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UNDERSTANDING THE CHEMICAL PROPERTIES OF MACERALS AND MINERALS IN COAL AND ITS POTENTIAL APPLICATION FOR OCCUPATIONAL LUNG DISEASE PREVENTION

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Recent increases in oil price further strengthen the argument that coal and coal products will play an increasingly important role in fulfilling the energy needs of our society. Coal is an aggregate of heterogeneous substances composed of organic (macerals) and inorganic (minerals) materials. The objective of this review was to assess whether some chemical parameters in coal play a role in producing environmental health problems. Basic properties of coal—such as chemical forms of the organic materials, structure, compositions of minerals—vary from one coal mine region to another as well as from coals of different ranks. Most importantly, changes in chemical properties of coals due to exposure to air and humidity after mining—a dynamic process—significantly affect toxicity attributed to coal and environmental fate. Although coal is an extremely complex and heterogeneous material, the fundamental properties of coal responsible for environmental and adverse health problems are probably related to the same inducing components of coal. For instance, oxidation of pyrite (FeS_2) in the coal forms iron sulfate and sulfuric acid, which produces occupational lung diseases (e.g., pneumoconiosis) and other environmental problems (e.g., acid mine drainage and acid rain). Calcite ($CaCO_3$) contained in certain coals alters the end products of pyrite oxidation, which may make these coals less toxic to human inhalation and less hazardous to environmental pollution. Finally, knowledge gained on understanding of the chemical properties of coals is illustrated to apply for prediction of toxicity due to coal possibly before large-scale mining and prevention of occupational lung disease during mining.

Should oil prices remain high, coal and coal products will play an increasingly important role in fulfilling the energy needs of our society and around the world. In fact, 51% of the electricity generated in the United States is by coal-fired power plants, in China coal accounts for 77% of their electricity, and in Poland coal generates 94% of the electricity (http://www.worldcoal.org). According to the forecasts of the Department of Energy (http://www.fossil.energy.gov), coal will account for about 57% of the power generated in the United States by the year 2030. According to the National Energy Technology Laboratory (http://www.netl.doe.gov), some 154 new coal-fired power plants are on the drawing board in 42 states of the United States. Besides power generation, coal as an energy resource is used for iron and steel and cement production, processes requiring coal for heating. Coal combustion products, the by-products generated by burning coal in coal-fired power plants, can be used to replace or supplement cement in concrete. Coal is readily converted into a variety of fuels, which are sulfur free and low in particulates and nitric oxides. South Africa has been producing coal-derived fuels since 1955 and has the only commercial coal to liquids industry in operation today, which currently produces around 30% of the country's gasoline and diesel needs from indigenous coal.

Coal resources are available in almost every country globally. According to the World Coal Institute, proven coal reserves at current production levels of approximately 5 billion tons per year are estimated to last at least 155 years (http://www.worldcoal.org). Therefore, environmental and health problems related to coal mining and coal use are of global concern. In contrast, proven oil and gas reserves are equivalent to around 41 and 65 yr at current production levels, respectively. Over 68% of oil and 67% of gas reserves are concentrated in the Middle East and Russia. Therefore, countries like the United States with significant coal resources have the benefit of energy security.

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Although coal is an extremely complex and heterogeneous material, many of its fundamental properties producing health problems seem to be related to coal structure and its dynamic interaction among organic and inorganic compounds after exposure to air. The environmental problems appear to be primarily produced by the components of the coal (e.g., S, As, Hg, and the combustion products such as CO_2, NO_X, SO_X). This review summarizes the current understanding of those aspects and proposes to use knowledge gained through studies on coal physicochemistry, toxicity, and epidemiology to predict and prevent environmental and adverse health problems produced by coal use.

COAL STRUCTURE

Coal is a combustible, sedimentary, organic-rich rock, composed mainly of carbon, hydrogen, and oxygen (Levine et al. 1982; Meyers 1982). A fossil fuel, coal is formed from vegetation that has been consolidated between rock strata and altered by the combined effects of pressure and heat over a million years. Coal is an aggregate of heterogeneous substances composed of organic and inorganic materials (Meyers, 1982). Figure 1 illustrates the complex structure of coal. Organic material dominates, typically representing 85–95% (w/w) of a dry coal. These organic materials occur in different petrographic types, called "macerals," which reflect the nature of the precursor plant material and differ in their color/reflectance, morphology, and chemical and physical properties. There are three basic groups of macerals: (1) vitrinite group derived from coalified woody tissue, (2) liptinite group derived from the resinous and waxy parts of plants, and (3) inertinite group derived largely from charred and biochemically altered plant cell wall material. In addition to its origin and appearance, properties of macerals change as a function of rank of maturation.

Coal rank is defined as the extent to which the organic materials have matured during geological time ongoing from peat to anthracite. Coal "rank" is the degree of change undergone by coal as it matures from peat to anthracite—a process known as coalification—and has an important bearing on the coal's physical and chemical properties. Coal rank is roughly estimated by the carbon content in the coal, molar ratio of carbon/hydrogen (C/H), heat value, volatile materials, moisture, or reflectivity of the vitrinite macerals. The four major coal types ranked in order of increasing heat value are: lignite < subbituminous < bituminous < anthracite.

Low-rank coals, such as lignite and subbituminous coals, are typically softer, friable materials with a dull, earthy appearance. They are characterized by high moisture levels and relatively low

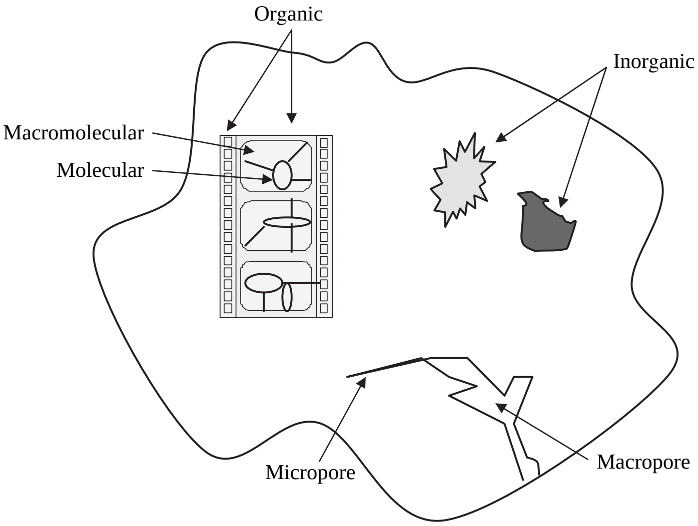

FIGURE 1. Diagrams of the major constituents in coal: organic materials and minerals, fragments of plant debris (macerals), and an extensive pore network consisting macromolecular and molecular states.

carbon content, and therefore lower energy content. Higher rank coals are generally harder and stronger and often have a black, vitreous luster. They contain more carbon, have lower moisture content, and produce more energy. Anthracite is at the top of the rank scale and has a correspondingly higher carbon and energy content and a lower level of moisture (Meyers, 1982).

The inorganic portion of coal comprises 5–15% (w/w) and is composed of phyllosilicates (kaolinite, illite, etc.), quartz, carbonates, sulfides, sulfates, and other minerals (Meyers, 1982). In general, Al and Fe are the main metals existing as aluminosilicates and pyrite in the coals, and As, Ni, Zn, Cd, Co, and Cu are trace metals that represent only a very small fraction of the inorganic constituents (Finkelman, 1995).

A third structural element, which is distinctive from other solid fossil fuel sources like petroleum and oil shale, is an extensive network of pores. Macropore represents diameter of pores >2500 nm and micropore comprises material with pore size <7.5 nm. These pores give coal a high surface area, allowing access to a significant fraction of the organic material.

Elemental analysis reveals that coal is deficient in hydrogen with a low atomic ratio of hydrogen to carbon (~0.9), which is only half of that for petroleum and oil shales, suggesting a chemical structure with high levels of aromatic and other unsaturated aliphatic hydrocarbons (Levine et al., 1982). On the other hand, level of oxygen in coal is high at one oxygen for every 5 carbon atoms, more than 10-fold higher than the oxygen levels in petroleum. Oxygen may be present as carboxyl or phenol groups attached at the edge of the aromatic rings or aliphatic chains or buried as heteroatoms in aromatic and naphthenic rings. The abundant oxygen in the coal influences not only coal's structure but also its reactivity (Levine et al., 1982). The oxidation converts aromatic carbons bonded to bridges into peripheral carboxyl groups on the neighboring clusters and also converts the other aromatic carbons into nonaromatic acids or carbon dioxide. Figure 2 shows a model of the types and arrangements of the organic groups in a bituminous coal. "Clusters" of aromatic and naphthenic rings are coupled to one another by "bridges" of aliphatic chains or heteroatoms. What this model cannot convey is the three-dimensional arrangement of these chemical constituents to form the system of micropores and macropores that permeate the solid.

