Silicosis and Coal Workers' Pneumoconiosis

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Exposure to coal mine dust and/or crystalline silica results in pneumoconiosis with initiation and progression of pulmonary fibrosis. This review presents characteristics of simple and complicated coal workers' pneumoconiosis (CWP) as well as pathologic indices of acute and chronic silicosis by summarizing results of *in vitro,* animal, and human investigations. These results support four basic mechanisms in the etiology of CWP and silicosis: *a*) direct cytotoxicity of coal dust or silica, resulting in lung cell damage, release of lipases and proteases, and eventual lung scarring; *b*) activation of oxidant production by pulmonary phagocytes, which overwhelms the antioxidant defenses and leads to lipid peroxidation, protein nitrosation, cell injury, and lung scarring; *c*) activation of mediator release from alveolar macrophages and epithelial cells, which leads to recruitment of polymorphonuclear leukocytes and macrophages, resulting in the production of proinflammatory cytokines and reactive species and in further lung injury and scarring; *d*) secretion of growth factors from alveolar macrophages and epithelial cells, stimulating fibroblast proliferation and eventual scarring. Results of *in vitro* and animal studies provide a basis for proposing these mechanisms for the initiation and progression of pneumoconiosis. Data obtained from exposed workers lend support to these mechanisms. *Key words*: black lung disease, coal mine dust, crystalline silica, cytokines, lung disease, occupational diseases, occupational exposures, pulmonary fibrosis, reactive oxygen species. — *Environ Health Perspect* 108(suppl 4):675–684 (2000).
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Silicosis and coal workers' pneumoconiosis (CWP) have long been recognized as significant occupational lung diseases. Silicosis and CWP continue to occur in several industrial workplaces even though these diseases are preventable by environmental dust control. Although significant insights have been gained into mechanisms involved in the initiation and progression of silicosis and CWP, it is difficult to conclude that these accomplishments have totally solved the problem of these occupational diseases. The knowledge acquired through research has been most valuable in determining the cause and pathogenesis of these occupational lung diseases. In industrialized countries, exposure–response information and the relationship among pathologic, radiologic, and physiologic abnormalities of these diseases have led to the recommendation and implementation of exposure limits. However, additional innovative research strategies are vital to identify susceptible individuals, diagnose these pneumoconioses in the early stages of development, and develop treatment strategies. In addition, research is needed to identify biologic mechanisms involved in unique occupational settings, for example, sandblasting, rock drilling, or exposure to mixed dusts, where risk of disease is unusually high.

The literature concerning symptoms, clinical manifestations, and mechanisms for initiation and progression of silica-induced lung diseases and CWP is extensive. By intent, this review is meant to be brief and somewhat selective. Readers are directed to other sources if more detailed information is desired (*1–12*). This review is an overview of exposures, toxicologic and pathologic responses, and possible mechanisms involved in silicosis and CWP.

Silica Exposures

Silicosis is caused by inhalation of crystalline silica, mostly in occupational settings. It is most common among workers in underdeveloped countries. However, silicosis occurs frequently even in developed countries, particularly in certain occupations such as mining, sandblasting, surface drilling, stone cutting, construction, pottery making, silica flour mill operations, and other occupations in which silica dust exposures occur (*1–3*). In addition, environmental exposure to crystalline silica is common because of its abundance in soil. Silica can become airborne in arid, windy conditions or during agricultural, urban, and construction activities. Indeed, lung fibrosis and pulmonary changes associated with environmental silica and mixed dust exposures have been observed in the lungs of farm animals and humans (*13*).

In 1983 the National Institute for Occupational Safety and Health (NIOSH) estimated that approximately 2.3 million workers at 238,000 work sites may be exposed to silica dust (*14*). NIOSH estimates that as many as 59,000 workers may be at risk of developing some degree of silicosis, with 250 deaths/year being attributed to silica exposure (*15*). Approximately 1,500 cases of silicosis are diagnosed annually in the United States (*16*). NIOSH also reported that between 1968 and 1990 there were 13,744 deaths with mention of silicosis in the United States (*16*). However, in recent years, the annual number of deaths has decreased from 1,157 in 1968 to 301 in 1988 (*16*).

Currently, several standards exist for the limitation of airborne levels of respirable crystalline silica. The Occupational Safety and Health Administration permissible exposure limit (PEL) is 100 $\mu g/m^3$ for an 8-hr work exposure. The NIOSH recommended exposure limit (REL) is 50 $\mu g/m^3$ for up to 10 hr/day for a 40-hr work week. The American Conference of Governmental Industrial Hygienists threshold limit value is 100 $\mu g/m^3$. In occupations such as rock drilling and sandblasting, measured respirable crystalline silica levels often far exceed such standards. It is likely that the majority of overt exposures occur in small, unregulated industrial settings or in high-hazard occupations such as sandblasting, drilling, tunneling, silica flour mill operations, and stone grinding. Little exposure–response information is available concerning mixed exposures such as silica and metal dust generated during abrasive blasting operations. Therefore, it is uncertain if such occupational exposures require unique exposure limits.

Physical and Chemical Properties of Silica

Silicons make up almost 28% of the earth's crust and are found in combination with many other minerals and metals. Silica can exist in either a crystalline or amorphous form. The crystalline types of silica (SiO_2) include five polymorphs, i.e., quartz, tridymite, cristobalite, coesite, and stishovite (*2,8*). All these polymorphs are fibrogenic and biologically toxic. In most occupational exposures, quartz is the major type of silica involved. Amorphous silica and silicates are relatively less fibrogenic than crystalline silica (*8*). In the case of α-quartz, as well as the other crystalline polymorphs with the exception of stishovite, the silicon dioxide (SiO_2) molecules are arranged as a tetrahedral crystal

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(*8*). In the presence of water, the surface of silica becomes hydrated to form silanol groups (-SiOH). It is believed that the high reactivity of crystalline silica to biologic membranes is due to the unique properties of these surface silanol groups. The first theory is that -SiOH groups are hydrogen donors, whereas most biologic macromolecules contain lone-pair electrons on oxygen or nitrogen that serve as hydrogen acceptors. The formation of hydrogen bonds would result in strong interaction between silica and biologic membranes, resulting in possible damage. A second theory is that the surface of silica is negatively charged. At pH 7.0, 1 in 30 -SiOH groups would be negatively charged ($-SiO^-$). Negatively charged silica particles would react strongly with scavenger receptors on alveolar macrophages and would activate the generation of reactive oxygen species (ROS) and inflammatory cytokines (*9,10*). A third theory is that cleavage of the silica crystal, as would occur in silica flour milling, rock drilling, and sandblasting, results in the generation of $Si^•$ and $SiO^•$ radicals on the fracture planes, which can induce oxidant damage (*9,17,18*). Stishovite is another polymorph of pure crystalline silica that is distinguished by its octahedral structure. Structural differences among these polymorphs are considered to be important in their biologic reactivity, i.e., > quartz > tridymite > cristobalite > coesite > stishovite.

