih.gov>.

Heyder J, Gebhart J, Stahlhofen W, Stuck B. 1982. Biological variability of particle deposition in the human respiratory tract during controlled and spontaneous mouth-breathing. *Ann Occup Hyg.* 26(1-4):137-47.

Hnizdo E, Murray J, Sluis-Cremer GK, Thomas RG. 1993. Correlation between radiological and pathological diagnosis of silicosis: an autopsy population based study. *Am J Ind Med.* 24(4):427-45.

Hnizdo E, Sluis-Cremer GK. 1993. Risk of silicosis in a cohort of white South African gold miners. *Am J Ind Med.* 24(4):447-57.

Hnizdo E, Vallyathan V. 2003. Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence. *Occup Environ Med.* 60(4):237-43.

Hughes JM. 1995. Radiographic evidence of silicosis in relation to silica exposure. *Appl Occup Environ Hyg.* 10(12) 1064-9.

Hughes JM, Weill H, Checkoway H, Jones RN, Henry MM, Heyer NJ, Seixas NS, Demers PA. 1998. Radiographic evidence of silicosis risk in the diatomaceous earth industry. *Am J Respir Crit Care Med.* 158(3):807-14.

Hughes JM, Weill H, Rando RJ, Shi R, McDonald AD, McDonald JC. 2001. Cohort mortality study of North American industrial sand workers. II. Case-referent analysis of lung cancer and silicosis deaths. *Ann Occup Hyg.* 45(3):201-7.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 68. Silica, Some Silicates, Coal Dust and para-Aramid Fibrils. Lyon: IARC, 1997.

ICRP. 1994. International Commission for Radiological Protection. Human Respiratory Tract Model for Radiological Protection. ICRP Publication 66. *Annals of the ICRP.* 24(1-3):1-482.

International Labour Office. 1980. Guidelines for the use of ILO International Classification of radiographs of pneumoconiosis. Rev. Ed. Occupational Safety and Health Services, No. 22 (Rev.). ILO, Geneva.

ISO. 1995. International Organization for Standardization. Air quality – Particle size fractionation definitions for health-related sampling. ISO No. 7708:1995. ISO, Geneva.

Katsnelson BA, Polzik EV, Privalova LI. 1986. Some aspects of the problem of individual predisposition to silicosis. *Environ Health Perspect.* 68:175-85.

Kielblock AJ, Franz RM, Unsted AD, vander Linde A, Ashworth SGE. 1997. Quantitation of occupational health risks in the South African mining industry and assessment of sources of uncertainty in the estimates. SIMRAC Safety in Mines Advisory Committee final project report, project no. SIMRISK 401. Johannesburg: CSIR Division of Mining Technology.

Kitto PH. 1960. Methods of dust measurement. In: Orenstein AJ (ed). *Proceedings of Pneumoconiosis Conference held at the University of Witwatersrand, Johannesburg 9th – 24th February, 1959.* London: J & A Churchill Ltd. pp. 13-20.

Kitto PH. 1970. South African methods for the assessment of dust in gold and coal mines. In: Shapiro HA (ed). *Pneumoconiosis. Proceedings of the International Conference.* Johannesburg 1969. Cape Town: Oxford University Press. pp. 457-61.

Kreiss K, Greenberg LM, Kogut SJ, Lezotte DC, Irvin CG, Cherniack RM. 1989. Hard-rock mining exposures affect smokers and nonsmokers differently. Results of a community prevalence study. *Am Rev Respir Dis.* 139(6):1487-93.

Kreiss K, Zhen B. 1996. Risk of silicosis in a Colorado mining community. *Am J Ind Med.* 30(5):529-39.

Kutzman RS. 1984a. A study of Fischer 344 rats exposed to silica dust for six months at concentrations of 0, 2, 10 or 20 mg/m³. Upton, NY: Brookhaven National Laboratory; report no. BNL 34617.

