

What Component of Coal Causes Coal Workers' Pneumoconiosis?

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Objective: To evaluate the component of coal responsible for coal workers' pneumoconiosis (CWP). **Methods:** A literature search of PubMed was conducted to address studies that have evaluated the risk of CWP based on the components of coal. **Results:** The risk of CWP (CWP) depends on the concentration and duration of exposure to coal dust. Epidemiology studies have shown inverse links between CWP and quartz content. Coal from the USA and Germany has demonstrated links between iron content and CWP; these same studies indicate virtually no role for quartz. In vitro studies indicate strong mechanistic links between iron content in coal and reactive oxygen species, which play a major role in the inflammatory response associated with CWP. **Conclusions:** The active agent within coal appears to be iron, not quartz. By identifying components of coal before mining activities, the risk of developing CWP may be reduced. (J Occup Environ Med. 2009;51:462–471)

The growing world economy will increase demand for energy on the order of a 100% by 2050, with coal combustion playing a major role, in particular in Asia and Africa.¹ This trend has already challenged occupational medicine in economically developing countries for many years.^{2,3} The extraction, transportation and use of coal, however, carry certain risks, most notably of injury in the extraction of coal and illness in the form of coal workers' pneumoconiosis (CWP), among those who extract the coal.⁴ Over many years of research, epidemiological studies have shown that decreasing dust exposure will lead to decreased risks of CWP.^{5–8} Questions remain, however, as to the active agent responsible for causing lung disease due to inhalation of coal. At this point, it is unclear as to the precise component(s) of coal that leads to this potentially disabling illness, although for many years quartz was considered the active agent.

Regulations for occupational exposure to coal have often focused on quartz content.⁹ Epidemiological studies, however, are conflicting about the level of quartz in coal in terms of its potential to cause pneumoconiosis. In fact, “dust dose and composition (of quartz) do not appear to account wholly for changes in the prevalence of CWP.”¹⁰

The purpose of this report is to assess the scientific literature related to studies that have investigated the active agent(s) within coal responsible for causing CWP. By understanding such risks, preventive efforts can be improved.

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Methods

To address the fundamental question as to the active agent within coal, an updated literature search was conducted through PubMed, a national search mechanism of the National Library of Medicine. References to other reports in the articles thus identified were examined in an effort to supplement the initial search.

Results

Coal Workers' Pneumoconiosis

CWP, which was originally thought to be a variant of silicosis, results from the inhalation of coal mine dust that usually contains relatively small amounts of free crystalline silica (quartz).^{11,12} This potentially disabling lung disease results from exposure to coal mine dust and its deposition in the lungs; the dust and resultant inflammatory reactions lead to the formation of coal macules and in some cases, coal nodules and progressive massive fibrosis (PMF).

People with CWP can experience symptoms such as cough and shortness of breath on exertion. The diagnosis is usually made based on a chest film; however, more recent diagnostic studies such as chest tomography can aid in the assessment of this disease. Treatment is usually symptomatic once the person is removed from exposure. Risk factors are primarily related to coal dust concentration, although genetics.¹³⁻¹⁶ and the characteristics of the coal mined (ie, rank and iron content) play a role.¹⁷

Numerous epidemiological studies in a variety of countries have consistently shown that the development of CWP is related to exposure to respirable mixed coalmine dust. Coal rank (age and hardness of the coal) has also been found to play a role because the risk of CWP increases with the carbon content of the coal. Quartz (silica) was found to be a minor contributor to CWP.^{18,19} The "main environmental factor involved in the development of simple CWP is

mixed coal dust exposure. Coal rank, age, and quartz exposure and dust residence time probably also play a role, although these effects appear to have secondary importance unless the silica levels are high."¹⁹

CWP is usually diagnosed based on findings on a chest film, in the context of occupational exposure to coal mine dust. Chronic interstitial fibrosis can develop. The degree of CWP (main parameters: profusion of small opacities and occurrence of large opacities) is assessed by using the International Classification of Radiographs.²⁰ If only small opacities (diameter <2 cm) are detected, CWP is called simple (coal workers' simple pneumoconiosis [CWSP]). Pathological findings usually consist of nodules, but CWSP can also result in mixed nodular and irregular opacities. A chest film with mostly irregular opacities in a coal miner, however, should raise concern about exposures to other occupational hazards, such as asbestos.