Human Pathologic Reactions to Crystalline Silica Exposure

Exposure to crystalline silica can result in adverse pulmonary responses such as acute silicosis, accelerated silicosis, chronic silicosis, and conglomerate silicosis (*1*). In addition, silica exposure may also be associated with systemic and autoimmune diseases such as scleroderma, rheumatoid arthritis, systemic lupus erythematosis, nephropathy, and proliferative glomerulonephritis (*1,12*). Tuberculosis is a common complication of silicosis often seen in severe grades of the disease. A possible association between silicosis and lung cancer is being accepted on the basis of evidence for a role of silica exposure in increased lung tumor formation in experimental animals and exposed human populations (*19*).

Acute Silicosis

Acute silicosis (silicolipoproteinosis) results from exposure to relatively high levels of silica (*3,20*). It has been reported in occupations such as sandblasting, surface drilling, tunneling, silica flour milling, and ceramic making. Morphologically the disease is characterized by pulmonary edema, interstitial inflammation, and the accumulation within the alveoli of proteinaceous fluid rich in surfactant (*1,12*). The exudate in the alveoli is eosinophilic, with a fine granular appearance (Figure 1). Radiographically, chest X rays exhibit a ground-glass appearance with diffuse lesions in the middle and lower lobes. Patients often suffer from labored breathing, fatigue, cough, weight loss, decreased pulmonary function, and compromised gas exchange. They develop cyanosis and respiratory failure, often complicated by mycobacterial infections. It has been proposed that acute silicosis occurs in workers exposed to freshly fractured silica dust and that surface $Si^•$ and $SiO^•$ radicals generated during fracturing play an important role in the rapid onset of this disease (*17,18*).

Accelerated Silicosis

Accelerated silicosis is commonly associated with heavy exposure as might occur in silica flour mill operations, sandblasting, and other crushing operations (*12,20*). It is similar in many respects to acute silicosis, exhibiting an exudative alveolar lipoproteinosis associated with chronic inflammation. In addition, accelerated silicosis is associated with fibrotic granulomas containing collagen, reticulin, and a large number of silica particles. The granulomas consist of a large number of mononuclear cells, fibroblasts, and collagen fibers with a predisposition for circular orientation showing the characteristic of immature silicotic nodules (*12*). The alveolar septa are lined with hypertrophic and hyperplastic alveolar type II epithelial cells with increased numbers of lamellar bodies. As with acute silicosis, accelerated silicosis also is associated with an increased morbidity and mortality.

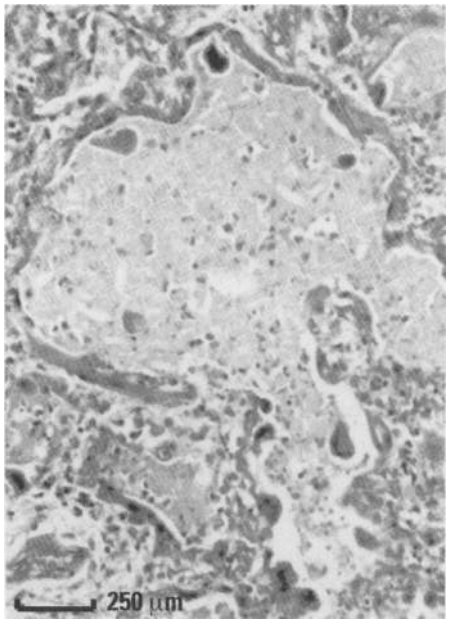

Figure 1. Acute silicosis showing granular eosinophilic exudate in alveolar spaces and interstitial inflammatory infiltration.

Chronic Silicosis

Inhalation of crystalline silica over prolonged periods promotes the formation of the classic fibrotic nodules having a typical histologic appearance of concentric arrangements of collagen fibers with central hyalinized zones (Figure 2). Typical concentric silicotic lesions with the whorled fibers of collagen are characteristic of silicotic lesions produced in humans by inhalation of crystalline silica and are morphologically distinct from lesions produced by other inorganic occupational exposures (*1,12*). The nodules show variable degrees of calcification and necrosis. Dust-containing macrophages, fibroblasts, and lymphocytes are often restricted to the periphery of the nodules. Microscopically, lesions of silicosis, which are sharply demarcated from the adjoining lung parenchyma, usually range in size from few millimeters to several centimeters in diameter. Nodules are often found predominantly in the upper zones of the lungs and in subpleural areas. In pure silicosis, nodules are free of pigmentation, and polarizing microscopy reveals dull birefringent particles, primarily in the center of the nodules. Radiographically, rounded opacities are evident initially in the upper lobes of the lung. As chronic silicosis progresses, pulmonary function deficits evidenced by decreases in static lung volumes and gas exchange become obvious.