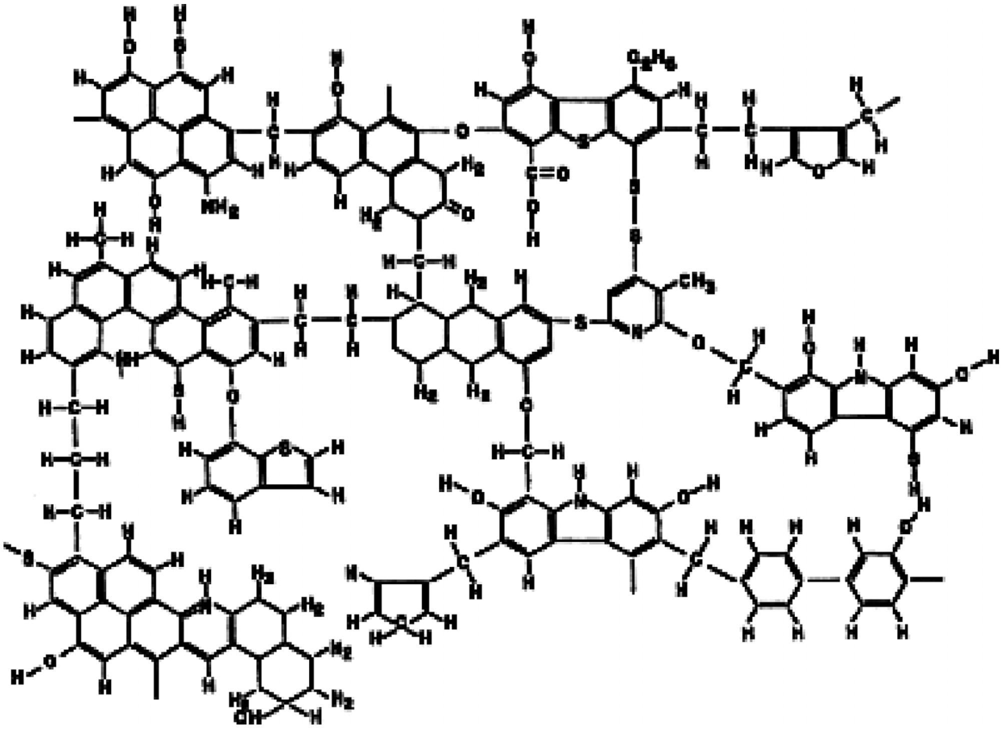

FIGURE 2. A representative structure of the chemical groups in a bituminous coal.

Now it is widely accepted that coal consists of two major structural elements, aromatic clusters (mono- or fused aromatic rings with peripheral groups) (molecular state) and intercluster bridges (cross-link of alkyl and ethers groups with aromatic clusters) (macromolecular state). The molecular/macromolecular model of coal was used to explain the dynamic of oxidation, swelling of coal in pyridine, molecular mobility, and extraction (Lucht et al., 1987; Lucht & Peppas, 2003; Takanohashi & Lino, 1994).

COAL MINING-RELATED ENVIRONMENTAL AND HEALTH PROBLEMS

Environmental Problems

Coal mining raises a number of environmental challenges, including soil erosion, dust, noise and water pollution, and impacts on local biodiversity. Although steps can be taken in modern mining operations to minimize these impacts, good planning and environmental management minimize the impact of mining on the environment and help to preserve biodiversity. According to the World Coal Institute, studies of the immediate environment can be carried out several years before a coal mine opens in order to define the existing conditions and to identify potential problems. Computer simulations can be undertaken to model impacts on the local environment. The findings are then reviewed as part of the process leading to the award of a mining permit by the relevant government authorities.

The impact of coal mining on land includes disturbance of surface water and groundwater, soils, native vegetation, and wildlife populations. Mine subsidence may be a problem with underground coal mining, if the ground level lowers as a result of coal being mined beneath. Water pollution in the coal mine region commonly is the result of acid mine drainage, which is metal-rich water formed from the chemical reaction between water and rocks containing sulfur-bearing minerals such as pyrite. The runoff formed is usually acidic and frequently comes from areas where coal mining activities exposed rocks containing pyrite. This acid runoff mobilizes heavy metals such as copper, lead, and mercury into groundwater and surface water.

Dust at mining operations is produced by trucks being driven on unsealed roads, coal crushing operations, drilling operations, and wind blowing over areas disturbed by mining. Dust levels need to be controlled by spraying water on roads, stockpiles and conveyors. Other steps are also taken, including fitting drills with dust collection systems and purchasing additional land surrounding the mine to act as a buffer zone. Trees planted in these buffer zones also minimize the visual impact of mining operations on local communities. Noise is controlled through the careful selection of equipment and insulation and sound enclosures around machinery.

Health Problems

In many ways, coal mining has become a much easier job than it was long ago. Still, coal miners face dangers and hardships that most Americans would find unacceptable in their daily lives. One of the dangers that coal miners face is exposure to dust generated by the various methods employed to extract the coal and transport it out of the mine. Black lung disease is a common name for coal workers' pneumoconiosis (CWP), the occupational lung disease that is contracted by prolonged breathing of coal mine dust. The term "pneumoconiosis" embraces nonneoplastic reactions of the lungs to inhaled mineral or organic dusts, and the resultant alterations in their structure, excluding asthma, bronchitis, and emphysema (Gross, 1962; Honma et al., 2004; Vallyathan et al., 1998). It can be defined as a dust burden disease in the lungs and the tissue's reaction to its presence (Castranova & Vallyathan, 2000). Unlike silicosis, being the fibrotic disease of the lungs produced by inhalation of dust containing silicon dioxide, primarily in the free crystalline form, CWP results from inhalation of coal dust, a complex mixture usually containing relatively small amounts of free crystalline silica (Honma et al., 2004).

According to the Work-related Lung Disease Surveillance Report (NIOSH, 2003), Federal "Black Lung" Program payments totaled more than $1.5 billion for nearly 190,000 beneficiaries in 1999. Coal workers' pneumoconiosis (CWP) deaths accounted for half of the pneumoconiosis

TABLE 1. COPD: Proportionate Mortality Ratio (PMR) Adjusted for Age, Gender, and Race by Usual Industry

CIC	Industry	Number of deaths	PMR	95% Confidence interval LCL	95% Confidence interval UCL
041	Coal mining	783	1.98	1.84	2.12
410	Trucking service	1281	1.29	1.22	1.37
751	Automotive repairs	627	1.26	1.17	1.37
760	Other repairs	183	1.23	1.06	1.42
060	Construction	4288	1.19	1.16	1.23
771	Laundry, cleaning	257	1.15	1.01	1.30
142	Yarn, fabric mills	1423	1.07	1.01	1.12

Note. CIC: Census industry code; LCL: lower confidence limit; UCL: upper confidence limit.

deaths during the 10-yr period from 1990 to 1999, clearly outnumbering deaths associated with other types of pneumoconiosis, such as asbestosis and silicosis. Among the occupations listed by the Census Industry Code, coal mining is the highest risk job associated with asthma and chronic obstructive pulmonary disease (COPD) deaths with a proportionate mortality ratio of 1.98 [95% confidence interval (CI) 1.84–2.12, adjusted for age, gender, and race], as compared to the second highest risk job of trucking service of 1.29 (95% CI 1.22–1.37) (NIOSH, 2003) (Table 1). In fact, energy costs from a new coal power plant are relatively low, between 3.5 and 4 cents per kilowatt-hour. However, health and environmental costs such as occupational lung disease compensation bring the total costs from 3.5–4 to as high as 5.5–8.3 cents per kilowatt-hour (Jacobson & Masters, 2001). Clearly, the health cost to the federal government in "black lung" disability benefits highlights the need for surveillance and screening programs to carefully monitor early adverse effects of coals. Knowing the active component(s) in the coal dusts will enable the assessment of the toxicity of the dusts. Knowing the molecular mechanisms of coal dusts-induced occupational lung diseases will help to identify markers of early adverse effects that will enable to conduct surveillance and screening programs.

EPIDEMIOLOGICAL STUDIES ON COAL DUST-INDUCED OCCUPATIONAL LUNG DISEASES

Mortality and morbidity studies of coal workers identified three pathologies that are related to coal dust inhalation: pneumoconiosis, including simple pneumoconiosis and progressive massive fibrosis (PMF); COPD, such as emphysema and/or chronic bronchitis; and stomach cancer (Meijers et al., 1997; Morgan, 1971; Rockette, 1980; Swaen et al., 1995; Vallyathan et al., 1998). These studies generally showed increased standard mortality rates for accidents, respiratory diseases, and stomach cancer (Miller & Jacobsen, 1985). Among the respiratory diseases, CWP received the most attention because of its clear occupational association. Asthma, emphysema, and chronic bronchitis in coal workers show a significant positive correlation with (a) the number of years worked at the coal mine independent of age at death; and (b) the severity of pneumoconiosis (Leigh et al., 1983, 1994). While mining exposures contribute significantly to lung disease, smoking is an important factor in the development of lung cancer and COPD, thus necessitating a comprehensive approach for prevention and control of mining-related occupational lung disease (Jacobsen et al., 1977; Ross & Murray, 2004).