The differential diagnosis of CWP includes other diseases that can produce acute nodular lesions, such as miliary tuberculosis and viral pneumonia, as well as conditions that result in chronic nodular patterns, such as metastatic disease and tuberculosis. Silicosis can present with similar radiographic patterns as CWP, which can only usually be differentiated by occupational history or tissue examination. The characteristic pathological lesion of CWP, however, is distinct from silicosis. The primary lesion of CWP is the coal macule, which occurs specifically among workers who have been exposed to coal mine dust. This lesion has been defined by the Pneumoconiosis Committee of the College of American Pathologists as follows: "The focal collection of coal dust laden macrophages, at the division of the respiratory bronchioles that may exist within alveoli and extend into the peribronchiolar interstitium with associated reticulum deposits and focal emphysema."²¹ The coal macule can be similar in appear-

ance to macules found in urban dwellers and smokers, but coal macules tend to be more profuse; macules range in size from 1 to 5 mm. Macules may be rounded, irregular or stellate. Because the macule can be associated with other occupational and environmental exposures, the nature of the dust particle should be identified. Bituminous and anthracite coal can usually be identified through light microscopy of lung tissue.

PMF is a more severe form of CWP, which can also occur secondary to coal exposure. This condition is defined based on the diameter of the lung lesions. For example, macules with a minimal diameter of 2 cm are necessary for the diagnosis of PMF. These PMF-related lesions can be unilateral or bilateral. However, there are discussions whether PMF should be considered a different disease entity with a different mechanistic background than CWSP.²² Coal miners may also show signs of silicotic nodules that can arise from free silica exposure, which is often a reflection of siliceous rock in the vicinity of coal seams. These nodules, which tend to be incidental in association with coal macules, include collagen fibers around a hyalinized center. Despite the potential for a significant percentage of quartz in coalmine dust and its potential for accumulation in the lungs, no excess mortality from lung cancer in coal miners has been noted.²³

Coal has been described as "able to mask the fibrogenic activity of quartz" and that there are "distinct pathological differences between simple pneumoconiosis of CWP and silicosis."¹¹

Mechanism. The manner in which coal dust induces pulmonary disease has been investigated by in vitro evaluations and appears to be based on inflammatory mechanisms, most notably by formation of reactive oxygen species. According to some authors, the following mechanism of initiation and progression of CWP occurs in coal miners: coal dust stimulates the production of reactive ox-

xygen species, which not only cause lung injury, but can also activate transcription factors, such as nuclear factor, kappa-B, and activator Protein 1, which induce messenger RNA to produce a host of chemokines, inflammatory cytokines, and growth factors associated with the formation of lung lesions and fibrosis.²⁴

Castranova and Valyathan¹² have proposed that the development and progression of CWP and PMF as well as silicosis occur with four fundamental molecular mechanisms:

1. Coal dust or silica react with epithelial and macrophage cells, resulting in the per oxidation of membrane lipids. This process damages the cell membrane, leading to the release of intracellular enzymes. These enzymes scar, or even destroy, the alveolar septa of the lung tissue.
2. Alveolar macrophages or alveolar epithelial cells interact with dust particles, resulting in the secretion of fibrogenic factors that induce fibroblast proliferation or collagen synthesis, causing fibrosis.
3. The interaction of dust particles with alveolar macrophages or alveolar epithelial cells stimulates the secretion of inflammatory chemokines and cytokines, leading to the displacement of macrophages and polymorphonuclear leukocytes from the pulmonary capillaries to the air spaces. These mediators can also activate pulmonary phagocytic production of oxidant species, which causes damage to lung tissue.
4. Coal dust or silica that becomes engulfed by alveolar macrophages can lead to the generation of reactive oxidant species, which overwhelms antioxidant defenses, resulting in lipid per oxidation and lung scarring.

Clinical Care. Shortness of breath is usually the symptom that most often prompts an evaluation for CWP. The shortness of breath can be evaluated based on standard questions of the American Thoracic Society²⁵

with the physical examination focusing on the lung fields. Initial laboratory studies include spirometry and a chest film. Clinical care of coal miners with lung impairment is similar to other patients with interstitial lung disease.

Prevention. The major means of controlling CWP is through reduction in exposure to coal dust. The occupational exposure to coal is 2 mg/m³ (and 0.1 mg/m³ for coal dust containing greater than 5% quartz).⁹ These levels were established to limit the progression of simple CWP to PMF. Recommendations for prevention of CWP have been proposed by the National Institute for Occupational Safety and Health.²⁶

In light of the continued hazards of exposure to coal dust, despite dust reduction methods, increased attention has focused on the role of prevention. It is important to note, however, that much of these measures are aimed at limiting (not preventing) simple CWP and PMF. A World Health Organization study group also made recommendations for prevention, which focused on dust control.²⁷

Other approaches used modeling of CWSP data to estimate threshold values for developing profusion category 1/1²⁰ while applying dosimetric models to take latency and internal dose accumulation into account.²⁸ A long-term limit for respirable coal mine dust of 1.5 mg/m³ to 6 mg/m³ was derived by this procedure. The range reflects uncertainties of data and model assumptions. This kind of approach was preferred by the German MAK committee to identify threshold limit values for coal mine dust. However, the committee did not recommend a limit value because of the suspicion that coal mine dust exposure may be linked to stomach cancer risk in coal miners.²⁹