Conglomerate Silicosis

Conglomerate silicosis results from the coalescence and agglomeration of several smaller

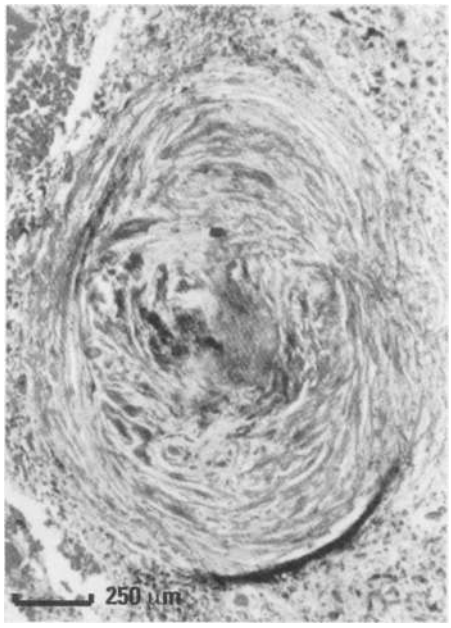

Figure 2. Chronic silicotic nodule showing characteristic features of this lesion. The amorphous center is surrounded by concentrically organized hyalinized collagen fibers. A cellular mantle of inflammatory cells is present at periphery. Mason's trichrome staining.

nodules. In addition to the enlargement of nodules, profusion of nodular lesions increases and results in progressive massive fibrosis (PMF). Cavitation and extensive destruction of the lung parenchyma, including bronchioles and blood vessels, are common with PMF. According to the Silicosis and Silicate Disease Committee, a PMF lesion is defined as a lesion greater than 2 cm in diameter in contrast to the 1-cm or larger radiographic size established by the International Labour Office (ILO) (*1*).

Silicosis and Tuberculosis

In the beginning of this century, tuberculosis reached epidemic proportions in workers with silicosis. The advent of drug therapy and dust control measures has considerably reduced the prevalence of silicotuberculosis. However, an increased risk for tuberculosis has recently been reported in Danish foundry workers with advanced silicosis (*21*). In addition, tuberculosis is still in great excess in South African gold miners and slate workers in Wales (*22–24*). The depressant effect of crystalline silica on the ability of alveolar macrophages to kill the tuberculosis mycobacterium was confirmed in experimental studies (*25*). It is believed that silicosis leads to a reduction in cell-mediated immunity with alterations in lymphocyte subsets and serum immunoglobulin levels (*26*). Microscopically, the silicotic nodules, concomitant with tuberculosis alterations, will have laminations and epithelioid cells with a lymphocyte collar. A caseation in the center of the silicotic nodule is common.

Rheumatoid Complications

Rheumatoid pneumoconiosis is rare in silicosis. It is characterized by rapidly developing large opacities in a size range of 1–5 cm located mostly in the periphery of the lungs, often with only mild silicosis. Rheumatoid silicotic complications are often seen in patients with rheumatoid disease or in patients with a rheumatoid positive factor. Macroscopically, the lesions appear to have dark and light laminating bands with central necrosis. Microscopically, a central zone of fibrinoid necrosis with silica is surrounded by palisading histiocytes, neutrophils, lymphocytes, and fibroblasts. Small blood vessels in the peripheral zones show clusters of lymphocytes and plasma cells.

Vascular Diseases

Chronic hypoxia is a common cause of death in severe acute silicosis. Chronic hypoxia can bring about pulmonary vascular spasms as a result of the pulmonary disease caused by severe involvement of lung parenchyma. Morphologic alteration of the vasculature is common as a result of dust accumulation and fibrosis in PMF. In such cases of severe conglomerate silicosis or PMF, pulmonary hypertension and cor pulmonale are common features and may become a cause of death.

Glomerulonephritis

Mild-to-moderate abnormalities in both renal function and structure have been observed in workers exposed to crystalline silica. Numerous case reports of severe glomerulonephritis with renal failure occurring in persons with acute silicosis have been described as "silicon nephropathy" (*27,28*). Immunologic abnormalities are often reported as common in these cases and a potential exists for immune-mediated renal injury. Direct injury to cells by the microcrystalline silica particles is suspected as a possible cause based on the demonstration of increased numbers of silica particles in kidneys of silicotic patients. The association of silica exposure with focal glomerular disease in several case reports is difficult to ignore.

Bronchogenic Carcinoma

Since the first proposed hypothesis by Goldsmith et al. in 1982 indicating a probable link between exposure to silica and lung cancer, several epidemiologic and pathologic studies have either supported or dismissed such a notion (*19,29,30*). In 1987, an International Agency for Research on Cancer (IARC) working group reviewed all the available evidence and concluded that there was insufficient evidence for the carcinogenicity of crystalline silica in humans (*30*). These conclusions about carcinogenicity of silica in humans were influenced by five major shortcomings: inappropriate controls, other occupational carcinogens, misclassification of silicotics, detection bias for silicosis, and chance of sampling variability (*19,30*). However, a recent working group organized by IARC in 1997 concluded that there is now sufficient evidence for the carcinogenicity of silica in humans (*31–33*). Several studies among the many reviewed by the IARC working group on the question of silica exposure and cancer risk in humans were negative or equivocal, and carcinogenicity of silica was not detected in all industrial operations. However, nine studies showed excessive risk for lung cancer (*19,32*). These included refractory brick workers, pottery workers, diatomaceous earth workers, foundry workers, granite workers, and mine workers (*19,32*). It appears that the carcinogenic property of crystalline silica may be dependent on its biologic activity, polymorphic nature, or specific industrial processes such as heat treatment and mechanical grinding. The relationship between the ability of silica to generate ROS and carcinogenesis has recently been reviewed (*34*).

Coal Mine Dust Exposures

Coal is a fossil fuel mined throughout the world. The generation of coal mine dust during underground coal mining is the most significant source of coal dust exposure. There are two basic types of coal mining operations, surface mining and underground mining, producing distinctively different exposure variables and disease entities. Underground coal miners are at greater risk of developing CWP than strip or surface miners because of the higher dust levels in the underground environment. In strip or surface mining, generated coal dust is diluted by outdoor air. However, rock-drilling operations associated with surface mining are associated with a greater risk of developing silicosis. Recent data indicate that approximately 200,000 workers are employed in the coal mining industry in the United States. The Mine Safety and Health Administration (MSHA) respirable coal mine dust PEL is 2 mg/m^3, while NIOSH has recently lowered its REL to 1 mg/m^3 (*35*). Although dust levels are below 2 mg/m^3 in most coal mines, MSHA has noted occasions in which the PEL is exceeded. High dust levels occur more often with long-wall mining than with conventional mining.

