# Understanding the pathogenesis of occupational coal and silica dust-associated lung disease

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**The re-emergence of CWP highlights a lack of knowledge of and/or effective safe level exposure limits for occupational exposure to dust. This review identifies and highlights potential factors and discusses parthenogenesis of silicosis and CWP in detail.** https://bit.ly/3Mwv6uN

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## Abstract

Workers in the mining and construction industries are at increased risk of respiratory and other diseases as a result of being exposed to harmful levels of airborne particulate matter (PM) for extended periods of time. While clear links have been established between PM exposure and the development of occupational lung disease, the mechanisms are still poorly understood. A greater understanding of how exposures to different levels and types of PM encountered in mining and construction workplaces affect pathophysiological processes in the airways and lungs and result in different forms of occupational lung disease is urgently required. Such information is needed to inform safe exposure limits and monitoring guidelines for different types of PM and development of biomarkers for earlier disease diagnosis. Suspended particles with a 50% cut-off aerodynamic diameter of 10 µm and 2.5 µm are considered biologically active owing to their ability to bypass the upper respiratory tract's defences and penetrate deep into the lung parenchyma, where they induce potentially irreversible damage, impair lung function and reduce the quality of life. Here we review the current understanding of occupational respiratory diseases, including coal worker pneumoconiosis and silicosis, and how PM exposure may affect pathophysiological responses in the airways and lungs. We also highlight the use of experimental models for better understanding these mechanisms of pathogenesis. We outline the urgency for revised dust control strategies, and the need for evidence-based identification of safe level exposures using clinical and experimental studies to better protect workers' health.

## Introduction

### *Burden of particulate matter*

Air pollution caused by suspended particulates in ambient air (particulate matter (PM)) is a critical health concern. Urbanisation and industrialisation arising from globalisation have resulted in reduced air quality in major cities around the globe. Air pollution can be defined as an accumulation of unwanted organic,

inorganic and biological matter with or without toxic gases (ozone ($O_3$), sulfur dioxide ($SO_2$), nitrogen dioxide ($NO_2$)) in ambient air at high concentrations and can potentially reduce the quality of life of populations [1]. It is estimated that 91% of the world's population lives in cities and towns that do not meet the minimum World Health Organization (WHO) air quality guidelines, leading to >4.2 million premature deaths worldwide [2]. The major causes of death associated with poor air quality are chronic obstructive pulmonary diseases (COPD) (43%), lung cancer (29%), ischaemic heart disease (25%), cardiac stroke (24%) and acute lower respiratory infection (17%) [3, 4]. A significant proportion of the world's air pollution-affected population is from low-income and middle-income countries, including poor and marginalised people living near industry and busy roads of developed countries. Thus, individuals with lower socioeconomic status generally disproportionately experience a greater pollution-associated disease burden [2].

### *Particulate matter types and classification*

The particulate matter (PM) levels in ambient air are crucial indicators for quantifying air pollution, and their concentration dictates air quality in the environment or workplace. Natural PM is a complex, heterogeneous mixture of different sized solid or liquid particles liberated from different sources. Some of the natural sources of environmental PM include dust generated from volcanic activity, desert dust, sea salt, landscape fires, pollen and other biological matter. Artificial PM is generated by human activity (anthropogenic), including partial combustion of fossil fuels (coal, diesel, firewood), mining operations, construction, industrial and vehicular exhaust and agricultural activities [5–7]. Airborne PM exists in a wide range of sizes and is often characterised based on its aerodynamic size and ability to penetrate the airways and lungs. PM is categorised as inhalable or thoracic PM and respirable PM [8, 9]. By definition, particles with a 50% cut-off aerodynamic diameter of $\leqslant$10 µm ($PM_{10}$) are classified as inhalable PM that can penetrate the respiratory tract upon inhalation and are considered biologically important [10]. These coarse particles enter the upper respiratory tract and can settle in the tracheobronchial region through impaction, inducing damage to the airways and upper thoracic region. Because of their harmful nature, the concentration of suspended $PM_{10}$ form the primary focus of WHO air quality standards and regulatory agencies monitoring air quality in populated urban areas, rural towns and workplaces. Fine and ultrafine particles that are $\leqslant$2.5 µm diameter (*i.e.* $PM_{2.5}$ and $PM_{0.1}$) are termed respirable PM. Their aerodynamic size enables the particles to escape the upper respiratory tract's primary defences and penetrate deep into the lower airways and lung parenchyma through sedimentation and diffusion processes, where the PM itself or associated chemical pollutants may interact with lung processes and cause dysfunction or disease [11, 12]. Air pollution caused by $PM_{2.5}$ is the fifth leading cause of mortality, with 103.1 million disability-adjusted life years (DALYs) [13]. According to WHO [14], DALYs represent the overall time lost due to years lost through premature death (YLLs) and years lost through poor health or disability (YLDs), *i.e.* DALYs=YLLs+YLDs. Brown *et al.* [8] suggested that inhaled dust particles ranging between 0.5 µm and 20 µm can penetrate below the larynx and cause pulmonary and cardiovascular complications in different age groups or exacerbate pre-existing disease conditions like asthma or COPD [15]. Further, literature shows strong links between exposed PM levels and increased mortality due to cardiovascular and lung cancer [16]. Studies using experimental models indicate that inhaled PMs have strong potential to produce reactive oxygen species (ROS) and reactive nitrogen species (RNS), which induce oxidative DNA damage and elevate the risk of cardiovascular and lung cancer [17–19].