Silicosis

In light of the potential role of quartz in CWP, a review of silicosis is appropriate. Silicosis refers to pulmonary diseases that can occur secondary to inhalation of various types

of free crystalline silica and silica-dioxide. Workers at risk of silicosis include sand blasters, miners, millers, pottery workers, glassmakers, foundry workers, and people who work in quarries or with abrasives. Pathological features associated with silicosis have been described by a special committee of the National Institute for Occupational Safety and Health.³⁰ The earliest parenchymal lesion in silicosis is a collection of dust-laden macrophages. Eventually, these lesions may become organized and lead to the silicotic nodule, which is the pathological hallmark of silicosis. The key pathological event in the onset of silicosis is the interaction between the silica particle and the alveolar macrophage and the resulting inflammatory process.

Chronic silicosis results from low to moderate exposure to silica dust for 20 years or more. Patients may experience cough and shortness of breath and have a predisposition to tuberculosis, as well as PMF, which can cause respiratory impairment.

The characteristic radiographic appearance of silicosis is rounded opacities that range in size from 1 to 10 mm. When these nodules coalesce into a larger mass, the diagnosis of PMF can be made. In approximately 10% of the cases, the hilar lymph nodes can calcify and produce the so-called eggshell calcification pattern, a condition can also occur in Hodgkin's disease, scleroderma and histoplasmosis. The presence of eggshell calcification, along with nodular parenchymal opacities, in light of exposure to silica, reinforces the diagnosis of silicosis.

Epidemiology of CWP and Findings From Animal Experiments

The active agent in coal responsible for CWP has attracted scientific inquiry for many years. Attention initially focused on quartz, a well known fibrogenic agent, as the component of respirable coalmine dust responsible for causing CWP. In two

of the earliest reports to address the role of quartz in CWP, a poor correlation was noted between radiological evidence of CWP and quartz concentration in the corresponding coal dusts.^{31,32} No pattern was noted between the quartz content of mixed dust and the probability of developing simple pneumoconiosis at quartz levels, averaging 5%.³² A case-control study reaffirmed the absence of an effect of quartz in causing CWP.³³

Studies in British coal mines showed that the risk of developing simple pneumoconiosis (ILO 2/1 categories) was primarily dependent on the mean concentration of dust and the duration of exposure. One colliery with high quartz content, had a prevalence of CWP 1/5th that of predicted, whereas another colliery with low quartz content had almost twice the prevalence of CWP.³⁴ The results of the British coal miners led critical observers to question the role of quartz in coal on the risk of CWP. For example, British collieries with low progression of simple CWP to PMF had the highest quartz concentration, whereas workers with a high progression of CWP to PMF had worked with coal that had the lowest quartz concentration.³⁵ In an analysis of 2600 British coal miners, a clear impact of coalmine dust exposure but no influence of quartz dust exposure was found.³⁴ The role of quartz in causing CWP to progress to PMF was evaluated in additional British studies. Coal mine dust exposure and degree of CWSP were clearly linked with PMF, but no definite effect of quartz could be identified.^{36–38}

Studies in other countries have also noted inverse links between risk of CWP and quartz concentrations in coal. Epidemiological studies from Germany, for example, indicated that the risk of CWP varied from 2% to 40%, although the miners had comparable levels of dust exposure.³⁹ In these studies, differences in the mineral content of respirable dust, such as quartz, did not explain the wide

range of the risk of developing CWP; moreover, it was clear that the hazard of CWP was not affected by quartz content. In fact, as in the British studies noted above, a lower prevalence of pneumoconiosis was noted in German coalmines with higher concentrations of quartz. Similar observations have been made among French miners.⁴⁰ In studies of Welsh miners, the quartz content averaged 2.8% of total lung dust with a range of 0.5% to 10.5%; the highest levels of quartz did not lead to silicotic responses.⁴¹ “Further evidence against the quartz hypothesis (as a cause of CWP) came from cases of massive fibrosis indistinguishable pathologically from the changes in coal workers who have been exposed to purified carbon, and from whose lungs quartz was only isolated in traces.” These studies led one author to conclude: “This component of the dust (quartz) does not play a specific or overriding role in the genesis of massive fibrosis in CWP.”¹⁰

In a summary of animal studies conducted at the time of the preparation of his report in 1988, Heppleston noted that “inhaled mixtures of anthracite and quartz in proportions ranging from 5% to 40% led to distinct fibrosis, (assessed histological and biochemically) only when the quartz level reached 20% and became severe at 40%.”⁴² In other animal studies, a fibrogenic role for quartz at concentrations noted in coal mine dust was not apparent. A working group of the German MAK committee (threshold limit value committee) summarized rat experiments with coal mine dust; experiments showed far lower fibrogenic risks than expected from the experiments with pure quartz of the same mass concentration; there was almost no correlation of fibrogenicity indices with varying quartz contents of coal mine dusts; the high variability of coal mine dust fibrogenicity suggest unidentified factors different from quartz.⁴³