During the last 30 years, the prevalence of CWP has fallen consistently in the United States. For example, in active underground mines included in the National Institute for Occupational Safety and Health (NIOSH) Coal Workers' Surveillance Program, rates fell from >10% in the early 1970s to <2% in the late 1990s (NIOSH, 2003). Similar trends were noted in Europe as well as in South Africa (Ross & Murray, 2004). The decrease in CWP prevalence may be partly due to lowered dust levels in coal mines. In the United States, the permissible exposure limit for respirable coal dust is

2 mg/m^3. In contrast to CWP, asthma, emphysema, and chronic bronchitis presently appear to be more relevant in contributing to the morbidity and mortality of coal workers (Baur & Latza, 2005; Meyer et al., 2001; NIOSH, 2003). Moreover, pneumoconiosis may become progressive after cessation of dust exposure. Therefore, at-risk populations consist of retired or former coal miners and those currently active in the workplace (Attfield & Seixas, 1995; Gautrin et al., 1994; Soutar et al., 1986).

It was found in the United States, Great Britain, France, and Germany that the prevalence and severity of CWP differs markedly among different coal mines despite comparable exposures to respirable dust (Amoudru, 1987; Attfield & Castellan, 1992; Hurley et al., 1982; Reisner & Robock, 1977). For example, the first round of the U.S. National Study of CWP (NSCWP), which was completed in 1971, examined a total of 9076 miners from 29 underground bituminous and 2 anthracite mines (Morgan et al., 1973). The average exposure concentration in these mines during that period was 3 mg/m^3 (Attfield & Morring, 1992a). It was found that 41% of the eastern Pennsylvania anthracite miners had simple pneumoconiosis and a further 14% had PMF, but the comparable figures for bituminous miners in Colorado and Utah were 4% and 0.4%, respectively (Attfield & Morring, 1992a; Morgan et al., 1973). Figure 3 shows that for the same number of years spent underground or for the same job category, the regional difference in the prevalence of CWP remains. The follow-up studies at the same mines (in 1972–1975, 1977–1981, 1985–1988, and 1996–2002) showed that the overall prevalence of CWP decreased in the United States but the regional differences persisted with a greater risk in Eastern coal miners (Pennsylvania and West Virginia) than in Western coal miners (Utah and Colorado) (Anonymous, 2003; Antao et al., 2005; Attfield & Seixas, 1995; Goodwin & Attfield, 1998).

Figure 3 also clearly shows that the prevalence of CWP in the four coal mine regions is related to years of underground exposure. It is apparent that overall CWP prevalence for miners who worked less than 10 yr is lower than those who worked underground for 30 yr or longer, regardless of coal mine regions. It is noteworthy that, as a result of increasing emphasis on exposure-response characterization for occupational hazards, quantitative estimation of exposure was developed in occupational epidemiology (Seixas & Checkoway, 1995; Seixas et al., 1991, 1992). Cumulative dust exposure estimates were calculated for each miner by multiplying the coal dust concentration and the time worked underground. It is commonly expressed as units of gram-years per cubic meter (g-yr/m^3) (Attfield & Morring, 1992a). Application of these exposures to exposure response led to detection of a relationship between dust exposure and prevalence of CWP and between dust exposure and ventilatory function (Attfield & Hodous, 1992; Attfield & Morring, 1992b; Naidoo et al., 2004; Soutar et al., 2004). These relationships were stronger than those obtained by using surrogate measure of exposure, such as tenure underground.

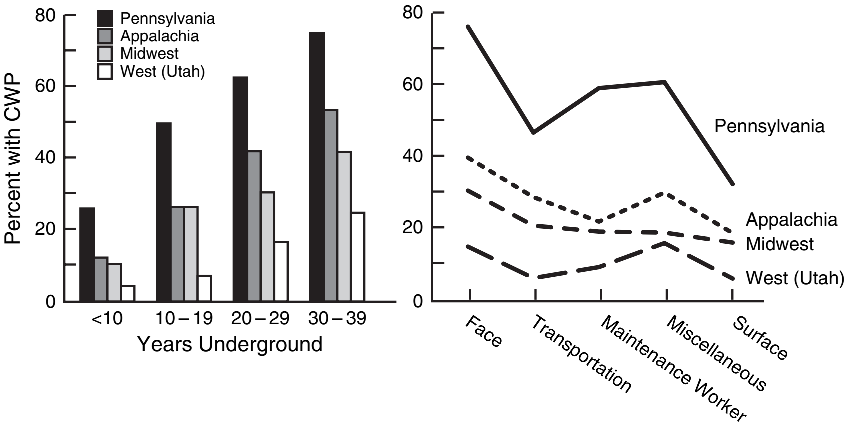

FIGURE 3. Relationship of CWP prevalence to years of underground exposure and to principal job according to the geographic region. Reprinted from Morgan et al. (1973) with permission.

The relationship of CWP to the miner's principal job is also shown in Figure 3. It is evident that the prevalence of CWP is highest at the mine face and least on the surface. The apparent anomaly of a high prevalence of the disease among miscellaneous underground workers may be explained by the fact that many of these workers have duties that, at times, involve face work, and also have duties at coal transfer points on conveyer systems where dust concentrations may be high (Morgan et al., 1973). Therefore, marked regional differences in the prevalence of CWP exist despite comparable levels of dust exposure and years spent underground. The disease is more common in Pennsylvania than in the rest of Appalachia. It occurs less frequently in the Midwest and much less so in the West. Such large regional differences in the prevalence of CWP cannot be explained by the slight differences present in exposure concentration or mining techniques (Attfield & Seixas, 1995; Morgan et al., 1973). Since the same techniques and technicians were used in each round of the NSCWP, factors such as the x-ray reader variation or changes in x-ray standard should not have contributed to the regional differences in CWP (Attfield & Morring, 1992a). In France, coal miners of Provence did not display CWP (0%), whereas the prevalence of CWP in coal miners of Nord Pas de Calais was 24% (Amoudru, 1987). In Great Britain, the proportional mortality ratios for CWP varied from 135 (95% CI 16–488) in Leicestershire county to 3825 (95% CI 1538–7881) in South Glamorgan county (Coggon et al., 1995). The observed regional differences in the prevalence of CWP indicate that chemical characteristics of coal mine dust responsible for CWP development may vary from region to region. Quartz, coal rank, carbon-centered free radicals, transition metals, and bioavailable iron (BAI) have been considered important components in the coal dusts that may contribute to the CWP development. In this review, we intend to summarize previous findings on these potential causative factors and to see whether differences in levels of these causative factors may be associated with the observed regional differences in the prevalence of CWP.

PATHOGENESIS AND MOLECULAR MECHANISMS OF COAL DUST-INDUCED OCCUPATIONAL LUNG DISEASES

Oxidative Stress

CWP and COPD are considered as human lung pathologies related to oxidative stress. Oxidative stress is a disturbance in the oxidant/antioxidant steady state in favor of oxidants, which lead to cellular damage. Accumulating evidence suggests that release of reactive oxygen species (ROS) plays an important role in diverse pathologies including inflammation, tissue aging, cardiac ischemia, arthritis, cancer, and fibrosis (Land & Wilson, 2005; Langen et al., 2003; Schins & Borm, 1999; Shi et al., 1998; Vallyathan & Shi, 1997). The presumed mechanism is through the ability of ROS to induce biochemical alterations in macromolecules such as DNA, lipids, and proteins (Shi et al., 1998). It was shown that ROS, produced by leukocytes and macrophages as a bactericidal mechanism of host defense, can also damage surrounding tissue. Recent evidence indicates that ROS either from endogenous (e.g., macrophages) or exogenous (e.g., coal dusts) sources also serve as signaling molecules, which activate transcription factors such as nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) and alter mitogenic and fibrogenic signals such as interleukin-6 (IL-6) (Chatterjee & Fisher, 2004; Frey & Malik, 2004).