Kutzman RS. 1984b. A study of Fischer 344 rats exposed to silica dust for six months at concentrations of 0, 2, 10 or 20 mg/m³, then maintained for six months prior to assessment. Upton, NY: Brookhaven National Laboratory; report no. BNL 35735.

Lapp NL, Castranova V. 1993. How silicosis and coal workers' pneumoconiosis develop--a cellular assessment. *Occup Med.* 8(1):35-56.

Legrand-Cattan K, Vuillaume M, Iwatsubo Y, Ameille J, Brochard P, Letourneux M, Housset B, Laureillard J, and Pairon J. 1998. Silicosis in the ceramic industry: dose-response relationship. In: *Advances in the Prevention of Occupational Respiratory Disease.* Chiyotani K, Hosoda Y, Aizawa Y (eds.). Amsterdam: Elsevier. Pp. 113-117.

Le Roux WL. 1970. Recorded dust conditions and possible new sampling strategies on South African gold mines. In: Shapiro HA (ed). *Pneumoconiosis. Proceedings of the International Conference.* Johannesburg 1969. Cape Town: Oxford University Press..

Lippmann N. 2001. Size-selective health hazard sampling. In: Cohen BS, McCammon Jr CS (eds.). *Air Sampling Instruments for Evaluation of Atmospheric Contaminants*. 9th ed. Cincinnati: ACGIH. pp. 93-134.

't Mannetje A, Steenland K, Attfield M, Boffetta P, Checkoway H, DeKlerk N, Koskela RS. 2002. Exposure-response analysis and risk assessment for silica and silicosis mortality in a pooled analysis of six cohorts. *Occup Environ Med*. 59(11):723-728.

McDonald AD, McDonald JC, Rando RJ, Hughes JM, Weill H. 2001. Cohort mortality study of North American industrial sand workers. I. Mortality from lung cancer, silicosis and other causes. *Ann Occup Hyg*. 45(3):193-9.

McDonald JC, Oakes D. 1984. Exposure-response in miners exposed to silica. In: Sixth International Pneumoconiosis Conference. 1983. Bochum, Germany. Vol 1. Geneva: International Labour Office (ILO). Pp. 114-23.

Mehnert WH, Staneczek W, Mohner M, Konetzke G, Muller W, Ahlendorf W, Beck B, Winkelmann R, Simonato L. 1990. A mortality study of a cohort of slate quarry workers in the German Democratic Republic. *IARC Sci Publ*. Vol. 97. pp. 55-64.

Mossman BT, Churg A. 1998. Mechanisms in the pathogenesis of asbestosis and silicosis. *Am J Respir Crit Care Med*. 157(5 Pt 1):1666-80.

Muhle H, Bellman B, Creutzenberg O, Koch W, Dasenbrock C, Ernst H, Mohr U, Morrow P, Mermelstein R. 1998. Pulmonary response to toner, TiO₂, and crystalline silica upon chronic inhalation exposure in Syrian golden hamsters. *Inhal Toxicol*. 10:699-729.

Muhle H, Takenaka S, Mohr U, Dasenbrock C, Mermelstein R. 1989. Lung tumor induction upon long-term low-level inhalation of crystalline silica. *Am J Ind Med*. 15(3):343-6.

Muir DC, Julian JA, Shannon HS, Verma DK, Sebestyen A, Bernholz CD. 1989. Silica exposure and silicosis among Ontario hardrock miners: III. Analysis and risk estimates. *Am J Ind Med*. 16(1):29-43.

Mukherji S, Petrini J, Murphy T. 1993. North Santa Barbara County Crystalline Silica Study. Prepared for U.S. Environmental Protection Agency Region IX. Goleta, CA: Santa Barbara County Air Pollution Control District.

Murray J, Kielkowski D, Reid P (1996). Occupational disease trends in black South African gold miners. An autopsy-based study. *Am J Respir Crit Care Med*. 153(2):706-10.