Heppleston concluded that “dust concentration and duration of expo-

sure remain the major determinants of disease prevalence in coal workers, but within the overall pattern exist anomalies that require explanation. Continued emphasis on the role of quartz is evident at all levels of inquiry, but without emergence of a consensus. The proportion of quartz in respirable coalmine dust varies considerably among British and German collieries.”¹⁰ “A specific role for quartz inhaled at the customarily low levels by coal workers’ is difficult to sustain and sometimes can be excluded.”¹⁰

In a study of coal miners exposed to unusually high concentrations of quartz at one specific mine (about 10% quartz in coalmine dust), high CWP rates were attributed to a misdiagnosis of silicosis.⁴⁴ The authors suggested that the rapid progression in radiological abnormalities, their relationship with quartz exposure estimates, and the strength of their relationship with lung function resembled classical silicosis rather than CWP.⁴⁴ Thus, the notion that the progression of CWP to PMF is caused by high concentrations of quartz in coal may be the result of a misdiagnosis of silicosis. Similar findings were reported in a case-control study with British coal miners: an effect of quartz on rapid CWSP-progression was noted when exposure to quartz was unusually high.⁴⁵

Subsequent to an IARC working group meeting that classified crystalline silica (quartz) as an IARC group I carcinogen,²³ a review attempted to shed light on the divergent results of lung cancer incidence in industries in which quartz exposure can occur.⁴⁶ The authors noted that the deposition of quartz in the lungs leading to silicosis was critically dependant on the surface reactivity of the crystalline silica. They proposed that the hazard posed by quartz is not a constant entity, but one that may vary dramatically depending on the origin of the silica sample or its contact with other chemicals and minerals within its complex constitution. Ac-

cording to their review, the risk of quartz exposure from coal is subject to considerable variation. In pointing out some of the epidemiological results of risks of CWP associated with different types of coal, the authors described a German study: although miners had comparable levels of exposure to coal, neither mineral content nor percentage of quartz accounted for differences in rates of CWP; in fact, a low prevalence of simple CWP occurred in collieries with high gravimetric concentrations of quartz. Similar findings were made in France.⁴⁶ In an American study, higher ranked coals were more fibrogenic. "The slope of the dose-response curve between cumulative exposure to coal and incidence of CWP (response) is different despite similar quartz content."⁵

To address some of these uncertainties, a variety of investigations have assessed quartz content, biological activity of the coal dust, and incidence of CWP. Some authors have noted that "quartz can be relatively easily modified in its ability to cause biological effects."⁴⁶ They also pointed out that "modification of the surface (quartz) could occur when substances such as iron or aluminum are present." They referred to studies in which clear differences in the slope of the dose-response curve relating incidence of CWP to years

of exposure in groups of miners can be profoundly different-despite minor differences in quartz content of the coal to which the miners were exposed.

In a review of mechanisms and mediators of coal dust-induced lung disease, inhaled coal dust particles were described as sources of reactive oxygen species in the lungs.⁴⁷

The Role of Coal Rank in Causing CWP

In addition to quartz, the "coal rank" (based primarily on the carbon content of the coal) has long been recognized as associated with risk of CWP. Coal rank is defined by the U.S. Department of Energy as "the classification of coals according to their degree of progressive alteration from lignite. In the United States, the standard ranks of coal include lignite, sub bituminous coal, bituminous coal, and anthracite are based on fixed carbon, volatile matter, heating value, and agglomerating (or caking) properties" (<http://www.eia.doe.gov/cneaf/coal/page/gloss.html>). Coal rank is linked to the stratigraphic horizon of coal deposits: the older the horizon, the higher the carbon content and the lower the quartz content.¹⁷

Several studies have focused on the effect of coal rank on CWP.^{5,48,49} Due to the wide range of coal types

naturally present in the United States, the nation is a desirable study subject for extrapolating a relationship between the rank of coal mines and the pneumoconiosis rates of coal workers. Table 1 illustrates the trend relating coal rank and the prevalence of pneumoconiosis as obtained from data collected between 1969 and 1971 as part of the U.S. National Study of CWP.⁵ The table notes the strong correlation between exposure to higher ranked coal and a higher prevalence of pneumoconiosis. The prevalence of pneumoconiosis spans an order of magnitude from anthracite to low volatile coal.