Oxidative Property of Coal Dusts

The oxidative property of coal dusts is primarily attributed to its transition metal constituents, which typically include Fe, Cr, Co, Ni, Mn, As, Zn, and V (Broeckaert et al., 1999; Finkelman, 1999; Zhang et al., 2002). Using electron spin resonance (ESR), it was found that aqueous coal filtrates containing Fe, Zn, Cu, Ni, and Co were able to produce ROS such as $^{\bullet}OH$ or ferryl ($Fe^{IV}{=}O$) (Huang et al., 1993). These species are very electrophilic, hence very toxic. It was further shown that ROS resulting from ROS-producing coal dusts are able to inactivate alpha-1-antitrypsin (α_1-AT), which is a major serum inhibitor of elastases, enzymes contributing to emphysema development (Huang et al., 1993). Inherited deficiency in α1-AT and inactivation of α1-AT by cigarette smoke show increased susceptibility to emphysema (Janoff, 1985; Snider, 1992). Average levels of BAI, an important fraction of total iron, which is capable of catalyzing ROS formation, may reach as high as 0.7% (w/w) in the Pennsylvania coal mine region (Huang et al., 1998; Zhang et al., 2002).

Oxidants, Cytokines, and Growth Factors in CWP

It is well known that dusts deposited on the alveolar epithelium are phagocytized by alveolar macrophages (AMs), which lead to ROS formation. It was shown that release of H_2O_2 and $O_2^{-\bullet}$ is increased in AMs from coal workers with emphysema and pneumoconiosis (Rom, 1991, 1990; Wallaert et al., 1990). Plasma levels of lipid peroxidation end products, such as malondialdehyde, were higher in coal workers with early and low-grade CWP than in control subjects (Altin et al., 2004). Concurrently, glutathione (GSH), a major cellular antioxidant known to protect the lung from oxidants, was significantly decreased. In contrast, glutathione peroxidase and Cu/Zn superoxide dismutase were increased in the red blood cells of miners with pneumoconiosis (Borm et al., 1990; Perrin-Nadif et al., 1996).

Interaction between AMs and epithelial cells may promote inflammatory responses to air pollution particles. Lung epithelial Type II pneumocytes are well known to grow and divide to epithelialize the alveolar surface through differentiation. Coculture of AMs and type II rat lung epithelial cells synergistically enhanced basal levels of proinflammatory cytokine tumor necrosis factor-α (TNF-α) (Tao & Kobzik, 2002). The extent of dust-induced lung injury may also be related to the amount of time a particle is present in the interstitial compartment (Brody, 1986; Davis, 1986). Particles on the alveolar surface, which are not cleared by AMs, are transported rapidly across the epithelium to the interstitium (Brody & Overby, 1989; Brody et al., 1982). Type II cells express proteases, which are likely playing a role in clearing fibrin deposits from the alveolar space in a number of forms of acute and chronic lung injury, including the inflammatory phases of hypersensitivity pneumonitis, toxin- and asbestos-mediated injury, idiopathic pulmonary fibrosis, and acute lung injury (Lee et al., 1994; Leikauf et al., 2002; Sitrin et al., 1987). It was suggested that although inflammatory events immediately following lung injury initiate the fibrotic process, the response of the pulmonary epithelium is a major determinant of the pattern of tissue repair and thus of the ultimate degree of a permanent lung damage (Crouch, 1990). There is strong evidence that fibroblasts are the predominant source of fibrous proteins of the extracellular matrix accumulated in the lung interstitium during the development of fibrosis (Olman, 2003). The interaction of AMs and fibroblasts is important in contributing to the accumulation of collagen in affected lungs (Castranova, 2004; Crouch, 1990).

Because cytokines generate ROS or deplete antioxidants such as glutathione, activation of cytokines is an important mechanism for CWP development (Jardine et al., 2002; Zhang & Huang 2003). IL-6, IL-8, granulocyte–macrophage colony-stimulating factor (GM-CSF), TNF-α and transforming growth factor (TGF) are the most important cytokines in inflammation, emphysema, and fibrosis (Borm & Schins, 2001; Kelley, 1990; Kelly et al., 2003; Morris et al., 2003; Piguet et al., 1990; Yucesoy et al., 2002). Cytokines/growth factors that are responsible for the development of inflammation and fibrosis are divided into two groups, i.e., mitogenic (those that increase cell proliferation) and fibrogenic (those that enhance extracellular matrix synthesis). Examples of mitogenic cytokines are TGF-α, IL-1, TNF-α, and insulin-like growth factor, while TGF-β is a fibrogenic cytokine and IL-6 can be both mitogenic and fibrogenic (Hirano, 1998; Pittet et al., 2001). It was shown that soluble IL-1β bioactivity and IL-1β-dependent IL-6 upregulation are critical mediators of fibroblast activation and proliferation in acute lung injury (Olman et al., 2004). A single instillation of silica in mice leads to a marked increase in the level of lung TNF-α production. Most interestingly, silica-induced lung fibrosis is almost completely prevented by anti-TNF-α antibodies (Piguet et al., 1990). It was shown that serum levels of TNF receptors and IL-6 may be associated with the fibrotic process occurring in CWP, while serum cytokine levels may be correlated with the severity of CWP (Zhai et al., 2002). It was found that a spontaneous release of TNF-α by AMs was significantly higher in active coal miners than in retired miners (Lassalle et al., 1990). Studies on the release of monocyte TNF-α after in vitro stimulation with coal dusts showed that TNF-α was increased in miners, especially in the early stages of pneumoconiosis. Miners who showed an abnormally high dust-stimulated release of TNF-α had an increased risk of progression to fibrosis (Kim et al., 1999; Schins & Borm, 1995). It was hypothesized that subjects carrying common functional polymorphisms in these inflammatory cytokines, chemokines, growth factors, and antioxidant enzymes may be more susceptible to coal dust-induced CWP development (details recently reviewed) (Yucesoy & Luster, 2007). Serum levels of these factors were proposed as biomarkers for early detection of CWP and other types of pneumoconiosis (Blackford et al., 1997; Gulumian et al., 2006).

Fibronectins and collagens are major constituents of extracellular matrix; they bind to other matrix components to promote adhesion, spreading, and migration of various cell types. Airway wall remodeling on an inflammatory basis is believed to be fundamental to the development of COPD in workers exposed to particles (Churg & Wright, 2002). AMs from miners with simple pneumoconiosis were shown to spontaneously release increased amounts of fibronectin (Rom et al., 1987; Vallyathan et al., 2000). Antioxidant enzymes, such as catalase, glutathione peroxidase, and superoxide dismutase, showed a significant increase above control in coal miners with category 2/2 CWP. Significant increases in the secretion of IL-1, IL-6, TNF-α, TGF-β, fibronectin, and α_1-AT also were evident in coal miners with disease. This upregulation of antioxidant defenses and cytokines was not evident in coal miners in the absence of clinically evident radiographic disease (Vallyathan et al., 2000).

Oxidant Signaling in Cytokine Formation and CWP

AP-1, NF-κB, and nuclear factor of activated T cells (NFAT) are important transcription factors sensitive to oxidative stress and were shown to play key roles in gene expression of many inflammatory cytokines (Castranova, 2004; Rahman, 2002). It was found that coal from the Pennsylvania coal mine region with a high prevalence of CWP transactivates both AP-1 and NFAT (Huang et al., 2002). In contrast, coal from the Utah coal mine region, which has a low prevalence of CWP, exerted no such effects. The Pennsylvania coals stimulate mitogen-activated protein kinase (MAPK) family members of extracellular signal-regulated kinases (ERKs) and p38 MAPK but not c-Jun-NH_2-terminal kinase (JNKs), as determined by the phosphorylation assay.

Increasing evidence demonstrates that IL-6 plays a central role in the acute-phase reaction and tissue inflammation, and therefore, may contribute to the initiation and progression of CWP (Ishihara and Hirano 2002; Vallyathan et al., 2000). It is known that human IL-6 gene promoter and enhancer region contains several binding sites of *cis*-activating transcription factors such as NF-kB, AP-1, NF-IL-6, and CREB (cAMP-responsive element binding protein) (Hirano, 1998; Mann et al., 2002). It was shown that levels of IL-6 in cells treated with coals from three coal mine regions correlated well with CWP prevalence from that region (Huang & Zhang, 2003). It was further shown that the increase in IL-6 protein and mRNA by the Pennsylvania coal was completely eliminated by the pretreatment of cells with PD98059, a specific ERKs pathway inhibitor, and SB202190, a p38 MAPK inhibitor.