### *Characteristics of particulate matter*

Unique characteristics of different types of PM, such as small particle size, high surface area and surface charge (electrostatic, hydrophobic), allow them to readily attract and harbour surrounding chemical and metal contaminants. Furthermore, their aerodynamic diameter and low density allow PM and PM complexes (PM harbouring contaminants) to remain airborne for extended periods, drift along the air currents and travel substantial distances from the point source. Their ability to harbour environmental or workplace contaminants allows them to act as potential carriers of toxic or carcinogenic agents, such as polyaromatic hydrocarbons (PAHs) and per- and poly-fluoroalkyl substances, into the human airway and lung [11, 20]. Once in the lungs, the particles and their contaminants can induce disease processes, resulting in pathophysiological changes that disrupt normal lung function and induce acute and chronic respiratory and cardiovascular illnesses [21–27].

Owing to their toxic potential, WHO has set current global standards for $PM_{10}$ and $PM_{2.5}$ in ambient air to a 50 $\mu g \cdot m^{-3}$ and 25 $\mu g \cdot m^{-3}$ per 24-h mean, and 20 $\mu g \cdot m^{-3}$ and 10 $\mu g \cdot m^{-3}$ annual mean, respectively [2]. However, these international standards are derived from spatial population and health data obtained from developed nations and do not consider variation in chemical composition and pollution sources and are not reflective of PM in over-populated developing countries. Notably, there is also variability in PM standards across different countries (table 1).

**TABLE 1** Safety standards of particulate matter (PM) in ambient air in different geographical areas

| Agency | $PM_{10}$ | $PM_{2.5}$ | Reference |
|---|---|---|---|
| **World Health Organization (2018)** | 20 μg·m$^{-3}$ (annual)<br>50 μg·m$^{-3}$ (24-h) | 10 μg·m$^{-3}$ (annual)<br>25 μg·m$^{-3}$ (24-h) | [2] |
| **US Environmental Protection Agency** | 50 μg·m$^{-3}$ (annual)<br>150 μg·m$^{-3}$ (24-h) | 12 μg·m$^{-3}$ (annual)<br>35 μg·m$^{-3}$ (24-h) | [28] |
| **New South Wales Environment Protection Authority (Australia)** | 25 μg·m$^{-3}$ (annual)<br>50 μg·m$^{-3}$ (24-h) | 8 μg·m$^{-3}$ (annual)<br>25 μg·m$^{-3}$ (24-h) | [29] |
| **UK and EU** | UK/EU: 40 μg·m$^{-3}$ (annual)<br>50 μg·m$^{-3}$ (24-h)[#] | UK: 25 μg·m$^{-3}$ (annual) | [30] |
| | Scotland: 18 μg·m$^{-3}$ (annual)<br>50 μg·m$^{-3}$ (24-h)[¶] | Scotland: 10 μg·m$^{-3}$ (annual) | |

$PM_x$: particles with a 50% cut-off aerodynamic diameter of x μm. [#]: not to be exceeded more than 35 times a year in the UK; [¶]: not to be exceeded more than seven times a year in Scotland.

## Occupational dust-associated lung diseases

Dust-associated diseases are common among many different populations and cohorts. However, exposure to high PM concentrations for extended periods in the workplace is more likely to lead to severe respiratory disorders or interstitial lung diseases in individuals. The global burden of occupational airborne PM accounts for ∼519 000 deaths (95% uncertainty interval), which includes 21 500 with pneumoconiosis, 37 600 with asthma and 460 100 with COPD, and estimated DALYs of 0.58 million for pneumoconiosis, 2.3 million for asthma and 10.7 million for COPD [31]. Significantly, PM-generating dust emissions from coal mining operations and construction pose a specific and significant threat to miners' and construction workers' health. PM generated in these work environments contain organic and inorganic constituents, including silica, iron, metalloids, heavy metals, PAHs and other contaminants, at varying concentrations that can cause chronic disease or be fatal upon long-term inhalation [32–35]. Coal miners are highly susceptible to occupational lung diseases like coal mine dust lung disease. Coal mine dust lung disease includes, but is not limited to, a range of occupational lung-associated diseases such as coal worker's pneumoconiosis (CWP), silicosis, mixed-dust pneumoconiosis, progressive massive fibrosis (PMF) and COPD (figure 1) [34, 35]. CWP, or black lung, is re-emerging in various major coal-producing countries, including Australia [36–39]. In addition, dust emissions generated from mining operations and construction sites positively correlate with the increased prevalence of chronic bronchitis, emphysema and COPD [37, 40]. Inhalation of dust particulates rich in inorganic metals such as aluminium, titanium and tin can also result in the development of rare lung disorders, such as alveolar proteinosis, an acute condition which involves an increased intra-alveolar deposition of surfactant, resulting in decreased gas-exchange, leading to hypoxia, which can be fatal [41]. Long-term exposure to iron or iron oxide-rich mining dust can also lead to pulmonary siderosis that may or may not be associated with fibrosis [42, 43]. Workers exposed to asbestos may also develop asbestosis. Asbestos is a fibrous silicate mineral (serpentine or amphibole) that is found naturally but that is incorporated into commercial, household and construction materials, including insulation, flooring and roofing materials, to increase tensile strength and reduce flammability. Asbestosis is characterised by an increased influx of macrophages, increased production of inflammatory cytokines such as tumour necrosis factor (TNF) and interleukins (IL-1β, IL-6), and increased generation of ROS. These inflammatory processes and increased ROS lead to the destruction of alveolar type 1 cells and the development of characteristic asbestos and ferruginous bodies associated with massive fibrosis [44, 45].