From these data, Attfield⁵ formulated graphs relating cumulative dust exposure to CWP and PMF (Fig. 1A-C). Such graphs demonstrate the correlation between cumulative dust exposure and pneumoconiosis. Perhaps, the most significant finding, however, is the highly influential effect of the rank of coal on the prevalence of pneumoconiosis. An approximate 6- to 10-fold increase in pneumoconiosis rates occurred for anthracite (~93% carbon) workers when compared with high volatile bituminous coal (generally <80% carbon) workers of the Western and Midwestern United States. These data demonstrate a gradual decrease in pneumoconiosis rates corresponding to decreases in coal rank. Anthra-

TABLE 1

Summary of the Distribution of the Rank of Coal Mined in the Particular Mines Which Participated in the NSCWP and the Corresponding Pneumoconiosis Rates Among the Workers in Those Mines

Variable	Coal Rank Region					All Coal Rank Regions
	Anthracite	Medium/Low Volatile	High Volatile "A"	High Volatile Midwest	High Volatile West	
Number of observations	521	1362	4934	1225	981	9023
Age (yr)	52 (9)	43 (11)	44 (13)	44 (12)	44 (13)	44 (12)
Tenure underground (yr)	29 (12)	20 (13)	18 (13)	21 (13)	19 (14)	21 (13)
Estimated dust concentration (mg/m ³)	3.2 (0.7)	3.1 (1.0)	3.0 (0.9)	3.0 (1.0)	2.8 (1.1)	3.0 (1.0)
Estimated dust exposure (g-hr/m ³)	158 (70)	109 (76)	98 (81)	113 (81)	101 (83)	112 (81)
Overall prevalence of category 1 or greater (%)	41	21	9	5	4	12
Overall prevalence of category 2 or greater (%)	24	10	3	1	1	5
Overall prevalence of PMF (%)	14.2	4.6	1.0	0.5	0.4	2.1

Adapted from *Am Ind Hyg Assoc J.* 1992;53:486-449.