Physical and Chemical Properties of Coal

Although coal is mainly carbon, coal mine dust contains hydrogen, oxygen, nitrogen, trace metals, inorganic minerals, and crystalline silica. Trace metals can include boron, cadmium, copper, nickel, iron, antimony, lead, and zinc. Some of these trace elements can be cytotoxic and carcinogenic in experimental models. Common mineral and elemental contaminants are kaolin, mica, pyrite, titanium, calcite, sulfur, sodium, magnesium, and silica. The rank of coal increases from peat to lignite, sub-bituminous to bituminous, and anthracite. As rank increases, the ratio of carbon to other chemicals and mineral contaminants increases. In general, anthracite coal mining has been associated with higher rates of pneumoconiosis than that found in bituminous miners (*36,37*). Anthracite coal mine dust contains more surface free radicals than bituminous coal, which may explain its higher cytotoxicity and pathogenicity (*38–40*). In addition, anthracite has a higher crystalline silica content than bituminous coal (*41*). However, experimental evidence suggests that silica particles from bituminous mines may be coated with clay, rendering them less active (*41*). Respirable coal mine dust has a relatively large surface area due to its small aerodynamic size and porous nature. Organic aromatic compounds present in the coal atmosphere, such as benzene, methylene, phenol, and phenanthrene,

can be adsorbed onto the surface of coal mine dust and may affect its biologic activity.

Human Pathologic Reactions to Coal Mine Dust

Inhalation of coal mine dust can lead to the development of several diseases including CWP, bronchitis, emphysema, Caplan syndrome, and silicosis (*42,43*). Coal miners typically develop one of two forms of disease patterns—simple CWP or complicated CWP. With chronic exposure, the milder form of CWP may become complicated CWP, with enlargement and profusion of lesions in the lung. Black lung is a legal term used to include CWP, bronchitis, emphysema, and silicosis when they are found in association with employment history in coal mines.

Coal Workers' Pneumoconiosis

The first case report on CWP was by Gregory (*44*) in 1831 in a British coal miner. Initially coal dust was considered innocuous, and CWP was thought to be a variant of silicosis due to similarities in chest radiographs. This hypothesis was disproved by Collins and Gilchrist (*45*). They studied the pathologic changes in the lungs of coal trimmers exposed to coal that was free of silica and showed that workers developed pneumoconiosis despite low silica exposure. Gough et al. (*46*) and Heppleston (*47,48*) confirmed these findings and showed that the histologic pulmonary lesions in coal trimmers were identical to those found in underground coal miners. CWP is now clinically and pathologically distinguished from silicosis.

The spectrum of lung lesions in coal workers is wide, and CWP is categorized according to the severity of disease (*42,43*). Simple CWP is characterized by the formation of black coal dust macules centered around the respiratory bronchioles, mostly in the upper lobes of the lung. The macules range in size from 1 to 6 mm in diameter and are irregular in size. Microscopically, macules contain coal dust-laden macrophages with a fine network of reticulin and some collagen fibers (Figure 3). Focal emphysema is a characteristic feature associated with these macules (*43*). These small coal dust- or carbonaceous material-laden pulmonary lesions have not been associated with pulmonary symptoms.

Increased exposure to coal mine dust results in the development of nodular lesions that are firm on palpation in contrast to nonpalpable macules. They are classified on the basis of size as micronodules (< 7 mm diameter) and macronodules, which range in diameter from 8 mm to 2 cm (*42*). They develop at the bifurcations of respiratory bronchioles and are commonly seen against a background of macules, mostly in the upper lungs. Nodules contain heavily coal dust-laden macrophages interlaced with collagen fibers oriented in a haphazard manner and may have round, irregular, or stellate borders (Figure 4). The fibrotic stroma is composed of mature and immature collagen and reticulin. With chronic exposure to coal mine dust, nodules may converge and coalesce to produce lesions measuring larger than 2 cm with a fibrous nature. At this stage, the disease is called complicated CWP or PMF.

Progressive Massive Fibrosis

Progressive massive fibrosis is a generic term common in many pneumoconioses, including silicosis and CWP. In complicated CWP or PMF, lung function is compromised due to extensive fibrosis and emphysema. Progression of simple CWP to the more aggressive form of PMF is thought to be associated with severe cumulative dust exposure, concentration of inorganic minerals and silica, impaired clearance, infections, and immunologic factors (*49–53*). There is a tendency for PMF to progress with or without further exposure (*49*). Progression from simple CWP to PMF has been related to radiographic severity of disease, to coal mine dust exposure level, and to total dust burden.

PMF lesions have a predilection to occur in the upper lobes of the right lung. However, in advanced cases, lesions are bilateral. Microscopically, PMF lesions appear as coal dust-laden irregular or round, well-demarcated fibrotic masses of collagen bundles and haphazardly laid hyalinized collagen fibers intertwined with reticulin (Figure 5). Lesions may also appear as amorphous collagenization or clusters of nodules. Necrosis is often associated with central cavitation, and cholesterol crystals are usually present. Vascular degenerative changes associated with bronchial and pulmonary arteries and lymphatic vessels are common in the lesions.

Rheumatoid Pneumoconiosis (Caplan Syndrome)

In coal miners with circulating rheumatoid factor, rheumatoid pneumoconiosis (Caplan syndrome) can occur (*54,55*). It is reported to be more common in Europe, particularly in Welsh miners. There is no evidence that coal mining predisposes workers to rheumatoid arthritis; however, it is often associated with severe categories of CWP (*56*). Macroscopically, the nodules are pale yellow and show variable layers of concentric dark bands. The central zone is eosinophilic, granular, and necrotic, with fragments of nuclear material, collagen, and elastin often associated with cavitation and calcification. Microscopically, the nodules are similar to rheumatoid nodules, circumscribed, and range in size from 0.5 to 5 cm in diameter. The periphery of the lesion is composed of concentrically arranged collagen with lymphocyte, plasma

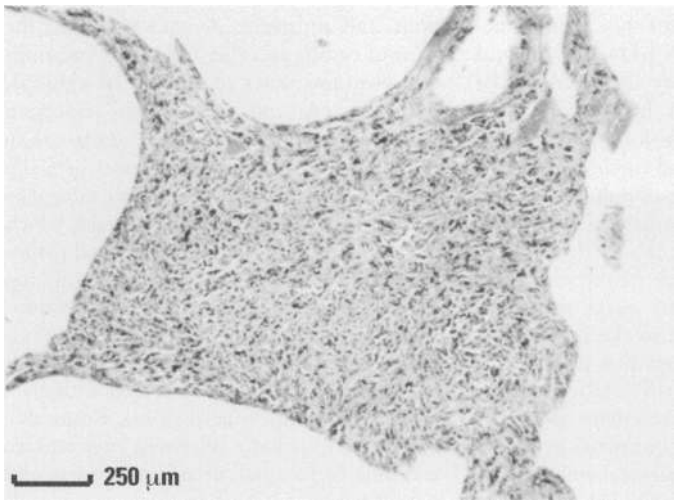

Figure 3. Typical coal macule in the walls of respiratory bronchioles, with focal emphysema surrounding the macule.