Inhaled dust particles (⩽1 μm) and contaminants (organic/biological) deposited in alveoli from repeated exposures can also trigger various allergy-induced lung disorders and the development of aberrant immunological responses, which are collectively termed hypersensitivity pneumonitis or extrinsic allergic alveolitis. Increased immunoglobulin G in bronchoalveolar lavage fluid and peripheral blood, increased Ki-67 in the nucleus and granuloma formation in the lungs are common clinical indications of hypersensitivity pneumonitis, and separate it from other dust-associated lung diseases [46, 47]. Depending on the intensity and type of exposure, hypersensitivity pneumonitis can vary from acute to chronic, and non-fibrotic (inflammatory) to fibrotic (inflammation±fibrosis). These allergy-induced occupational lung diseases are mainly driven by aberrant type III or type IV hypersensitivity responses. The pathogenesis and manifestation of symptoms and patient outcomes of occupational dust diseases vary greatly. This

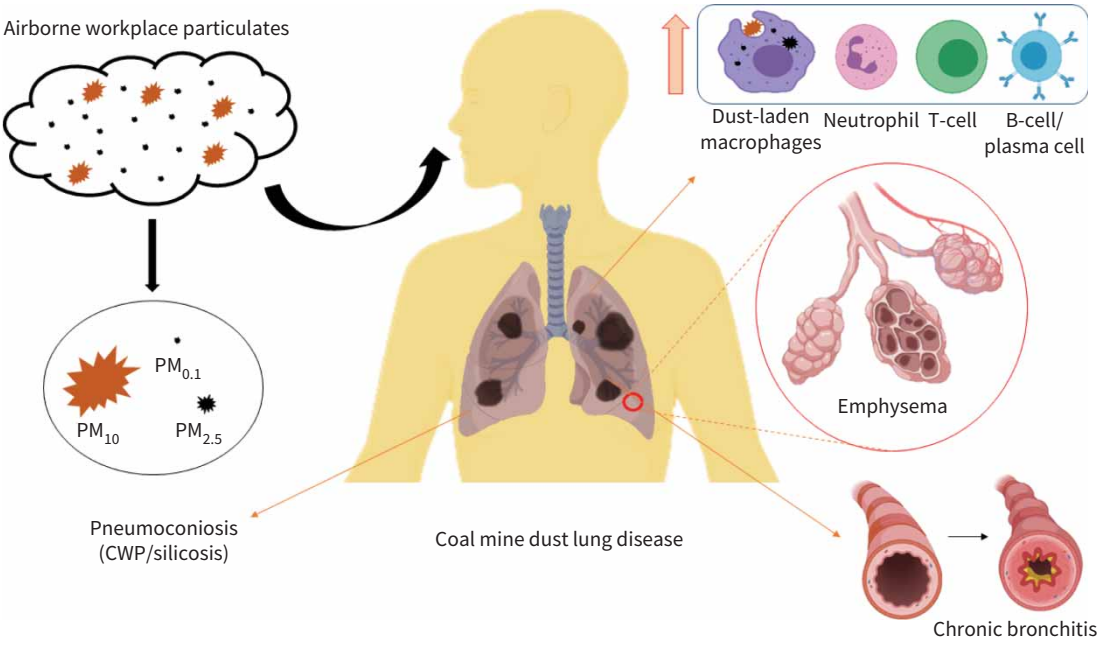


**FIGURE 1** Pathogenesis of dust particulate matter (PM)-associated occupational lung diseases. Schematic shows the entry of particulate matter ($PM_{10}$ and below) through environmental/occupational exposure into lungs and development of subsequent respiratory complications, which include increased cellular influx (macrophages, neutrophils, T-lymphocytes and B-cells), alveolar destruction (emphysema) and structural changes (collagen and mucus deposition) leading to chronic bronchitis. $PM_x$: particles with a 50% cut-off aerodynamic diameter of x µm; CWP: coal worker's pneumoconiosis.