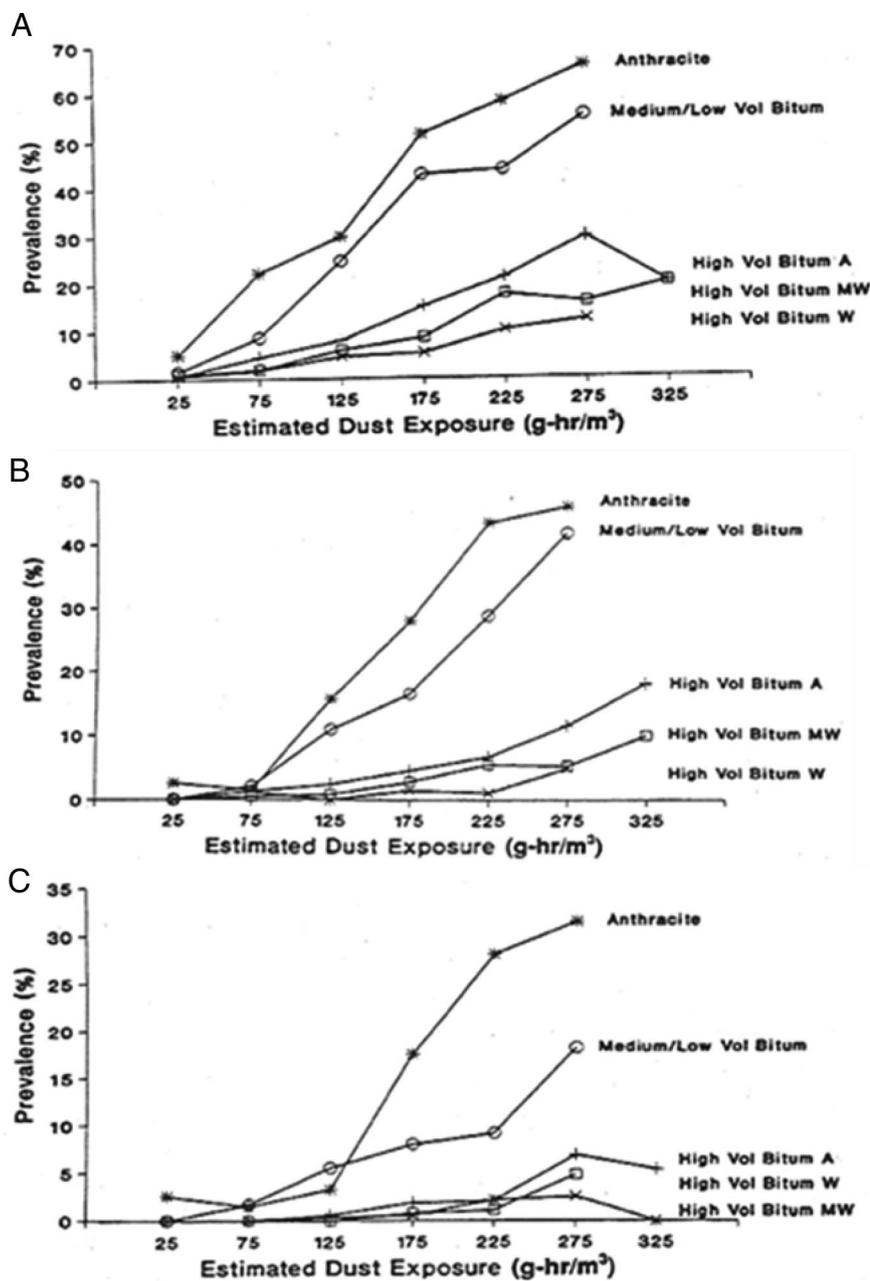


Fig. 1. A, The dose-response relationship between the prevalence of CWP category 1 or greater to the estimated dust exposure levels for various coal ranks. B, The dose-response relationship between the prevalence of CWP category 2 or greater to the estimated dust exposure levels for various coal ranks. C, The dose-response relationship between the prevalence of PMF to the estimated dust exposure levels for various coal ranks. Adapted from *Am Ind Hyg Assoc J*. 1992;53:486-449.

cite miners were more likely to develop pneumoconiosis at any stage of their careers than low volatile bituminous coal workers. The low volatile bituminous coal workers were significantly more likely to develop pneumoconiosis than high volatile bituminous "A" coal workers. Finally, these bituminous "A" miners

were more likely to show signs of pneumoconiosis than those working with lower-rank high volatile bituminous coal (generally <80% carbon). With each successive drop in coal rank, a corresponding decrease in pneumoconiosis prevalence was noted. Considering the large cohort that Attfield examines in this study

(9023 miners), it is evident that the effect of coal rank on pneumoconiosis is substantial. These results have led to the adoption of lower threshold limits for anthracite coal exposure in the US (ACGIH TWA value: 0.4 mg/m^3).⁹

A subsequent detailed analysis of CWSP prevalence restricted to a well-defined subgroup of 3194 coal miners,⁵⁰ again found a clear impact of coalmine dust exposure and a higher risk when exposed in older horizons.

Similar epidemiological observations were made in other countries. In a study on 4122 British coal miners, no impact of quartz on CWSP-progression could be identified; a positive association, however, was noted with the stratigraphic horizon of coal.¹⁸ In one of the most extensive longitudinal studies on British coal miners data on the prevalence and progression of CWSP and PMF were analyzed over 5-year intervals.⁵¹ A clear-cut effect of coalmine dust exposure on CWSP and PMF was observed; higher risks occurred in coal miners exposed to coal mine dust with higher carbon content.

A study on 18,166 German coal miners revealed a clear impact of coalmine dust exposure and coal rank.³⁹ Two other German studies specifically designed to assess coal rank noted a higher CWP risk in the older horizon.^{52,53}

There are a few reasons for the significant effect of coal rank on observed cases of CWP. First, coal dust from mines of high coal rank can result in hemolysis, thereby destroying the integrity of red cell membranes.⁵⁴ In vivo studies of rats chronically exposed to coalmine dust suggest that the retention time of dust particles varies in accordance with coal rank. It was observed that retention post-exposure was greater for anthracite dust when compared with low rank coal.⁵⁵ It has also been suggested that anthracite dust is more pathogenic because it contains more surface free radicals than lower ranked coals.¹² These radicals were present in significantly higher con-

centrations in the lungs of autopsied anthracite miners than in the lungs of autopsied lower ranked coal miners.⁵⁶ Lastly, it has also been suggested that the larger relative surface area among higher ranked coals may cause greater irritation to lung tissue.⁵⁷ Some combinations of the above characteristics of higher ranked coal likely contribute to the varying prevalence of CWP among miners.

A Role for Iron in Causing CWP?

After Heppleston's report in 1988, Ghio and Quigley⁵⁸ addressed the role of iron in CWP. After noting that the characteristics of coal dust responsible for CWP are not known, they pointed out that certain types of transition metals, such as iron, tend to be concentrated in the lungs of miners with CWP. "The accumulation of iron could result in part from its coordination by humic-like substances (HLS), which comprise up to 30% of dust weight in certain coals."⁵⁸ They suggested that HLS in coal dust with iron clad-ions which subsequently catalyze oxidant generation and the accumulation of this metal in the lungs. They noted the accumulation of iron in the tissue of CWP.