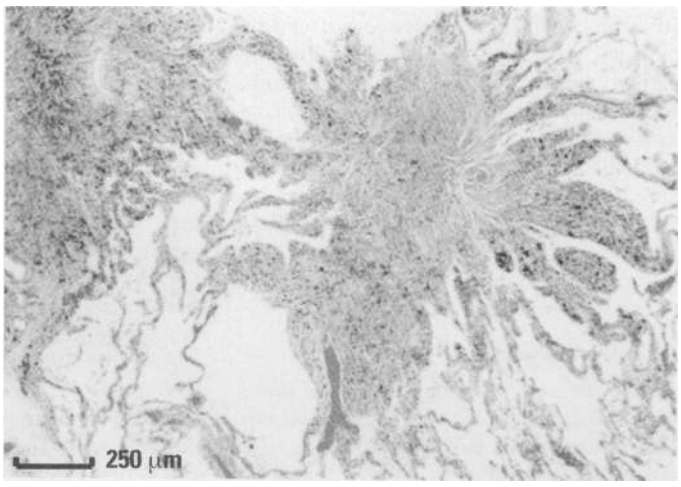

Figure 4. Stellate-shape micronodules developing around respiratory bronchioles. Greater collagen and fewer coal dust particles are distinguishable compared to macules.

cells, and macrophages containing coal dust. Palisading fibroblasts and plasma cells are a characteristic feature of these lesions; they are rare in tuberculosis and other infectious granulomata (*43*).

Silicosis in Coal Workers

Silicosis in coal miners is rarely an isolated form of pneumoconiosis and is usually found in conjunction with simple CWP. Microscopically, silicotic nodules appear with the typical concentric laminations of mature collagen surrounding a hyalinized and partially necrotic or calcified center. The nodule is surrounded by a pigmented zone often containing histiocytes in reticulin stroma (Figure 6). Nodules are found more frequently in the upper lung zones but are also found in subpleural and peribronchiolar locations. Polarized light microscopy may reveal numerous weekly birefringent particles within the nodules and highly birefringent particles in the peripheral mantle. With chronic exposure to silica, confluence and profusion of lesions may occur, resulting in the development of conglomerate silicosis or PMF.

Prevalence of silicosis in coal miners can be reliably determined only in autopsy studies because of the inability of chest radiography to distinguish between silicosis and CWP. Furthermore, eggshell calcification indicative of silicosis in radiographs is often not associated with parenchymal silicosis in autopsy studies. Pathologic evaluations of 4,115 autopsy cases from the National Coal Workers' Autopsy Study from 1972 to 1996 have found 23% of coal miners with pulmonary silicosis and 58% with lymph node silicosis (*57*). Certain job categories such as tunnel drilling, roof bolting, and transportation are associated with increased risk for developing silicosis (*58*).

Relationship between Radiographic Category and Morphology of CWP

Radiographically, simple CWP is classified according to the number, size, and shape of small opacities, which are most prevalent in the upper zones of both lungs. Multiple small rounded opacities on the chest radiographs are classified and categorized based on size (i.e., p, q, or r), shape (i.e., s, t, u), and profusion (i.e., 0, 1, 2, or 3) using standard reference films developed by the ILO (*59*). In simple CWP, radiographic opacities range in size from 0.001 to 1.0 cm, and in complicated CWP they are greater than 1.0 cm in diameter. Complicated CWP with opacities greater than 1.0 cm are defined in terms of their dimension as A (< 50 mm), B (50 mm plus but not greater than right upper lung lobe), and C (exceeding the size of right upper zone). In general, there is good correlation between pathologic grading of disease severity and X-ray category; large opacities showed a better correlation with pathologic PMF (*59*). However, moderate-to-severe pathologic abnormality has to be present before abnormality can be detected radiographically with certainty. In cases with a radiographic profusion of 0/0, moderate numbers of macules and miconodules were present in pathologic evaluation (*59*). PMF may be confused in chest radiography with carcinoma, tuberculosis, or bacterial infectious lesions (*59*).

Respiratory Symptoms of CWP

Coal miners with milder forms of simple CWP usually have no symptoms. Nevertheless, in a small proportion of coal miners' abnormal pulmonary function tests, airflow obstruction and changes in diffusing capacity were observed with macules (pea-size small opacities) (*60*). A 9-year follow-up study of coal miners with simple CWP (small rounded opacities) showed only a small fall in gas exchange (*61*). Such a small drop in gas exchange would not be expected to compromise arterial oxygen content even during mild exercise (*62*). It was, however, shown that lung mechanics are decreased in simple CWP, leading to an increase in residual volume (*63*). Focal emphysema associated with coal macules is thought to be involved in collapse of small airways. In addition, a condition known as industrial bronchitis is reported in coal miners with and without radiographic evidence of CWP (*64*).

In complicated CWP, premature death is associated with pulmonary disability. Higher grades of PMF are associated with severe airway obstruction, restrictive defects, abnormalities in ventilation and perfusion, reduced diffusing capacity, and low arterial oxygen pressure (*65*). These progressive changes eventually lead to pulmonary hypertension and cor pulmonale (*65*).