Chemical Characteristics Thought to be Important in Coal Dust-Induced CWP: Quartz

Epidemiological studies of the relationship between the prevalence of CWP and environmental measurements consistently revealed that the predominant adverse exposure factor is respirable mixed coal dusts (2004; Attfield & Wagner, 1993). Because silica (SiO_2) is an important component of the mixed coal dust and free crystalline silica (quartz) is a well-known mineral in inducing silicosis, a fibrotic lung disease (Shi et al., 1998), CWP was originally thought to be a variant of silicosis (Borm & Tran 2002). Indeed, quartz is more biologically active than the mixed coal dust (Albrecht et al., 2002; Ernst et al., 2002), and the high biological reactivity of quartz may be due to the unique properties of the silanol groups (-SiOH) (Castranova & Vallyathan, 2000; Fubini et al., 2001). For example, it was shown that quartz as cumulative exposure was a highly significant predictor of polymorphonuclear leukocytes (PMNs) counts in bronchoalveolar lavage fluid, a marker for lung injury. PMNs are small, actively motile white blood cells containing many lysosomes (a vesicle containing hydrolytic enzymes) and specializing in phagocytosis, a process of ingestion and digestion of particles within cells. Cumulative coal dust exposure did not significantly add to the prediction of PMNs above that predicted by cumulative quartz exposure (Kuempel et al., 2003). Separate testing of coal or quartz in rats each showed an increase in PMNs in the lung lavage fluids, indicating an inflammatory response (Blackford et al., 1997). However, CWP also results from the inhalation of coal mine dust that usually contains relatively small amounts of quartz. It was found that quartz could contribute to CWP development in general but acts independent of coal dusts (Borm & Tran, 2002; Walton et al., 1977). Moreover, pneumoconiosis was also found in coal trimmers who shoveled coal that contained little or no silica and in graphite and carbon electrode workers who were exposed to carbonaceous materials free of silica (Lister & Wimborne, 1972; Miller & Ramsden< 1961). Since the presence of silica or silicates was found not to be necessary for the development of pneumoconiosis, the question arises of what other factor(s) in the coal dust is responsible for the disease.

Coal Rank

Coal rank was found to play a role in CWP, since risk increases with coal rank (Attfield & Morring, 1992b; Kuempel et al., 1995; Miller & Jacobsen, 1985). Laboratory coal breakage studies showed a positive correlation with the amount of respirable-size particles found in the product increasing with coal rank (Moore & Bise, 1984). It was suggested that higher rank coals with a higher electrostatic charge on breakage may contribute to the increased incidence of CWP in high rank coal regions (Page, 2000; Page & Organiscak, 2000). As mentioned earlier, coal rank is only an indicator of the carbonization of organic materials in the coals and is not an active component, chemically speaking, that can induce lung injury. Investigation on the cytotoxic characteristics of coal mine dust yielded opposite results: Coal dust from low-rank coal produces a greater cytotoxicity than coal dust from high-rank coal. Leaching of coal dust by dichloromethane and physiological fluids (aqueous solution in the presence of lecithin, a lung surfactant) shows that high concentrations of phenolic compounds are extracted from low-rank coals (Schulz, 1997). Values of phenol index decrease with increasing coal rank. The amounts of phenolic compounds leached by the fluids were correlated with high cytotoxicity of the coal dusts. Using two coals of Pennsylvania and Utah with high and low prevalence of CWP, respectively, the leachate from the Pennsylvania coal inhibited cell growth while chemicals leached from the same size particles of the Utah coal stimulated cell growth (Christian & Nelson, 1978; Christian et al., 1979). Results of mineralogical analyses of coal dust samples and cytotoxicity tests showed that the mineral content and cytotoxic potential of dusts collected from the same mine, and even from the same underground site, at different times varied considerably. Using Affymetrix GeneChip arrays, it was shown that the coal from Pennsylvania coal mine region with a high rank and a high prevalence of CWP altered 908 gene expressions in primary human bronchial epithelial cells (Hu et al., 2003). The coal from Utah with a low rank and a low CWP prevalence modified 356 genes out of 12,000 genes examined. It was suggested by Hu et al. (2003) that differences in levels of metals, particularly bioavailable iron but not coal rank of the two coals, may contribute to the differences in the gene expression profile. In conclusion, a relationship between coal rank and CWP prevalence was established by epidemiological studies. However, a correlation between coal rank and cell cytotoxicity has not yet been established in biological studies (Gormley et al., 1979; Reisner & Robock, 1977).

Carbon-Centered Free Radicals

Since the discovery of the paramagnetic property of coal-like materials, coal and carbon are known as a "tank" of carbon-centered free radicals, also termed as "fossil radicals" (Ubersfeld et al., 1954). ESR demonstrated that two types of carbon-centered free radicals exist in coals, which might respectively be attributed to the macromolecular phase and molecular phase of coal (Huang et al., 1999). It was suggested that coal consists of a macromolecular phase cross-linked to form a three-dimensional network and a molecular phase situated in the pores of the macromolecular phase (see Figure 1) (Duber & Wiekowski, 1982; Retcofsky, 1982). It was postulated that the types of free radicals in coals might play a role in the fibrogenicity of coal dust (Artemov & Reznik, 1980; Dalal et al., 1990; Dalal et al., 1989). It was shown that the free radicals in anthracite as well as low rank coal are very sensitive to air (Huang et al., 1999). Grinding produced more free radicals in anthracite coals than in bituminous coals, which mimic the breakage of coal during mining processes (Dalal et al., 1989). Exposure of freshly ground bituminous coals to air induced a quantitative increase of free radicals and a decrease after long-term exposure (e.g., months). The lung tissue samples of deceased coal workers due to CWP showed ESR spectra and free radical intensities similar to those of coal samples, indicating that these free radicals are very stable, even after 20 yr of staying in the pulmonary medium (Dalal et al., 1989; Huang et al., 1999). Treatments of coal samples with O_2, glutathione (GSH), and H_2O_2 showed that the carbon-centered free radicals had little chemical reactivity in high-rank coals, adding further evidence that these types of free radicals are very inert (Huang et al., 1999).

Transition Metals

Asbestos, silica, and coal dusts have long been known to produce various types of lung diseases. Due to the mixed nature of various chemical compositions in these dusts, it is extremely difficult to identify the active compound(s) in the dusts that is responsible for the disease (Broeckaert et al., 1999; Costa & Dreher, 1997). Recently, progress has been made in metal-induced parenchymal lung disorders. For example, lung disorders may arise from exposure to aluminum, beryllium, cadmium, cobalt, copper, iron, mercury, and nickel (Kelleher et al., 2000). Metal fume fever, an inhalation fever syndrome, is a common condition among welders, with onset of symptoms typically 4–12 h after the inhalation of high levels of respirable metal fumes (Antonini et al., 2003, 2004). Metalworking fluids, along with microbial changes that occur in fluid composition, during use and storage in the workplace, were shown to be responsible for the pulmonary effects reported for workers exposed to metalworking fluid aerosols (Gordon, 2004). Beryllium may act as an antigen, and chronic beryllium disease is a hypersensitivity disorder produced by beryllium exposure in the workplace, characterized by the accumulation of beryllium-specific $CD4^+$ T cells in the lung and granulomatous inflammation (Fontenot & Maier, 2005). $CD4^+$ T cells are T helper cells, a subgroup of leukocytes, expressing CD4 protein, a glycoprotein. These cells play an important role in establishing and maximizing the capabilities of the body immune system. Other metals such as iron, cadmium, and mercury induce nonspecific damage, probably by initiating production of reactive oxygen species (Kelleher et al., 2000; Valko et al., 2005).

Based on the observation that transition metals, especially iron, are concentrated in the lungs of miners with pneumoconiosis (Guest, 1978), Ghio and Quigley (1994) postulated that the body's endogenous iron (Fe^{3+}) sequestered by humic-like substances in certain coals may play a role in pneumoconiosis (Ghio & Quigley, 1994). It was shown that oxidants generated by coal dusts after exposure to exogenous $FeCl_3$ increased with the concentration of humic-like substances. By studying the ability of different coals to catalyze the generation of •OH from H_2O_2, Dalal et al., (1995) found that the potential to induce •OH formation and lipid peroxidation by the coal dusts exhibits a good correlation with the available surface iron (Dalal et al., 1995). The leachable Ni^{2+} content of coal dust was proposed to be an additional cytotoxic parameter (Carlberg et al., 1971; Sichletidis et al., 2004). Using a system mimicking phagolysosomes, it was found that besides Fe^{2+}, Fe^{3+}, and Ca^{2+}, trace amounts of Ni, Cu, and As were released in proportion to the CWP prevalence among three coal mine regions of Pennsylvania, West Virginia, and Utah (Zhang et al., 2002). However, it has not yet been shown that the levels of humic-like substances or the available surface iron in the coals correlate with the prevalence of CWP from various coal mine regions. Moreover, it is questionable that humic-like acid can sequester the endogenous iron in vivo, since the body iron is tightly bound to iron proteins such as ferritin. Ferritin is an iron storage protein with a high binding affinity for iron ($>10^{36}$) and a large capacity of binding up to 4500 atoms of iron per molecule of ferritin (Harrison & Arosio, 1996; Torti & Torti, 2002). As shown later in this article, the surface iron in certain coals is leachable under acidic conditions, suggesting that these coals might release a much larger amount of bioavailable iron (BAI) in cells.