variability is dependent on multiple factors, *e.g.* dust source, chemical composition, and intensity and duration of exposure. Furthermore, biological and behavioural aspects such as age, sex, genetics, immune response, smoking status and underlying comorbidities like obesity and pre-existing respiratory conditions play important roles in influencing the risk of developing occupational lung disease [36, 48–50]. These issues have led to the development of occupational exposure limits (OELs) of workplace dust, but these vary widely between and within different countries, and rarely consider the different physicochemical characteristics of different dust types inhaled in different workplaces. Furthermore, biological and behavioural factors are also rarely factored into risk matrices. A greater understanding of how different types of dust and biological responses to these dusts affect disease in workers is required to help determine which workers are at greatest risk and inform better prevention strategies, develop earlier diagnostic tests and highlight pathogenic processes that can be targeted with novel therapeutics. This review describes our current knowledge of occupational lung disease and includes a description of the currently limited understanding of mechanisms of pathogenesis. Though multiple lung disorders are associated with occupational dust exposure, in this article we focus mostly on CWP and silicosis owing to the alarming increase in case numbers in the Australian mining industry and elsewhere.

### *Coal worker's pneumoconiosis*

It is estimated that ~7.3 billion tons of coal is mined worldwide each year. While the world has advanced into an era of higher implementation and use of renewable energy and resources, coal is still a primary source of energy, producing 37% of the world's electricity, and 74% of global steel is produced in processes involving burning coal [51]. CWP, also commonly known as black lung disease, is an irreversible but preventable respiratory disorder in coal miners and workers exposed to coal dust for prolonged periods. It is characterised by chronic inflammation and the formation of nodules in the lungs and can lead to PMF, which is typically fatal [37]. According to WHO, 25 000 deaths occur annually due to CWP [52]. The first case of CWP was reported in 1831 by British coal miners. By the mid-1900s, the disease was prevalent among coal miners in major coal-producing countries like Australia (16%) and the USA (6.5%); however, by the end of the 1990s, disease prevalence had declined owing to the implementation of strict dust control and surveillance measures, which included personal protective equipment, ventilation, periodic health surveillance, chest radiography and the implementation of an independent dust monitoring system [48, 53]. Subsequently, however, by the early 2000s disease prevalence

in the USA had increased to 3.2% accompanied by an increase in PMF cases from 0.14% to 0.31% [48]. Furthermore, there was an increase in lung transplants related to CWP in the USA, with 62 CWP-related lung transplants occurring over the past decade alone. Moreover, 27 patients were waitlisted but died before transplant. The average cost associated with a single bilateral lung transplant in the USA is ~$1.2 million, with a median 3.7 years post-transplant survival rate [54]. Similarly, according to statistics from the Department of Resources, Australia, one confirmed CWP case was documented between 1984 and 2014 in Queensland, but the case numbers increased substantially in the following years, with 37 confirmed CWP cases reported between 2014 and 2021 [55]. Though the reported mortality in Australia is insignificant compared to confirmed CWP cases/deaths from other coal-producing countries like the USA (>10 000 CWP-related deaths between 1995 and 2004) [49] or other aggressive respiratory illnesses like COPD and asthma, CWP still poses a significant economic burden (lung transplants) and compromised lifestyle [34, 35, 56]. The exact reason behind the reoccurrence is unclear. However, it is believed that the use of new practises and modern mining technologies, such as heavy machinery and mountain top removal, results in the generation of finer dust clouds with high respirable crystalline silica content, which, when combined with new diagnostic techniques, contribute to the rising case numbers [37].

### *Symptoms and pathophysiology of CWP*

Patients are asymptomatic during the early stages of CWP; however, as the disease manifests, patients exhibit symptoms of coughing, sneezing, increased sputum production, breathlessness and breathing difficulties [57]. These symptoms are often misinterpreted as the side-effects of cigarette smoke when the affected individual is a smoker. According to Health Australia, 27% of miners are active smokers [58]. Based on aetiology, CWP can be categorised into simple or complicated CWP or PMF. The development of small opacities characterises simple CWP: coal macules or lesions <10 mm in diameter occurring mostly in the upper lung lobes due to the accumulation of dust particles and dust-laden macrophages are usually associated with focal centrilobular emphysema. There are no visible symptoms to indicate simple CWP apart from normal cough and black sputum production and there are no significant changes in lung function (forced expiratory volume in 1 s). Further prolonged exposure to coal dust can result in disease progression to complicated CWP or PMF, characterised by dust-laden lesions ⩾10 mm diameter with irregular or round symmetry. This is associated with increased collagen deposition and fibrosis around the airways and within the parenchyma, exertional breathlessness, haemoptysis and lung scarring. Individuals with pre-existing chest infections or autoimmune disorders may also show signs of Caplan syndrome, which is CWP associated with rheumatoid arthritis and pulmonary necrobiotic nodules [59]. In patients with both simple and complicated CWP, the lesions and macules comprise inhaled coal dust particles engulfed in alveolar macrophages and surrounded by inflammatory cells. Patients with PMF often experience increasing breathlessness and severe deterioration in lung function, resulting in hypoxaemia and pulmonary hypertension that eventually leads to cardiac and respiratory failure [60]. It is estimated that <5% of simple CWP cases progress into PMF, with symptoms and disease manifestations dependent on the inhaled PM's physical and chemical constituents, duration of exposure, host immune factors and disease stage. CWP can be diagnosed by periodic chest radiography to examine the size, shape and number of macules according to the International Labor Office (ILO) [61] to determine the stage of the disease. The smaller opacities are scored in comparison with standard radiographs into four categories, *i.e.* Category 0, 1, 2, 3 and 4, which are further classified based on profusion into 12 ordered subcategories. The larger opacities (>10 mm) are categorised as follows [48, 61–63]: Category A: one opacity, ranging up to 50 mm in diameter or several large opacities for which the sum of the dimensions does not exceed 50 mm; Category B: one or more opacities >50 mm in diameter but not exceeding the right upper zone's equivalent area; and Category C: greater than Category B.