Lung Cancer in Coal Miners

Lung cancer in coal miners occurs less frequently than in the general population after adjustment for age and smoking (*66,67*). Epidemiologic studies of British and U.S. coal miners reported a lower risk of lung cancer for miners compared to that in nonminers, and there was no apparent influence of mining tenure on the prevalence of lung tumors. There were also no changes in the histopathology of lung cancer cell types in coal miners, a point of view critically evaluated to assess the relationship of smoking (*68*). The tumors were mostly squamous cell (30%), adenocarcinoma (27%), and small cell (26%), again showing no influence of mining tenure on the frequency of these cell types. From these histopathologic studies, it is

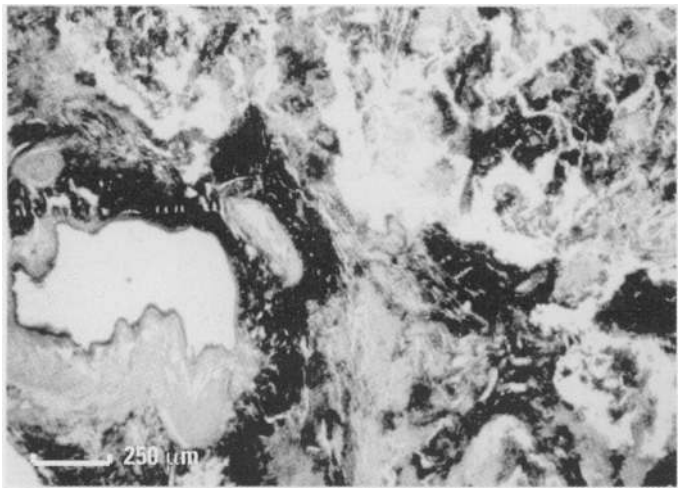

Figure 5. Progressive massive fibrosis lesion showing cavitation and distortion of the bronchiole and blood vessels. Necrosis in the cavity contains coal dust and dust-containing macrophages.

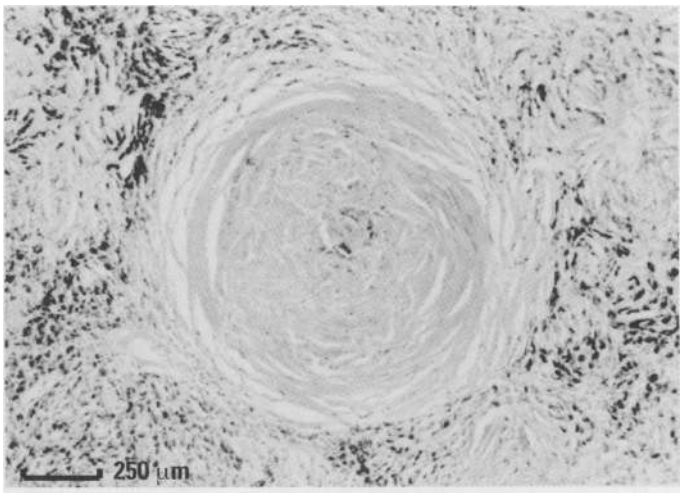

Figure 6. Silicotic lesion in a coal miner's lung showing characteristic features of silicotic nodule, such as an amorphous center with concentrically arranged collagen fibers. Note the nodule is surrounded by coal dust.

evident that there are no apparent cellular differences in lung cancer of coal miners who smoke and the cigarette-smoking general population (*68*).

In contrast to lung cancer, epidemiologic studies have revealed a higher-than-normal incidence of mortality from gastric cancer in coal miners compared to that in nonminers (*69–71*). A significant relationship between cumulative dust exposure and increased mortality from cancers of the digestive system was also evident from these studies. It has been suggested that nitrosation of ingested coal dust in the acidic gastric environment could result in the production of carcinogenic products, which may lead to the higher incidence of gastric cancer in coal miners (*72*). In support of this hypothesis, it was shown that upon nitrosation of coal dust extracts they become mutagenic and are able to induce neoplastic transformation of mammalian cells (*72,73*).

Mechanisms of Silica and Coal Pathogenicity

Interstitial lung disease caused by exposure to silica and/or coal dust is the consequence of damage to lung cells and the resultant lung scarring associated with activation of the fibrotic process. The following mechanisms have been proposed to characterize this cycle of damage and scarring (*9,10*):

- Direct cytotoxicity: Chemical features of silica or coal dust result in reaction with lung cells, leading to peroxidation of membrane lipids and damage to cell membranes. Damaged cells may release intracellular enzymes, which would cause further tissue damage, leading to scarring or destruction of alveolar septa.
- Activation of oxidant generation by alveolar macrophages: Silica or coal dust stimulates the generation of ROS from alveolar macrophages, which overwhelms antioxidant defenses of the lung and causes lipid peroxidation and cell damage. Such damage may lead to scarring or destruction of alveolar septa.
- Stimulation of the secretion of inflammatory cytokines and chemokines from alveolar macrophages and/or alveolar epithelial cells: These inflammatory mediators act as chemoattractants to recruit polymorphonuclear leukocytes (PMNs) and macrophages from pulmonary capillaries to the air spaces. These cytokines also activate pulmonary phagocytic generation of oxidant species, leading to tissue damage and scarring.
- Stimulation of secretion of fibrogenic factors from alveolar macrophages and/or alveolar epithelial cells: Release of fibrogenic factors results in induction of fibroblast proliferation and/or the stimulation of collagen synthesis, leading to fibrosis.

Direct Cytotoxicity

The ability of silica or coal dust to cause lipid peroxidation and induce damage to cells or lung tissue is summarized in Table 1. *In vitro* and *in vivo* damage resulting from silica exposure has generally been reported to be more severe than with coal dust.

Christian and Nelson (*78*) have correlated the cytotoxicity of coal dust with the nickel content of the mine dust samples. Samples from Pennsylvania coal mines had higher nickel content and exhibited greater cytotoxicity than samples from Utah coal mines. This cytotoxicity was related to the higher rates of CWP in Pennsylvania mines than that reported in Utah. Dalal et al. (*39*) have found radicals on the fracture surfaces of freshly ground anthracite coal and noted that hemolytic activity of this coal dust decreased as these surface radicals decayed.

Nash et al. (*87*) have suggested that SiOH groups on the surface of crystalline silica are capable of forming hydrogen bonds with membrane components, resulting in membrane injury and leakage. Polyvinylpyridine-*N*-oxide is thought to detoxify silica by acting as a proton acceptor and shielding the SiOH groups on quartz. Nolan et al. (*88*) have proposed that the negative surface charge of the SiO^- groups is critical to cytotoxicity. It is possible that this negative charge allows silica to interact with scavenger receptors on alveolar macrophages (*80,89*). Indeed, neutralization of the surface of quartz with aluminum salts markedly reduces cytotoxicity (81).