Ghio and Quigley⁵⁸ also pointed out that differences in mineral content of coals, including quartz, do not account for the variation in the onset of pneumoconiosis. The relevance of iron coordination by HLS in lung injury after exposure to coal dust can assist in the understanding of certain clinical features of CWP. Occurrence of massive fibrosis after inhalation of coal dust can occur without quartz in the lungs. They concluded: "it is likely that ionizable and chelatable iron in the dust and the consequent capacity to catalyze oxidant production approximate the toxic effects of coal."⁵⁸

To address the hypothesis that different levels of bioavailable iron (BAI) in coal account for regional

differences in both the prevalence and severity of CWP, coal samples in Utah, West Virginia, and Pennsylvania were analyzed; these areas had a prevalence of CWP of 4%, 10%, and 26%, respectively.⁵⁹ The results suggested that BAI in West Virginia and Utah Coal is the main metal species that induced ferritin and lipid peroxidation. The authors claimed that their results provided further evidence that "metals, particularly iron, play important roles in coal dust induced cellular damage ultimately leading to the development of CWP and contributing to the regional differences in the prevalence of the disease." In assessing their results, the authors noted studies (described earlier in this report) in the United States, the United Kingdom, France, and Germany, in which the prevalence and severity of CWP varied markedly among different coal regions; the results varied despite controlling for confounders, such as dust concentration, years of exposure, smoking status, job titles, mining techniques and variations among the radiologists in assessing the quality of the films. The authors noted: "average levels of low molecular weight iron, ferritin and lipids for oxidation induced by the coal samples from each region correlated well with the prevalence of CWP, indicating that BAI in the coals contributes to the regional differences in the prevalence and severity of CWP."⁵⁹ Such links between these agents and CWP is consistent with a "cause-effect relationship." The authors suggested that they suggested that "levels of ferritin in coal miners resulting from alterations due to coal dust inhalation may be used as a biomarker of exposure to coal dust."⁵⁹

Further efforts to understand the active agent responsible for coal-induced lung disease followed. To evaluate the potential link between iron in coal and risk of CWP, Zhang and Huang⁶⁰ showed that the prevalence of CWP in seven coal-mine regions correlated with levels of BAI in the coals from that particular re-

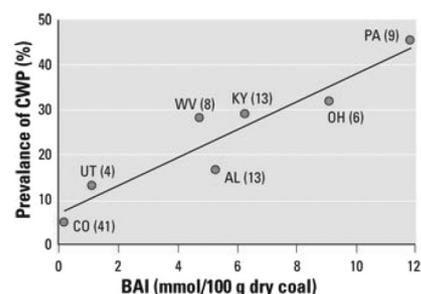


Fig. 2. Correlation between prevalence of CWP and BAI in seven U.S. states' coal mine regions. Numbers in parentheses indicate the number of coal samples per state for which analytical data were available. The expected prevalence of CWP (%) = 3.11 BAI + 7.04. Adapted from *Environ Health Perspect.* 2005;113:964-968.

gion (correlation coefficient $R = 0.94$; $P < 0.0015$). The prevalence of CWP was also correlated with pyretic sulfur or total iron, but not coal rank or silica content ($R = 0.28$; $P < 0.54$). They noted that iron in coal can become bioavailable by a process known as pyrite oxidation. Using a linear fit of CWP and BAI in the seven coal mining regions, they mapped pneumoconiotic potencies of 7000 coal samples and concluded: "Levels of BAI in the coals may be used to predict coal's toxicity, even before large scale mining."⁶¹ The relationship between CWP and BAI was well described by a linear model (Fig. 2).

In an in vitro comparison of coal from Pennsylvania and Utah, BAI in the coal played a major role in activation of factors associated with the pulmonary inflammatory response associated with CWP.⁶¹ The authors claimed their findings supported the hypothesis that "the prevalence of CWP correlates well with levels of BAI in coals from various mining regions." (Table 2 and Fig. 2 in this report have been abstracted from the Huang et al. study.⁶¹)

Commentary from the Huang et al⁶¹ article follows: "CWP, which was originally thought to be a variant of silicosis, results from the inhalation of coal mine dust that usually contains relatively small amounts of free crystalline silica (quartz) . . . It has

TABLE 2

Average Levels (mmol/100 g Dry Coal) of Total H_2SO_4 ($1/2 S_{py} + SO_4$), Available Amount of Acid ($1/2 S_{py} + SO_4 - CaO$), Total Iron, and Predicted BAI*

State	No. of Mines	CWP (%)	$1/2 S_{py} + SO_4$	$1/2 S_{py} + SO_4 - CaO$ †‡	Fe_2O_3	BAI§
PA	9	45.35	18.61	14.63	12.48	11.82
OH	6	31.80	19.91	14.69	12.86	9.07
KY	13	29.00	13.17	7.49	9.78	6.25
WV	8	28.25	9.15	4.57	7.27	4.77
AL	13	16.70	9.65	6.77	8.85	5.29
UT	4	13.10	4.14	-3.19	2.69	1.09
CO	41	4.60	1.92	-2.69	3.68	0.15

*Levels of S_{py} , SO_4 , CaO , and Fe_2O_3 were obtained from the USGS database for each coal mine.

† CaO was presented as percentage of high-temperature ashes in the USGS database and was converted to percentage of dry coal based on the ash yield. Because 1 mol $CaCO_3$ produces 1 mol CaO in the ashes, the molar amount of CaO per 100 g coal was used as a measure of $CaCO_3$ levels in the coals.