Though the ILO system is a widely accepted and used method for the classification of chest radiography to identify CWP, the two-dimensional resolution of chest radiography limits the ability to observe the structural changes occurring in the parenchyma. As a result, radiologists increasingly use high-resolution computed tomography (HRCT) to better resolve the changes in lung parenchyma and detect pleural abnormalities. Similar to ILO classification, HRCT scans use ICOERD classification (International Classification of High-Resolution Computed Tomography for Occupational and Environmental Respiratory Diseases) to identify and distinguish pneumoconiosis from other dust-associated interstitial lung diseases [64]. ICOERD commonly uses a 4-point grading scale based on six lung segments and assigns a score for each parameter [64, 65]. Round opacities are graded by size as P (<1.5 mm), Q (1.5–3 mm) and R (3–10 mm). For linear/irregular opacities, intralobular and interlobular opacities of diameter >1 cm–large are graded A; the sum of one or more opacities between 1 cm and one quarter of CT, or greater than A and less than one quarter is graded B; and opacities greater than B and at the level of the carina are graded C. Ground-glass opacity, honeycombing grade and emphysema are classified as mild (<15%), moderate (15–30%) and severe (>30%) for each zone, and the sum of the six zones is used to determine the presence or absence

and severity of pneumoconiosis. It is well documented that CWP, chronic bronchitis and emphysema are associated with coal dust exposure and increased risk of death from COPD. Reports show that newly employed coal miners can exhibit bronchitis symptoms with a rapid decline in lung function within 2 years of dust exposure [56]. No known treatments exist for CWP, apart from lung transplantation. While the harmful effects of coal mining dust on CWP and human health are well understood, the underlying mechanisms that underpin the initiation and progression of diseases are still debated. Little is known of the immunopathological mechanisms that underpin disease pathogenesis following exposure to different PM forms generated during coal mining operations. Possible disease mechanisms could include cell toxicity, oxidative stress, inflammation, DNA damage and tissue scarring (figure 2) [59, 66]. A greater understanding of what types of PM drive the development and progression of CWP and how the different PM constituents promote disease may inform better prevention strategies (improved safety and/or exposure standards) and targeted therapies.

### *Mechanisms of the pathogenesis of CWP*

The inhalable and respirable portion of the PM that escapes the upper respiratory tract defences can interact with lung tissue and cells in one or more ways. Some of the common pathways are listed below.

#### *Direct cell toxicity*

Upon inhalation of coal dust, the respirable portion of PM, along with silica, especially quartz and associated contaminants, penetrates the lung parenchyma and passageways. Here it interacts with surface cells or markers, causing structural damage and release of lipases and proteases, leading to eventual lung scarring. In addition, *in vitro* studies involving human cell lines have confirmed PM toxicity induces cell death mechanisms and increases apoptosis [67].

#### *Oxidative stress*

Inhaled dust particles are often scavenged by immune cells, especially alveolar macrophages, which are activated to produce ROS and RNS that cause lipid peroxidation, protein nitration and DNA damage [68].