Bioavailable Iron (BAI)

Iron is the best-known transition metal capable of producing oxidants through Fenton, Haber–Weiss, or autoxidation reactions (Dunn et al., 2007; Huang, 2003). However, not all iron compounds in coal are bioavailable for oxidant formation and subsequent adverse health effects. Because ferric ion (Fe^{3+}) is a weak oxidant, it was first postulated that acid soluble Fe^{2+} is the active compound in the coal in inducing CWP (Huang et al., 1993). Later on, BAI was defined as iron (both Fe^{2+} and Fe^{3+}) released by coal in 10 mM phosphate solution, pH 4.5, which mimics conditions in the phagolysosomes of cells (Zhang et al., 2002).

Acid Solubilization of Iron in Coals

Particles deposited on the alveolar epithelium are phagocytosed by alveolar macrophages (AMs) (Stuart & Ezekowitz, 2005). Particles are entrapped in a membrane-bound phagosomal vacuole, which subsequently fuses with lysosomes to form secondary lysosomes or phagolysosomes. AMs dissolve many inorganic particles at a faster rate than simulated lung fluid or saline. The low phagolysosomal pH is suggested to be one mechanism underlying the ability of AMs to efficiently dissolve inorganic particles (Beletskii et al., 2005; Kreyling et al., 1991; Lundborg et al., 1985).

Using the pH 4.5, 10 m*M* phosphate solution, it was shown that average levels of bioavailable Fe^{2+}, Fe^{3+}, Ni, and Cu are high in Pennsylvania coal samples, lower in West Virginia coals, and lowest in Utah coals (Huang et al., 1998; Zhang et al., 2002). Levels of bioavailable Cr were below detection limit (<0.1 mg/L) in all of the coal samples. Because of the heterogeneity of the coal samples, the standard deviations in each region are large as reflected by the wide range of each metal measured. Ca^{2+} is present in all coals, though the Utah coals have highest levels of Ca^{2+} released. Epidemiological studies showed that CWP is frequent in Pennsylvania coal workers (Attfield et al., 1984; Attfield & Althouse, 1992; Morgan et al., 1973). In contrast, coals from Utah, with low prevalence of CWP, had little acid soluble Fe^{2+} and Fe^{3+}. The coals from West Virginia, with an intermediate prevalence of CWP, released a moderate level of acid soluble Fe^{2+} and Fe^{3+}. It was further found that the pH values of aqueous coal suspensions from Pennsylvania were acidic and those from Utah were basic or neutral (Huang et al., 1998).

Buffering Capacity of Coals

By titrating the Utah coals with sulfuric acid (H_2SO_4), these Utah coals consumed large amounts of acid in order to reduce the pH of the aqueous coal suspensions to 4.5. These results suggest that buffering capacity of the Utah coals is one of the chemical parameters controlling the dissolution of a particle. Interestingly, the buffering capacities of Utah coals were shown to correlate positively with the calcium oxide (CaO) content in the high-temperature ash of each coal (Huang et al., 1998). These results indicate that high buffering capacities of Utah coals are related to the presence of calcite ($CaCO_3$) in the coals. Calcite easily reacts with sulfuric acid to produce $CaSO_4$. It was observed that coals associated with a high prevalence of CWP contain much less calcite (Huang et al., 1993, 1998; Zhang et al., 2002). Thus, these coals have low buffering capacity, and Fe^{2+} is readily released in AMs. In contrast, coals that were shown to induce a low prevalence of CWP contained more calcite. For example, the coals from Gardanne of Provence, France, which contains a high % of calcite ($>10\%$ w/w), had a very high buffering capacity (Huang et al., 1993). This coal did not even release any detectable Fe^{2+} in 50 m*M* HCl and no CWP was reported in the miners who worked in these Gardanne coal mines (Amoudru, 1987; Huang et al., 1993). The coals from the western United States, such as from Utah and Colorado, also contain higher levels of calcite than those from Pennsylvania and West Virginia coal mines. Interestingly, the western U.S. coals did not release iron under phagolysosomal conditions (pH 4.5, 10 m*M* phosphate solution) but released iron in 50 m*M* HCl. Epidemiological studies showed that coals from Utah and Colorado are less hazardous to coal workers than the coals from Pennsylvania and West Virginia. These results indicate that calcite may play an antagonistic role in CWP development by preventing acid solubilization of iron and, thus, making iron non-bioavailable for oxidant formation and adverse health effects.

Pyrite Oxidation as a Source of BAI and Calcite as Inhibitor of Iron's Bioavailability

It is well known that pyrite (FeS_2, including its polymorph marcasite, the same chemistry as pyrite but a different crystalline structure) is a typical constituent of coal (Meyers, 1982). The surface oxidation in air and air-saturated aqueous solutions of the iron subsulfide was studied in detail (Lowson, 1982; Usher et al., 2004; Usher et al., 2005). Previous studies showed that pyrite-rich coals tend to undergo rapid low-temperature oxidation (Huggins et al., 1983). This oxidation may give rise to mining complications, including acid mine drainage from abandoned mine faces and coal-refuse piles, roof weakness, pillar collapses in underground mines, and spontaneous combustion of stock piles (Huang et al., 1994; Younger, 1997; Zodrow & McCandlish, 1978). Multiple chemical factors, such as oxygen partial pressure, temperature, particle size, crystallinity, and relative humidity, play a role in pyrite oxidation, and these conditions are likely to vary in different coal mines (Huang et al., 1994; Huggins et al., 1983; Lowson, 1982). Iron present in coal may become bioavailable by pyrite oxidation, which produces ferrous sulfate and sulfuric acid as follows:

$$2FeS_2 + 7O_2 + 2H_2O \rightarrow 2FeSO_4 + 2H_2SO_4 \qquad (1)$$

$FeSO_4$ is water soluble (150 g/L at 20°C) and thus readily bioavailable for oxidant formation. However, the subsequent human exposure to coal dust containing $FeSO_4$ depends upon the stability of the formed $FeSO_4$. If $FeSO_4$ is oxidized prior to inhalation by coal workers, there is no iron available for oxidant formation and lung injury. It was found that pH of the coal played the most important role in stabilizing $FeSO_4$, such that a final $pH < 4.5$ after oxidation of pyrite stabilized $FeSO_4$, whereas at high pH the conversion of Fe^{2+} to Fe^{3+} was immediate (Huang et al., 1994). Increasing the pH would facilitate ferrous ion oxidation to goethite (FeOOH), which is water-insoluble and thus not bioavailable for redox reactions. Moreover, it was shown that the rate of oxidation of Fe^{2+} by oxygen in abiotic system is a function of pH. It was estimated that the reaction half life of Fe^{2+} at pH 3.5 and 7 is 1000 d and 8 min, respectively (Singer & Stumm, 1969; Stumm & Lee, 1961). Therefore, there is little toxicity in the gastric system (pH 1–2) produced by oral uptake of a normal dose of ferrous sulfate because Fe^{2+} oxidation is slow at $pH < 3.5$. However, in lung medium in which the pH is usually near 7, oxidation of Fe^{2+} proceeds quickly and oxidants resulting from the interaction of Fe^{2+} and O_2 may damage lung cells and induce cytotoxicity. This suggests that the inhalation of iron may be more hazardous than ingestion of iron. Indeed, pulmonary injury after aspiration of $FeSO_4$ was reported in a patient showing acute bronchial damage and early histological change in the biopsy specimens after the exposure (Godden et al., 1991). A delayed occurrence of bronchial stenosis after inhalation of iron was also described (Mizuki et al., 1989; Tarkka et al., 1988).

The pH of water in contact with a particular coal depends not only on the origin of the coal but also on the various factors that, over geological time, influence the formation of macerals and sulfide and carbonate minerals in the coal. Coals rich in carbonates such as calcite have high pHs, whereas coals rich in sulfides such as pyrite have rather low pHs. The functional chemical groups (carboxyl, phenol, or quinone) on the coal's surface may also influence the pH of a particular coal. The acidity of a particular coal is not constant and can vary at different coal mines due to the vertical and lateral variations in coal composition. This can be explained by the ongoing oxidation of coal and its accompanying minerals, such as pyrite.

Calcite ($CaCO_3$) is the major component in coal that consumes acid and neutralizes the pH as follows:

$$CaCO_3 + H_2SO_4 \rightarrow CaSO_4 + H_2O + CO_2 \qquad (2)$$

Therefore, little BAI accumulates when calcite is present, such as in the coals from the Utah coal mine region (Huang et al., 1998; Zhang et al., 2002). If calcite is absent in the coals, sulfuric acid produced from reaction (1) solubilizes other iron compounds (e.g., $FeCO_3$) and releases more BAI. To demonstrate the protective role of calcite in inhibiting BAI, predetermined proportions of calcite were added into three Pennsylvania coals. After suspending the mixtures in the aqueous phosphate solution (10 m*M*, pH 4.5), it was shown that the level of pH and the Ca^{2+} in the coals were increased in a calcite concentration-dependent manner (Zhang & Huang, 2005). In contrast, levels of BAI (both Fe^{2+} and Fe^{3+}) were decreased. Interestingly, calcite also showed a significant inhibitory effect on Pennsylvania coal-induced ferritin formation in human lung epithelial A549 cells.