‡Values in the individual coal samples were calculated first and then averaged for the coal mine region for each of physicochemical parameters listed.

§BAI was calculated as follows: if the difference in ($1/2 S_{py} + SO_4 - CaO$) is ≤ 0 for the individual coal mine, the BAI is given as 0. If the difference in ($1/2 S_{py} + SO_4 - CaO$) is > 0 , a lesser value between ($1/2 S_{py} + SO_4 - CaO$) or total iron (Fe_2O_3) is given for BAI (see text for details).

Adapted from *Environ Health Perspect.* 2005;113:964–968.

been suggested that higher rank coals with a higher electrostatic charge on breakage may contribute to the increased incidence of CWP in the high-rank coal regions. However, a correlation between coal rank and cell cytotoxicity has not yet been established in biologic studies. In the present study, no significant correlation between CWP prevalence and coal rank or silica was observed ($r = 0.59$, $P < 0.16$ for coal rank and $r = 0.28$, $P < 0.54$ for silica).⁶¹

Huang et al further discuss their results: “Based on the present study using the calculated model of BAI, we believe that it may be possible to predict which coal is likely to be toxic, even before large-scale mining. However, this study is far from concluding the cause-and-effect relationship between BAI and CWP and the associated COPD development. Further studies on the role of BAI in cell and lung injury, as well as the protective role of $CaCO_3$ in inhibiting BAI and the associated injuries, are still needed.”⁶¹ The authors also referred to some of their earlier studies in which coal appeared responsible for oxidant formation and subsequent cytokine (inflammatory mediators) release in the lung after inhalation (of coal).^{62–64} These in vitro evalu-

ations support the epidemiological findings that associate different risks of CWP with different types of coal; moreover, different types of coal have various levels of metals, such as iron.

The same investigators assessed how reactive oxygen species formed by BAI in coal function. Using human lung epithelial cells, they noted that levels of interleukin-6 (IL 6), a key inflammatory protein varied between the Pennsylvania and Utah coal. They noted that BAI in the Pennsylvania Coal may induce interleukin, a key inflammatory mediator, via peroxidation and formation of hydroxyl radicals.⁶⁰

Further in vitro studies provided additional support for the role of iron in the development of CWP. One particular inorganic component in coal, pyrite (FeS_2), has been shown to spontaneously form reactive oxygen species, a key component in the inflammatory response associated with CWP. In experiments to evaluate the role of pyrite and coal dust reactivity, investigators concluded that “the prevalence of CWP can be correlated with the amount of FeS_2 in the coals.”⁶⁵ The authors pointed out that coal is a variable mixture of organic carbon and inorganic mate-

rials, such as quartz, clays, carbonates, pyrite, kaolin, and mica; the iron in coal is associated predominantly with sulfur (FeS_2). The results indicated that “formation of reactive oxygen species from coal samples that contain pyrite is consistent with previous findings and that the pyrite content of coal may be a factor that contributes to the difference in the prevalence of lung disease among coal miners in different mining regions.”⁶⁵ They further hypothesized that “the pyrite content of coal is a significant factor in determining the prevalence of lung disease among coal miners.”

Support of the iron hypothesis was found in a German investigation that analyzed coal mine dust particles with Laser Microprobe Mass Spectroscopy and correlated the findings with cytotoxicity indices from in vitro experiments.⁶⁶ Iron and heavy-metal containing mineral particles were identified as possible toxic determinants but no clear quartz effect was shown.

SUMMARY

In summary, it can be stated with some scientific certainty based on human epidemiology studies, animal investigations and in vitro evalua-

tions—that quartz is not the predominant factor in the development of CWP. To the contrary, large scale epidemiological studies in Germany, the United Kingdom, France, and the United States indicate varying levels of risk of CWP, based on the type of coal regardless of silica content. Epidemiological studies, however, have confirmed that the rank of coal mined greatly influences CWP rates among coal workers, suggesting that coal's carbon content is a critical factor in assessing CWP risk. In addition, coal from regions with lower rates of CWP (while considering similar levels of exposure to coal, both in concentration and duration) show that coal high in BAI is associated with the highest risk of CWP. The link between quartz and the development of CWP is minimal, aside from circumstances associated with high concentrations of quartz (usually >10%) in which the pulmonary response is more typical of silicosis as opposed to CWP. Results of in vitro studies with human and animal cell lines are consistent with the epidemiological data that suggest that risk of CWP is not based on quartz, but most likely due to the concentration of BAI. In vitro studies provide further support for the role of iron in the inflammatory process associated with CWP. Although CWP and silicosis may have some similar clinical patterns, their etiology is different. However, without knowing the disease mechanism of CWP in greater detail, coal mine dust concentration should continue to be controlled by appropriate limit values to minimize disease risks.

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