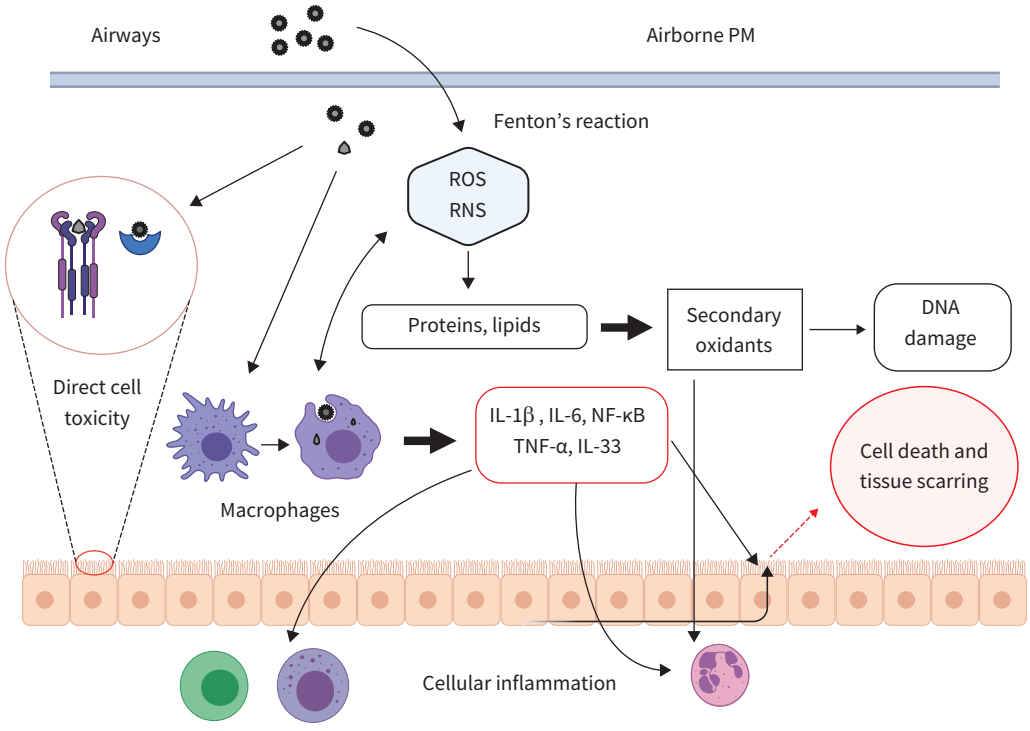


**FIGURE 2** Mechanisms of dust particulate matter (PM) toxicity. Schematic representation depicting ambient airborne PM with various cellular mechanisms and triggering cascade reactions, *i.e.* cellular inflammation, reactive oxygen species (ROS) and reactive nitrogen species (RNS) production, cytokine production and DNA damage, leading to cell death and scar tissue formation. Created with BioRender.com. IL: interleukin; NF-κB: nuclear factor-κB; TNF: tumour necrosis factor.

In particular, respirable coal dust fractions elicit oxidative stress either by blocking redox signalling pathways or increasing endogenous ROS production [7]. Freshly ground coal surfaces contain free radicals produced through the Fenton reaction because of the high iron content in coal. Excessive ROS and RNS overwhelm the lung's antioxidant capabilities, resulting in inflammation, which drives disease. Heavy metals, transition metals and PAH contaminants associated with particulates play a vital role in inducing oxidative stress, leading to the activation of cell death pathways (apoptosis, autophagy) [69, 70].

#### *Inflammation and production of growth factors*

In response to inhaled PM, airway and alveolar epithelial cells, macrophages and other cells produce a variety of cytokines and growth factors, including IL-1β, IL-6, TNF-α, macrophage inflammatory proteins (MIP1, MIP2), transforming growth factor-β (TGF-β), monocyte chemoattractant protein 1 [26, 27, 71] and platelet-activating factor. These pro-inflammatory factors recruit other immune cells to the lungs, which produce inflammatory mediators and cell damage [72], and activate fibroblasts, which increase the production of extracellular matrix proteins, leading to collagen deposition and eventual scarring of lung tissue [73, 74]. No known genetic factors are associated with CWP; however, single nucleotide polymorphisms in the genes for TNF-α, specifically at the −308 position in the promoter region, and lymphotoxin-α are associated with genetic susceptibility and increased risk of CWP [62, 75]. Another study showed that increased concentrations of plasma TNF-α receptors (p55 and p75) and IL-6 in patients (n=182, 71 CWP, 111 control) were associated with disease severity [76], and these may be helpful biomarkers in the early detection of CWP.

### *Silicosis*

Silicosis is a spectrum of interstitial lung diseases caused by inhalation of reactive crystalline silica (RCS) from various occupational and non-occupational sources. Recent increases in silicosis incidence in construction and mining workers, particularly in young workers involved in sandblasting, bolting, cutting, shaping and installing kitchen countertops made from quartz conglomerates (engineered stones), is a serious concern [77]. Although the disease itself is not new, the current understanding of its development, manifestation and safe levels of exposure are still mostly unknown. Crystalline silica is constituted of silica (Si) and oxygen (O) atoms arranged in three-dimensional space. Silica is the most abundant mineral on Earth and usually exists as silicon dioxide ($SiO_2$) or silicon tetraoxide ($SiO_4$). Based on the elemental arrangement of atoms, silica exists in seven polymorphs, among which quartz (α-quartz) is dominant, and exposure to respirable quartz is found to induce various interstitial lung diseases such as silicosis [78] and pulmonary sarcoidosis [79]. Owing to its toxic potential, the OEL for RCS is regulated according to nationally determined standards. Most standards exceed those proposed by the American Conference of Governmental Industrial Hygienists (ACGIH) and show variation between countries in classification and thresholds.

### *Symptoms and pathophysiology of silicosis*

Silicosis develops following the inhalation and deposition of RCS into the smaller airways and lung parenchyma. Disease severity and pathogenicity depend on the quantity of inhaled dust and exposure time. Although the disease has been recognised for decades, the underlying mechanisms are still unclear. It is thought that alveolar macrophages phagocytose the inhaled crystalline silica (quartz) particles in the lungs. This causes lysosomal damage and subsequent activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome (occurs in severe asthma) [80], which in turn triggers a cascade of reactions involving the secretion of the inflammatory and pro-inflammatory cytokines IL-1β and TNF-α and production of ROS and RNS intermediates, which drives the apoptotic cell death cycle and development of lung fibrosis [81, 82]. Following prolonged exposure, the disease may manifest into irreversible fibrotic pulmonary disease [83, 84]. Impairment of lung function continues to progress even after the exposure to silica dust ceases [77], which explains the development of occupational accelerated silicosis (AS) in silica-exposed workers in later stages of life. Based on clinical and pathological variations, silicosis can be differentiated into simple (or nodular) silicosis, complicated silicosis or PMF, AS, acute silicosis (silico-proteinosis) and true diffuse interstitial fibrosis.