NIOSH. 1974. National Institute for Occupational Safety and Health. Criteria for a Recommended Standard. Occupational Exposure to Crystalline Silica. DHEW (NIOSH) Publication No. 75-120.

NIOSH (1994, 1996, 1998, 2003) Manual of Analytical Methods, 4th ed. DHHS (NIOSH) Publication 94-113 (August, 1994), 1st Supplement Publication 96-135, 2nd Supplement Publication 98-119, 3rd Supplement 2003-154. Schlecht PC, O'Connor PF, eds.

- Ng TP, Chan SL. 1992. Lung function in relation to silicosis and silica exposure in granite workers. *Eur Respir J*. 5(8):986-91.
- Ng TP, Chan SL. 1994. Quantitative relations between silica exposure and development of radiological small opacities in granite workers. *Ann Occup Hyg*. 38 Suppl 1:857-63.
- OEHHA. 1999. Air Toxics Hot Spots Program Risk Assessment Guidelines. Part I. The Determination of Acute Reference Exposure Levels for Airborne Toxicants. Available online at <http://www.oehha.ca.gov>.
- Oldham MJ, Mannix RC, Phalen RF. 1997. Deposition of monodisperse particles in hollow models representing adult and child-size tracheobronchial airways. *Health Phys*. 72(6):827-34.
- Olivetti L, Grazioli L, Milanesio L, Provezza A, Chiodera P, Tassi G, Bergonzini R. 1993. Anatomico-radiologic definition of minimal interstitial silicosis and diagnostic contribution of high-resolution computerized tomography [in Italian]. *Radiol Med (Torino)*. 85(5):600-5.
- Oxman AD, Muir DC, Shannon HS, Stock SR, Hnizdo E, Lange HJ. 1993. Occupational dust exposure and chronic obstructive pulmonary disease. A systematic overview of the evidence. *Am Rev Respir Dis*. 148(1):38-48.
- Page-Shipp RJ, Harris E. 1972. A study of dust exposure of South African white gold miners. *South Afr Inst Mining Metall*. 73:10-24.
- Park R, Rice F, Stayner L, Smith R, Gilbert S, Checkoway H. 2002. Exposure to crystalline silica, silicosis, and lung disease other than cancer in diatomaceous earth industry workers: a quantitative risk assessment. *Occup Environ Med*. 59(1):36-43.
- Parks CG, Conrad K, Cooper GS. 1999. Occupational exposure to crystalline silica and autoimmune disease. *Environ Health Perspect*. 107 Suppl 5:793-802.
- Phalen RF, Oldham MJ, Beaucage CB, Crocker TT, Mortensen JD. 1985. Postnatal enlargement of human tracheobronchial airways and implications for particle deposition. *Anat Rec*. 212(4):368-80.
- Rando RJ, Shi R, Hughes JM, Weill H, McDonald AD, McDonald JC. 2001. Cohort mortality study of North American industrial sand workers. III. Estimation of past and present exposures to respirable crystalline silica. *Ann Occup Hyg*. 45(3):209-16.
- Rendall REG. 1999. The nature of dusts in the air of gold mines and foundries and the risk of silicosis. Thesis submitted (posthumously) to the University of the Witwatersrand.
- Rice CH, Harris RL, Checkoway H, Symons MJ. 1986. Dose-response relationships for silicosis from a case-control study of North Carolina dusty trades workers. In: Goldsmith DF, Winn DM, Shy CM (eds). *Silica, Silicosis, and Cancer. Controversy in Occupational Medicine*. New York: Prager. Pp. 77-86.

Rice FL, Stayner LT. 1995. Assessment of silicosis risk for occupational exposure to crystalline silica. *Scand J Work Environ Health*. 21 Suppl 2:87-90.