These results indicate that the addition of calcite inhibited the bioavailability of iron in the iron-containing Pennsylvania coals.

Besides pH and calcite, it was shown that oxidizing activities and iron levels of coal samples decrease as a function of the duration of exposure to air (Huang et al., 1994). It was shown that BAI content, even in low pH coals (e.g., pH 4.5), decreases to half after 2 mo of exposure to air (Chen et al., 1996). These results indicate that the formation of $FeSO_4$ is a dynamic process and that the oxidizing activity generated by coal samples varies from the time when the coal dust is extracted to the time when it is tested in biological studies. Oxidizing activity of these coal dusts had already disappeared before any cell or animal treatments were performed. Coal dusts exposed to air for too long (days to months) loses their oxidizing activity, hence biological activity. This might explain why no significant effects of coal dusts were observed in previous in vitro and in vivo studies (Castranova et al., 1985; Castranova & Vallyathan, 2000), because the coal dusts that were recovered from respirators or sample collectors were exposed to air for months if not years.

In conclusion, three factors are important in controlling levels of BAI in the coals. The first factor is pH of coals: The initial low pH favors the stabilization of $FeSO_4$, but is not a determinant factor. $FeSO_4$ may be originally present in the coals. The majority of $FeSO_4$ is from oxidation of pyrite, which yields BAI and simultaneously stabilizes BAI by lowering pH. The second factor is the presence of calcite in the coals: The buffering capacity of the coal dust must be low so that H_2SO_4 produced by pyrite oxidation may sufficiently lower the pH to 4.5 and stabilize $FeSO_4$ prior to inhalation by coal workers. Excessive H_2SO_4 can release BAI from other iron compounds in the coal dusts, such as siderite ($FeCO_3$), and further enhance oxidizing potential of coal dusts in the lung after they are inhaled. If the levels of calcite in the coals are high, calcite neutralizes sulfuric acid and thus increases the pH of the coals. At a relatively high pH (>4.5), BAI may be readily oxidized to biologically inactive goethite before they are inhaled into the lung. The third factor is the duration of coal's exposure to air prior to inhalation: Levels of BAI as well as oxidizing activities of coals decrease as a function of time of exposure to air. Therefore, the longer the duration of coal's exposure to air is, the less the cytotoxicity of coal will be. In summary, BAI may be the active component in coal dust-induced lung disease, but BAI is a transient component in coal dusts. The formation and stabilization of BAI may vary from one place or time to another due to the many factors related to the chemical properties of the coals and the heterogeneity of coal samples taken from different areas of certain mines.

APPLICATION OF KNOWLEDGE GAINED ON THE INTERACTION OF PYRITE AND CALCITE IN COALS

Mapping and Prediction of Coals' Pneumoconiotic Potencies in the U.S. Coals

Based on the hypothesis that BAI is the active component in the coals inducing CWP, the differences in the levels of BAI in the coals may be responsible for the observed regional differences in the prevalence of CWP. CWP prevalence data from the first National Study of CWP (NSCWP) as well as chemical data from the U.S. Geological Survey (USGS) coal quality database were used for the correlation studies (Finkelman & Gross, 1999; Morgan et al., 1973). According to the names of the coal mines, counties, and states, several thousand analyses of coal samples contained in the USGS coal quality database were searched. Ninety-four coal samples from 24 coal mines within 7 states matched the locations in the NSCWP.

BAI mainly consists of water-soluble iron, such as ferrous and ferric sulfate, which was originally present in the coals or obtained by the oxidation of pyrite (Huang et al., 1998; Zhang et al., 2002). Another possible source of BAI is acid solubilization of siderite or ferrous silicate ($FeSiO_3$). Using the USGS coal database, levels of BAI in each coal were calculated. It can be seen from reaction (1) that 1 mole of pyrite produces 1 mole of BAI as ferrous sulfate and 1 mole of sulfuric acid. However, levels of pyrite in the USGS coal database were not measured directly. Since only pyritic sulfur content is available in the database, reaction (1) shows that 1 mole of pyritic sulfur produces half a mole of BAI and half a mole of sulfuric acid.

Previous studies showed that BAI is stable only in an acidic environment (Huang et al., 1994; Singer & Stumm, 1969; Stumm & Lee, 1961). If there is calcite in the coal, calcite consumes the acid and neutralizes the pH as shown in reaction (2). If calcite is absent in the coals, sulfuric acid produced from reaction (1) solubilizes other iron compounds (e.g., $FeCO_3$) and releases more BAI as follows:

$$FeCO_3 + H_2SO_4 \rightarrow FeSO_4 + H_2O + CO_2 \tag{3}$$

According to the chemical reactions (1), (2), and (3), it was concluded that the total available molar amounts of sulfuric acid in a given amount of coal would be $[H_2SO_4] = [\frac{1}{2}$ pyritic sulfur (S_{py}) + sulfate − calcite]. If $[H_2SO_4] \leq 0$, this indicates that acid is completely consumed by calcite and, concomitantly, iron is oxidized. Therefore, there was no BAI in that coal. If $[H_2SO_4] > 0$, the excess acid stabilizes BAI and, possibly, also leach out other iron compounds, such as siderite, thus releasing additional BAI.

Based on the USGS coal database (http://energy.er.usgs.gov/products/databases/CoalQual), pyritic sulfur and sulfates as percent of coal are available for calculations. Calcite and siderite in the coals were not measured. However, levels of calcium oxide (CaO) and the total amount of iron (shown as Fe_2O_3) were measured in high-temperature ashes of the coals, and the ash yield in the coal is also available from the USGS database. It was assumed that the calcium oxide was all derived from calcite and the iron was derived from pyrite, two of the most common minerals in coal, thus maximizing the calcite and pyrite estimates. Since 1 mole of CaO is formed by the decomposition of 1 mole of calcite at high temperature, the same molar amounts of CaO may be used as measures of calcite. Therefore, the millimolar amounts of pyritic sulfur and sulfates per 100 g dry coal in each individual coal are calculated. The millimolar amounts of CaO and total iron (Fe_2O_3) per 100 g dry coal are also calculated after taking into consideration the ash yield in each individual coal.

The average levels of total sulfuric acid ($\frac{1}{2}S_{py}$ + sulfate), amount of acid available for solubilization of other iron compounds ($\frac{1}{2}S_{py}$ + sulfate − calcium oxide), total iron, and BAI in each coal mine region with known CWP prevalence was also calculated (Huang et al., 2005). To determine BAI, it was discovered that the amount of BAI in the coal needs to be equal to the lesser value between the amount of available acid ($\frac{1}{2}S_{py} + SO_4^{2-} - CaO$) and Fe_2O_3, because (1) if the coal has an excessive amount of acid and a limited amount of iron, BAI will be limited by the amount of iron present, and (2) if the coal has less acid but more iron present, BAI will then be limited by the amount of acid since excess iron cannot be solubilized and, therefore, can not become bioavailable. Table 2 shows the average levels of BAI (millimoles/100 g dry coal) from seven states with corresponding CWP prevalence reported in the first NSCWP.

TABLE 2. Average Levels of Total Sulfuric Acid ($\frac{1}{2}S_{py} + SO_4$), Available Amount of Acid ($\frac{1}{2}S_{py} + SO_4 - CaO$), Total Iron, and Predicted BAI

State	Number of mines	CWP (%)	$S_{py}/2 + SO_4$	$S_{py}/2 + SO_4 - CaO$	Fe_2O_3	BAI	Silica	Coalrank[a]
Pennsylvania	9	45.35	18.61	14.63	12.48	11.82	1.23	1.28
OH	6	31.80	19.91	14.69	12.86	9.07	1.37	1.09
Kentucky	13	29.00	13.17	7.49	9.78	6.25	0.43	1.20
West Virginia	8	28.25	9.15	4.57	7.27	4.77	0.21	1.32
Alabama	13	16.70	9.65	6.77	8.85	5.29	0.11	1.26
Utah	4	13.10	4.14	−3.19	2.69	1.09	0.16	1.08
Colorado	41	4.60	1.92	−2.69	3.68	0.15	0.21	1.04

Note. Units for the chemicals are millimoles per 100 g dry coal. Levels of pyrytic sulfur, sulfate, CaO, and Fe_2O_3 were obtained from the USGS database for each coal mine. Values in the individual coal samples were calculated first and then averaged for the coal mine region for each of the chemical parameters listed in the table.

[a] Coal rank was presented as molar ratio of carbon to hydrogen. Reprinted from Huang et al. (2005).