#### *Simple silicosis*

Patients with simple silicosis are generally asymptomatic and retain normal pulmonary function with only a slight decrease in vital lung capacity, but they may develop a dry cough caused by irritation of the trachea. Histological examination of lung biopsies, chest radiography and HRCT scans reveal the development of silica nodules up to 10 mm in diameter in the upper lobes, associated with enlarged hilar peribronchial lymph nodes that are frequently calcified.

### *Complicated silicosis or PMF*

This is characterised by the confluent growth of nodules extending into the lower lobes with a diameter of >1 cm. The nodules' colour depends on the dust exposure's chemical profile, *e.g.* grey to blue nodules from pure silica, black nodules in coal miners and red nodules in haematite miners. The nodules are often associated with dust-laden macrophages and increased central collagen deposition. Continuous exposure to dust may further recruit immune cells and progression of disease into idiopathic pulmonary fibrosis [45, 85]. PMF predominantly affects the upper lobes with progressive loss of lung volume and mediastinal structures' traction cranially.

### *Accelerated silicosis*

Unlike traditional silicosis, AS is characterised by a short latency period of <10 years, resulting from high exposure to RCS particles. The radiological features range from simple to complicated silicosis, but there are substantial lung function decreases over a comparatively short period. The major contributing factor associated with silicosis's resurgence is the poor understanding of the risks involved or non-adherence to workplace safety regulations. Hoy *et al.* [86] reported six Australian workers involved in dry cutting of artificial stone for 7 years who developed radiological features of PMF. 6.6% of Australian workers are exposed to crystalline silica dust. Relying on traditional diagnostic methods such as plain chest radiographs could limit early detection owing to low sensitivity and frustrate efforts to halt disease progression before the development of irreversible pathology. Applying proven biomarkers as early detection tools among the at-risk workforce would be highly beneficial to prevent progressive disease. Several potential biomarkers have been identified, *e.g.* increased plasma levels of TNF-α, IL-8, ROS, glutathione, glutathione peroxidase, glutathione S-transferase, club cell secretory protein (CC16), 8-isoprostane and platelet-derived growth factor [87]. A cross-sectional study of former and currently exposed workers who developed silicosis revealed increased levels of plasma CXC motif chemokine ligand 16 (CXCL16), a chemokine released by respiratory epithelial cells, as a biomarker of early disease [88]. Furthermore, patients with silicosis have increased susceptibility to infection with *Mycobacterium tuberculosis* and progression from latent to active tuberculosis [89] and fungal infections, which may progress to life-threatening illnesses.

### *Mechanisms of the pathogenesis of silicosis*

Fresh silica particles can produce reactive free radicals on their surface; following inhalation, these cause DNA damage, mutations and eventual cell death [90]. Freshly fractured silica can stimulate a respiratory burst in lung macrophages, as occurs with asbestos fibres, and this results in the release of oxidants, proteolytic enzymes and inflammatory factors, including TNF-α and IL-1β, that recruit other inflammatory cells, leading to severe pulmonary inflammation (figure 3) [91]. The concomitant exposure of silica dust with other environmental contaminants induces silicosis; however, the exact nature of the effects and mechanisms of pathogenesis is not completely understood. Having virtually no information on the effects or pathogenesis of other crystalline forms of silica could pose a future threat. RCS is recognised as a highly potent carcinogen by international agencies, including the International Agency for Research on Cancer, the US National Institute of Occupational Safety and Health and the British Health and Safety Executive [92]. High levels of RCS exposure are also associated with COPD development, and low levels possibly lead to the development of bronchitis, emphysema and even non-malignant renal diseases. Boffetta *et al.* [93] reported an increased risk of lung cancer with elevated crystalline silica concentrations, especially cristobalite exposure in silicon carbide production workers. Though silicosis is predominantly seen in construction and stone workers, miners and coal workers involved in mining operations like sandblasting, surface drilling and roof bolting are exposed to high levels of RCS dust clouds for extended periods. This cohort of miners/workers is at heightened risk of developing silicosis during or after their tenure in coal sectors [59].