Rosenman KD, Reilly MJ, Rice C, Hertzberg V, Tseng CY, Anderson HA. 1996. Silicosis among foundry workers. Implication for the need to revise the OSHA standard. *Am J Epidemiol*. 144(9):890-900. Saiyed HN, Chatterjee BB. 1985. Rapid progression of silicosis in slate pencil workers: II. A follow-up study. *Am J Ind Med*. 8(2):135-42.

Saiyed HN, Parikh DJ, Ghodasara NB, Sharma YK, Patel GC, Chatterjee SK, Chatterjee BB. 1985. Silicosis in slate pencil workers: I. An environmental and medical study. *Am J Ind Med*. 8(2):127-33.

Saiyed HN, Sharma YK, Sadhu HG, Norboo T, Patel PD, Patel TS, Venkaiah K, Kashyap SK. 1991. Non-occupational pneumoconiosis at high altitude villages in central Ladakh. *Br J Ind Med*. 48(12):825-9.

Scheuchenzuber WJ, Eskew ML, Zarkower A. 1985. Effects of prolonged inhalation of silica and olivine dusts on immune functions in the mouse. *Environ Res*. 38(2):389-99.

Schiller-Scotland CF, Hlawka R, Gebhart J. 1994. Experimental data for total deposition in the respiratory tract of children. *Toxicol. Lett*. 72(1-3):137-44.

Seixas NS, Heyer NJ, Welp EA, Checkoway H. 1997. Quantification of historical dust exposures in the diatomaceous earth industry. *Ann Occup Hyg*. 41(5):591-604.

Sichel HS (1957). On the size distribution of airborne mine dust. *J S Afr Inst Min Metal*. 58(5):171-225.

Steenland K, Brown D. 1995. Silicosis among gold miners: exposure--response analyses and risk assessment. *Am J Public Health*. 85(10):1372-7.

Steenland K, Goldsmith DF. 1995. Silica exposure and autoimmune diseases. *Am J Ind Med*. 28(5):603-8.

Stratta P, Canavese C, Messuerotti A, Fenoglio I, Fubini B. 2001. Silica and renal diseases: no longer a problem in the 21st century? *J Nephrol*. 14(4):228-47.

Suhr H, Bang B, Moen BE. 2003. Respiratory health among quartz-exposed slate workers--a problem even today. *Occup Med (Lond)*. 53(6):406-7.

Theriault GP, Burgess WA, DiBerardinis LJ, Peters JM. 1974. Dust exposure in the Vermont granite sheds. *Arch Environ Health*. 28(1):12-7.

USEPA. 1995. U.S. Environmental Protection Agency. The Use of the Benchmark Dose Method in Health Risk Assessment. EPA/630/R-94/007. Washington, DC: U.S. EPA.

USEPA. 1996. U.S. Environmental Protection Agency. Ambient Levels and Noncancer Health Effects of Inhaled Crystalline and Amorphous Silica: Health Issue Assessment. EPA/600/R-95/115. Office of Research and Development. Washington, DC: U.S. EPA.

Vallyathan V, Kang JH, Van Dyke K, Dalal NS, Castranova V. 1991. Response of alveolar macrophages to in vitro exposure to freshly fractured versus aged silica dust: the ability of Prosil 28, an organosilane material, to coat silica and reduce its biological reactivity. *J Toxicol Environ Health*. 33(3):303-15.

Vallyathan V, Castranova V, Pack D, Leonard S, Shumaker J, Hubbs AF, *et al.* 1995. Freshly fractured quartz inhalation leads to enhanced lung injury and inflammation. Potential role of free radicals. *Am J Respir Crit Care Med*. 152(3):1003-9.

Verma DK, Sebestyen A, Julian JA, Muir DC, Schmidt H, Bernholz CD, Shannon HS. 1989. Silica exposure and silicosis among Ontario hardrock miners: II. Exposure estimates. *Am J Ind Med*. 16(1):13-8.

Wagner G. (1995). The inexcusable persistence of silicosis. *Am J Public Health*. 85(10):1346-7.