It has been shown that CWP prevalence correlated well with BAI, as well as with pyritic sulfur, and total iron, but not significantly with coal rank or silica. No association of CWP with CaO itself was observed.

The relationship between CWP and BAI was described by a linear model (Huang et al., 2005). Based on the levels of BAI in each coal that was calculated with the method mentioned above, each coal's pneumoconiotic potency was derived in 7000 coal samples collected and analyzed by the USGS. Figure 4 shows that there is a geographic distribution of coals with different levels of BAI and, therefore, possibly different pneumoconiotic potencies. For example, in the Western states, most coals do not have BAI, which may pose less risk for CWP to coal miners, as shown in the gray color. In the Eastern states, there is a trend for possibly high CWP risk coals (black color), ranging from Pennsylvania to OH to West Virginia and Kentucky. There is also an apparent trend of low CWP risk coal (gray color) from West Virginia to Tennessee to Alabama. In the tristate areas of

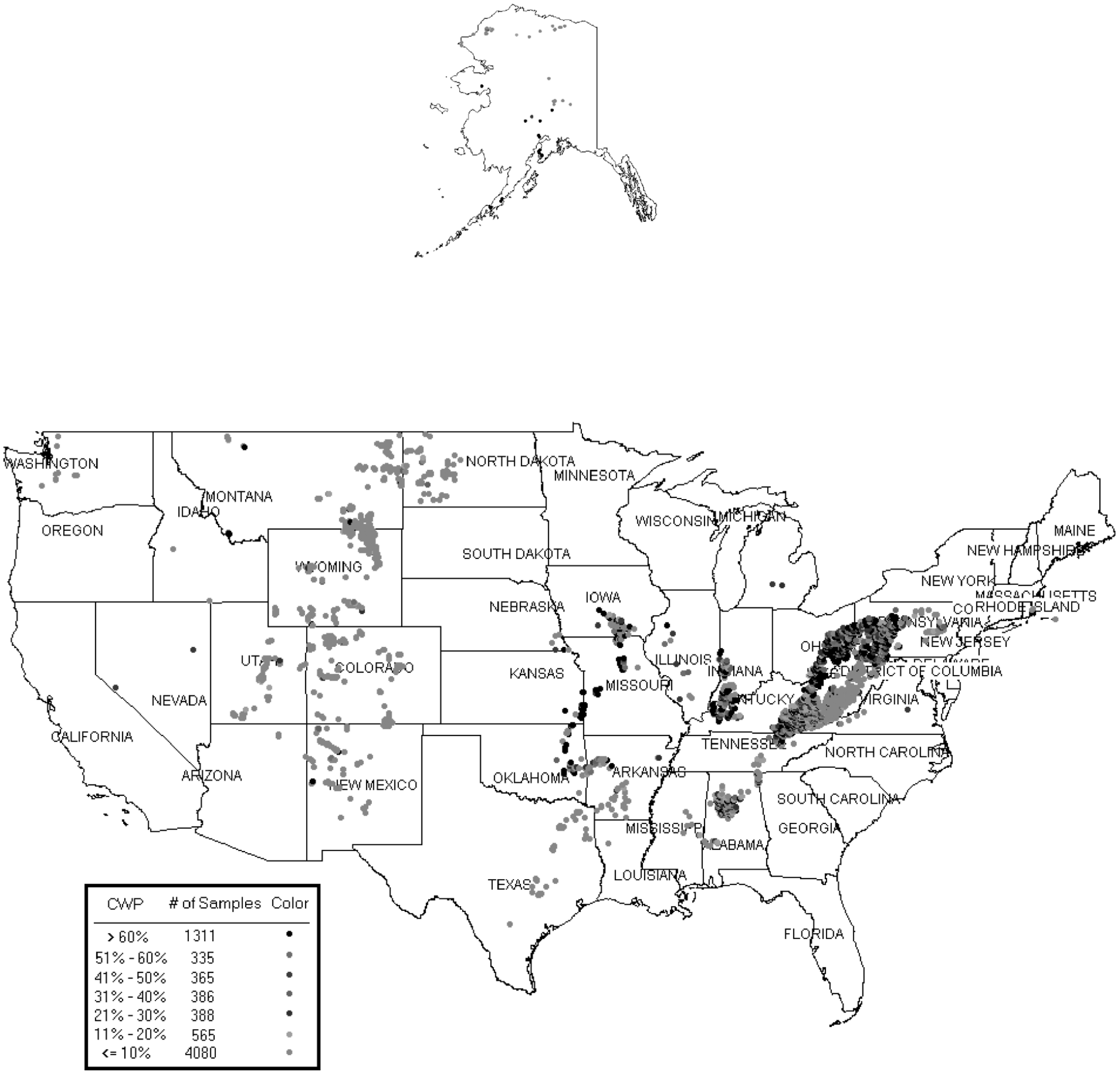

FIGURE 4. Mapping and prediction of coal's pneumoconiotic potency in the U.S. coal mines. (\Top left: Alaska coal mine region)\. Reprinted from Huang et al. (2005) with permission.

eastern Kentucky, southwestern Virginia, and northern Tennessee, it appears that the predicted CWP risks vary from one coal mine to another without apparent geological pattern. Recent evaluations in this region reported rapidly progressive CWP (Anonymous, 2006; Antao et al., 2005). Since CWP prevalence was much higher at the first round of the NSCWP than the current epidemiological data, the prevalence of CWP in the map is probably overestimated, in part due to reduced dust exposure. However, the indication of the relative risk of CWP in coal mining in various coal mine regions may still be valid and useful for CWP prediction.

In Vitro Study on the Addition of Calcite Into the Pennsylvania Coals as a Preventive Agent for CWP

Based on the observations of the Gardanne coal containing large amounts of calcite ($CaCO_3$, as high as 10% w/w) and workers in that coal mine region in France never having had CWP, it was tested whether the addition of calcite into the Pennsylvania coals reduces levels of BAI (Zhang & Huang, 2005). Unlike the Utah coals in which BAI is limited by the presence of calcite, the Pennsylvania coals already contain BAI. If calcite inhibits BAI activity in the Pennsylvania coals, then calcite may be used for the prevention of coal workers' lung diseases.

Experiments tested whether the addition of calcite to the Pennsylvania coals with high levels of BAI and high prevalence of CWP might limit BAI in a cell-free system as well as in vitro under cell culture conditions. Predetermined proportions of calcite (0, 1, 2, 5, or 10% w/w) were added to three Pennsylvania coals (Zhang & Huang, 2005). After suspending the mixtures in an aqueous phosphate solution (10 m*M*, pH 4.5), levels of pH as well as calcium ions (Ca^{2+}) in the coals were increased in a calcite concentration-dependent manner. In contrast, levels of BAI (both Fe^{2+} and Fe^{3+}) were decreased. The inhibitory effects of calcite on the bioavailability of iron in human lung epithelial A549 cells and primary rat AMs were also examined. It was found that levels of low-molecular-weight (LMW) iron were significantly decreased in both A549 cells and AMs treated with the 10% calcite–Pennsylvania coal mixture compared to those treated with the Pennsylvania coal alone, while calcite itself exerted no effect on intracellular LMW iron. Calcite also showed a significant inhibitory effect on Pennsylvania coal-induced ferritin synthesis in A549 cells. Reverse-transcription polymerase chain reaction (RT-PCR) studies revealed that the iron-containing Pennsylvania coal downregulated levels of transferrin receptor mRNA in A549 cells, which was partially restored by the addition of calcite (Zhang & Huang, 2005).

In summary, pyrite and its oxidation products may contribute to the adverse environmental and health effects of coal, and calcite may play a protective role in inhibiting iron's bioavailability. Pyrite is present in almost every coal, while calcite exists in abundance only in certain coal mine regions. In the absence of calcite, oxidation of pyrite results in the formation of BAI, which leads to the ROS formation in the lung. Pyrite oxidation also leads to acid mine drainage in coal mining area, and burning of pyritic sulfur contributes to acid rain in coal-fired power plants (Anonymous, 1999; Carmichael et al., 2002). Calcite may play a protective role in coal dust-induced lung disease by (1) increasing pH resulting in rapid oxidation of BAI prior to coal workers' inhalation and (2) inhibiting acid solubilization of iron compounds and preventing iron from becoming bioavailable. Calcite is already used for acid mine drainage treatment and as a desulfurizing agent in coal-fired power plants (Aziz et al., 2004; Cravotta, 2003; Hossner & Doolittle, 2003; Srivastava & Jozewicz, 2001). In nutrition, calcite is the most common calcium supplement and was found to decrease iron's bioavailability (Cook et al., 1991; Prather & Miller, 1992; Wienk et al., 1996). Therefore, addition of calcite into the water spray when mining may present a new methodology for controlling or eliminating BAI in the coal dusts.

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