The grinding of silica results in the generation of $Si^•$ and $SiO^•$ radicals on the fracture planes (*17,90*). Upon contact of these surface radicals with aqueous solution, hydroxyl radicals are generated (*17*). There appears to be a direct relationship between the ability of silica particles to generate hydroxyl radicals and the potential to cause lipid peroxidation and cytotoxicity *in vitro* (*17,91*). A similar relationship has been demonstrated *in vivo* as well (*18,86*). Surface iron plays an important role in augmenting silica-induced hydroxyl radical production and cytotoxicity both *in vitro* and *in vivo* (*17,92*).

Activation of Oxidant Species Production by Alveolar Macrophages

The production of reactive species (superoxide, hydrogen peroxide, nitric oxide) from alveolar macrophages has been associated with cell damage and disease (*93*). Indeed, a relationship has been reported between the level of oxidant production by pulmonary phagocytes and lung damage and severity of pneumoconiosis (*84,94*). Silica- and/or coal dust-induced oxidant production from alveolar macrophages has been measured directly or by monitoring chemiluminescence in cellular, animal, and human exposure studies. The data are summarized in Table 2. As with direct cytotoxicity, silica appears to be a more potent stimulant of oxidant production than coal dust.

Freshly fractured silica is a more potent stimulant of oxidant species production by alveolar macrophages than aged silica where surface radicals had decayed. This greater potency of fresh silica dust has been demonstrated after both *in vitro* and inhalation exposures of rat alveolar macrophages (*86,99*). Similarly, extremely high levels of chemiluminescence have been reported from a rock driller who was exposed to fresh silica and was diagnosed with acute silicosis (*97*).

Stimulation of Inflammatory Cytokine Release

As discussed above, silica and, to a lesser extent, coal dust can stimulate oxidant generation. Evidence indicates that oxidant stress can activate the nuclear transcription factor NF-κB (*100*). Data indicate that silica can simulate NF-κB binding to DNA (*101*). Such binding to various gene promoters can result in mRNA production for a variety of inflammatory cytokines. Recent evidence indicates that silica-induced activation of another transcription factor, activation protein-1, also may play an important role in the regulation of inflammatory cytokines (*102*).

Table 1. Direct cytotoxicity of silica or coal mine dust.

Toxic reaction	Silica	Coal dust	Reference
In vitro studies			
Lipid peroxidation	++	+	(*74,75*)
Hemolysis	++	+	(*74–76*)
LDH release from alveolar macrophages	++	+	(*76,77*)
Inhibition of mammalian cell growth	NR	+	(*78*)
Increased permeability of T_{II} monolayers	++	NR	(*79*)
Apoptosis	++	NR	(*80*)
In vivo studies			
Lipid peroxidation	++	NR	(*18*)
Lavage enzyme levels	++	—	(*81,82*)
Lavage protein	++	+	(*83–85*)
Lavage red blood cells	++	NR	(*18,86*)
Lavage lactate dehydrogenase	++	NR	(*83,85*)

Abbreviations and symbols: —, no significant response; +, significant response; ++, greater response than +; NR, response has not been reported.

Excessive and prolonged inflammation of the lung has been associated with the development of pulmonary disease. In studies of silica exposure of rats, the recruitment of PMNs from the pulmonary capillaries to the alveolar airspaces is a hallmark of the initiation and progression of silica-induced lung disease (*83,85,86,103*). As with cytotoxic responses, the degree of pulmonary inflammation is related to the ability of the silica particles to generate radicals, i.e., freshly fractured silica exhibits more surface radicals and causes more PMN recruitment than aged silica (*18,86*). PMN recruitment has also been demonstrated as a hallmark of acute silicosis in humans (*97*). Exposure of animals to coal dust also results in inflammation characterized as an increase in the number of macrophages and PMNs in the alveolar space (*82,104*). In general the magnitude of the inflammatory response to coal dust exposure is smaller than that to silica (*84*) and is less dominated by PMN recruitment (*104*). An increased number of alveolar macrophages have also been reported in coal miners, with the number of lavagable macrophages increasing with the severity of CWP (*105*).

This recruitment of phagocytic cells into the alveolar spaces is in response to the particle-induced production of chemotactic cytokines and chemokines by alveolar macrophages and alveolar type II epithelial cells (*106*). A list of inflammatory cytokines and chemokines produced in response to silica or coal dust exposure is given in Table 3. Leukotriene B_4, platelet-activating factor (PAF), and interleukin (IL)-1 are chemotaxins for PMNs and in the case of IL-1 lymphocytes as well (*6*). Tumor necrosis factor alpha (TNF-α) may not be a direct chemoattractant factor; however, it is a potent stimulant of chemokines, such as macrophage inflammatory protein (MIP-1 or MIP-2) and cytokine-induced neutrophil chemoattractant (*118*). Indeed, the importance of TNF-α in the inflammatory reaction to silica has been emphasized by the fact that *a*) PMN recruitment exhibits a direct, linear relationship to TNF-α production in silica-exposed rats (*119*); and *b*) treatment of silica-exposed rats with anti–TNF-α dramatically attenuates PMN recruitment (*118*).

Once PMNs are recruited into the alveolar spaces, several inflammatory cytokines act to stimulate oxidant production by these phagocytes. This would increase the oxidant burden in the lung, overwhelm antioxidant defenses, and cause lung injury and scarring. Indeed, activation of ROS production by PMNs has been demonstrated in response to PAF, TNF-α, and IL-1 (*107,119*).

Table 2. Silica or coal dust-induced activation of oxidant release from alveolar macrophages.

Response	Silica	Coal dust	Reference
In vitro studies			
Superoxide anion	++	NR	(*95*)
Hydrogen peroxide	++	NR	(*95*)
Chemiluminescence	++	NR	(*95*)
In vivo animal studies			
Hydrogen peroxide	++	NR	(*95*)
Chemiluminescence	++	+	(*82,86,95*)
Nitric oxide	++	+	(*84,86,96*)
Human studies—patients with silicosis or CWP			
Superoxide anion	++	+	(*94,98*)
Hydrogen peroxide	++	NR	(*98*)
Chemiluminescence	++	+	(*96,97*)
Nitric oxide	+	+	(*96*)

Abbreviations and symbols: +, significant response; ++, greater response than +; NR, response has not been reported.