Wagner WD, Fraser DA, Wright PG, Dobrogorski OJ, Stokinger HE. 1968. Experimental evaluation of the threshold limit of cristobalite--calcined diatomaceous earth. *Am Ind Hyg Assoc J*. 29(3):211-21.

Witschi HR, Last JA. 2001. Toxic responses of the respiratory system. In: Casarett and Doull's Toxicology. The Basic Science of Poisons. 6th Ed. Klaassen CD (ed). New York: McGraw-Hill.

World Health Organization (WHO). 1986. Recommended health-based limits in occupational exposure to selected mineral dusts (silica, coal). Geneva, Switzerland: World Health Organization, Technical Report Series 734.

X. AppendixParticulate Levels of Interest for Exposure to Respirable Crystalline Silica Isomorphs

150 $\mu\text{g}/\text{m}^3$	Federal 24 hour PM_{10} standard
65 $\mu\text{g}/\text{m}^3$	Federal 24 hour $\text{PM}_{2.5}$ standard
50 $\mu\text{g}/\text{m}^3$	California 24 hour PM_{10} standard
50 $\mu\text{g}/\text{m}^3$	Federal PM_{10} annual standard (chronic exposure)
50 $\mu\text{g}/\text{m}^3$	8 hour TLV for quartz, cristobalite, and tridymite for workers (ACGIH Method)
50 $\mu\text{g}/\text{m}^3$	estimated workplace LOAEL for silicosis from studies by Theriault <i>et al.</i> (“)
20 $\mu\text{g}/\text{m}^3$	CA annual PM_{10} standard (chronic exposure) (arithmetic mean)
15 $\mu\text{g}/\text{m}^3$	Federal annual $\text{PM}_{2.5}$ standard (chronic exposure)
12 $\mu\text{g}/\text{m}^3$	CA annual $\text{PM}_{2.5}$ standard (chronic exposure) (arithmetic mean)
12 $\mu\text{g}/\text{m}^3$	current silica TLV adjusted to equivalent continuous exposure (50 $\mu\text{g}/\text{m}^3 \times 8 \text{ h}/24 \text{ h} \times 5 \text{ d}/7\text{d}$) (ACGIH)
10 $\mu\text{g}/\text{m}^3$	TLV for silica proposed by Greaves (2000) (ACGIH)
8 $\mu\text{g}/\text{m}^3$	current silica TLV further adjusted by 46/70 years occupational exposure (ACGIH)
8 $\mu\text{g}/\text{m}^3$	estimated high-end ambient crystalline silica level in US (USEPA, 1996) (PM_{10})
6.7 $\mu\text{g}/\text{m}^3$	lower bound on 1% risk of silicosis estimated by USEPA (1996) (PM_{10})
5 $\mu\text{g}/\text{m}^3$	TLV for silica proposed by Chen <i>et al.</i> (2001) (ACGIH)
5 $\mu\text{g}/\text{m}^3$	“acceptable” ambient level for silica (10% of PM_{10}) (USEPA, 1996)
5 $\mu\text{g}/\text{m}^3$	RfC for diesel exhaust particulate, a respirable PM ($\text{PM}_{2.5}$)
3 $\mu\text{g}/\text{m}^3$	estimated average ambient exposure to crystalline silica (USEPA, 1996) (PM_{10})
3 $\mu\text{g}/\text{m}^3$	draft silica chronic REL proposed by OEHHA (ACGIH)
2.3 $\mu\text{g}/\text{m}^3$ (1.17-3.46; n=12)*	silica level during 1989 in Santa Maria, CA (urban site) (PM_{10})
0.6 $\mu\text{g}/\text{m}^3$ (0-1.44; n=16)*	silica level during 1989 in Santa Ynez, CA (rural site) (“)
0.2 $\mu\text{g}/\text{m}^3$ (0-1.15; n=18)*	silica level during 1989 in Buellton, CA (remote background)(“)

* mean, range, and number of crystalline silica measurements (Mukherji *et al.*, 1993)