Table 3. Silica or coal dust-induced stimulation of cytokine and chemokine secretion from lung cells.

Response	Silica	Coal dust	Reference
In vitro studies			
Platelet-activating factor	++	+	(*107*)
Leukotriene B_4	++	+	(*108*)
Prostaglandin E_2	NR	+	(*109*)
Thromboxane A_2	NR	+	(*109*)
TNF-α	++	+	(*108,110*)
IIL-1	++	+	(*111*)
IL-6	NR	+	(*110*)
In vivo animal studies			
Leukotriene B_4	+	+	(*112,113*)
Prostaglandin E_2	+	NR	(*112*)
Thromboxane A_2	NR	+	(*113*)
TNF-α	++	NR	(*114*)
IL-1	+	NR	(*114*)
Macrophage inflammatory protein	++	NR	(*106*)
Human studies—patients with silicosis or CWP			
TNF-α	NR	+	(*115*)
IL-1	NR	+	(*115*)
Monocyte chemoattractant peptide-1	NR	+	(*116*)
IL-6	NR	+	(*117*)

Abbreviations and symbols: +, significant response; ++, greater response than +; NR, response has not been reported.

Stimulation of Fibrogenic Factor Release

A number of cytokines produced by alveolar macrophages have regulatory effects on fibroblast growth and/or collagen synthesis. When the balance between fibrotic and antifibrotic mediators shifts, pulmonary fibrosis can develop. IL-1 (*120*), TNF-α (*121*), platelet-derived growth factor (PDGF) (*122*), fibronectin (*123*), alveolar macrophage-derived growth factor (*123*), and type 1 insulinlike growth factor (*124*) have been reported to increase fibroblast proliferation. PDGF and fibronectin are competence factors, whereas alveolar macrophage-derived growth factor is a progression factor for proliferation of fibroblasts. IL-1 has also been described as a direct stimulant of collagen production (*125*). TNF-α is not only a direct proliferative agent for fibroblasts but also stimulates the secretion of PDGF *in vitro* (*126*). A critical role of TNF-α in pulmonary fibrosis is demonstrated by the fact that anti-TNF-α significantly decreased silica-induced pulmonary fibrosis in a mouse model (*127*).

In contrast, IL-6 exhibits antifibrotic activity (*128*). Prostaglandin E_2 and transforming growth factor beta (TGF-β) exhibit a depressive effect on cell growth (*122,124*). However, under certain conditions, TGF-β can stimulate collagen synthesis *in vitro* (*129*).

The effects of silica or coal dust exposure on alveolar macrophage production of cytokines that regulate fibrogenesis are listed in Table 4. Although exposure has been reported to stimulate both fibrogenic and antifibrogenic factors, it appears the balance shifts toward fibrotic stimuli. For example, TNF-α, type 1 insulinlike growth factor, and PDGF all increase as simple CWP progresses to PMF.

Data Gaps and Unresolved Issues in Silicosis

- Controversy over the relationship between crystalline silica exposure and the development of lung cancer still exists. Further evidence from both experimental animal studies and human investigations is desirable.
- Why does silica induce lung tumors in rat models but not in mice or hamsters? What is the mechanistic reason for this difference?
- In rats, silica-induced lung tumors have been associated with a particle overload. Is silica overload a prerequisite for the neoplastic response in humans?

Table 4. Silica or coal dust-induced stimulation of fibrogenic factor secretion from lung cells

Response	Silica	Coal dust	Reference
In vitro studies			
TNF- α	++	+	(108,110)
IL-1	++	+	(111)
Prostaglandin E_2	NR	+	(109)
IL-6	NR	+	(110)
In vivo animal studies			
TNF-α	++	NR	(114)
IL-1	+	NR	(114)
Fibronectin	+	NR	(114)
TGF-β	+	NR	(130)
Prostaglandin E_2	+	NR	112)
Human studies—patients with silicosis or CWP			
TNF-α	NR	+	(115)
IL-1	NR	+	(115)
Fibronectin	+	+	(98)
Alveolar macrophage-derived growth factor	+	+	(98)
Platelet-derived growth factor	NR	+	(124)
Type I insulinlike growth factor	NR	+	(124)
TGF-β	NR	+	(124)
IL-6	NR	+	(117)

Abbreviations and symbols: +, significant response; ++, greater response than +; NR, response has not been reported.

- Lung carcinomas in silica-exposed rats tend to be mostly in peripheral airways and adenocarcinomas/bronchoalveolar carcinomas are the frequent cell types. Is there a predilection in humans for similar tumors?
- Dose–response relationships between tumor incidence and exposure to crystalline silica is required in both animal models and human studies.
- Is silicosis in the lymph nodes associated with excess lung cancer? Does this impede the clearance of other carcinogens from the lung and provide an increased residence time? If so, what evidence is available to support DNA damage or increased frequency of mutations?
- Is pulmonary fibrosis a prerequisite for silica-induced lung cancer in humans?
- Is an oxidant burden (particle derived and/or inflammation derived) an intrinsic mechanism involved in triggering silica-induced tumors?
- Is crystalline silica a direct-acting carcinogen or cocarcinogen? Is it an initiator or promoter?
- Why do different strains of mice exhibit different susceptibilities to silica-induced fibrosis? What are the mechanistic differences involved?
- Since freshly fractured silica is more cytotoxic and inflammatory than aged silica, does this necessitate a lower exposure standard in occupations that generate freshly fractured silica dust? How much lower should the standard be?
- What is the toxicity of abrasive blasting substitutes in relationship to silica? Do safe substitutes exist?
- Can biomarkers be developed to identify adverse reactions to silica before disease becomes irreversible?
- Can silicosis be treated or its progression inhibited?

Data Gaps and Unresolved Issues in CWP

- Controversy over the relationship between the extent of exposure to crystalline silica or silicates and the development of lung lesions such as nodules or PMF is unresolved.
- Is impaired clearance or dust overload a requirement for the progression of simple CWP to PMF?
- Is an oxidant burden (particle derived and/or inflammation derived) an intrinsic mechanism involved in the development of CWP?
- Why do coal miners have a lower than normal risk of lung cancer? Does coal dust inhibit the metabolic activation of chemicals to carcinogens?
- What is the true incidence of lung cancer in never-smoker coal miners? Is there a dose response?

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