## Occupational exposure limits

Dust exposure standards at workplaces are often stricter than environmental standards because of continuous dust generation and prolonged exposures in the former. Owing to their toxic potential, the OELs for RCS are regulated according to nationally determined standards (figure 4a). Most standards exceed those proposed by the ACGIH and show variation between countries in classification and thresholds. Similarly, international exposure standards for coal dust vary considerably among major coal-producing countries (figure 4b). Australia, being one of the major coal-producing countries, used to operate with two different safe exposure standards, 2.5 $mg \cdot m^{-3}$ for New South Wales [53] and 3 $mg \cdot m^{-3}$ for the Queensland mining industry [94]. However, due to the increased prevalence of CWP in the Australian mining industry, exposure to airborne coal dust containing <5% quartz (*i.e.* respirable dust) is now set to a time-weighted average of 1.5 $mg \cdot m^{-3}$ (standard set in February 2021, applicable from October 2022) [95]. US mining industries operate at much lower workplace concentrations of

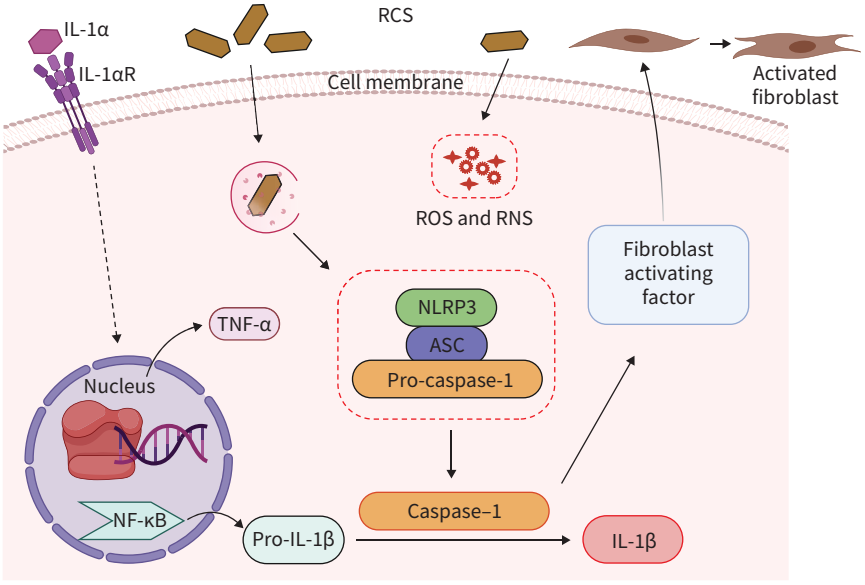


**FIGURE 3** Pathogenesis of reactive crystalline silica (RCS). The illustration depicts the interaction of RCS with lung epithelial cells and subsequent activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome pathway and production of pro-inflammatory cytokine interleukin (IL)-1β, free radicals and fibroblast-activating factor leading to fibrosis. Created with BioRender.com. ROS: reactive oxygen species; RNS: reactive nitrogen species; ASC: apoptosis-associated speck-like protein containing a caspase activation and recruitment domain; TNF: tumour necrosis factor; NF-κB: nuclear factor-κB.

1–1.5 $mg \cdot m^{-3}$ [96] and higher ambient PM levels (table 1), which raises questions about safe PM levels globally. In 2001, the ACGIH recommended 0.9 $mg \cdot m^{-3}$ as a respirable fraction in lignite coal dust and 0.4 $mg \cdot m^{-3}$ for anthracite coal dust. The UK in 2011 set the OELs for coal dust respirable fraction to 1.6 $mg \cdot m^{-3}$ with 0.4 $mg \cdot m^{-3}$ for anthracite and 0.9 $mg \cdot m^{-3}$ for bituminous dust over a time-weighted average of 8 h [97]. Currently, there is an ongoing debate on OELs and safe levels of exposure to dust [97]. Moreover, there are no specific monitoring standards for specific dust types. This is important because the dust produced during underground mining generates inhalable and respirable PM at much higher exposure levels than open-cut mining. Furthermore, PM produced during the different stages of the mining process (drilling, blasting, roof bolting, coal handling, preparation for transportation) in both open-cut and underground mining are different in terms of their physicochemical properties. For example, the initial mining stages in both operations have higher silica levels and other contaminants, and the later stages have higher carbon (by weight) [98]. Thus, a single OEL may not be ideal for all dust types in open-cut/underground coal mining because the PM generated from different operations is diverse, giving rise to differential effects on the respiratory system. Consequently, research into the effects of current exposure standards for different PM and types of exposure is needed to provide evidence to better inform and improve safe exposure guidelines.

The specific reasons behind the resurgence of CWP and other occupational lung diseases in coal mining remain debatable. However, increased production, extended shift hours, use of large equipment, sandblasting and over-exposure to larger concentrations of respirable or RCS content in PM generated during operations are the likely key factors [37]. Importantly, evidence suggests that the coal mine's geographical location plays a major role [99]. CWP varies considerably between countries and even between regions within countries. Prevalence in China (6.02%) and India (3.03%) is relatively high and increasing, while CWP cases in UK and Germany are decreasing or absent [48]. The US National Institute for Occupational Safety and Health study among active coal miners working outside central Appalachia found that 2.1% of miners had CWP. Further, the prevalence of CWP was much higher in the eastern region compared to the western or interior region, *i.e.* 3.4%, 1.7% and 0.8%, respectively, with a similar pattern for PMF, *i.e.* 0.5%, 0.1% and 0%, respectively. Of this 2.1% of miners, 9.3% had abnormal spirometry parameters [100]. It is unknown whether the difference in prevalence between geographical locations is due to differing mining operations, safety standards, disease monitoring/reporting or the PM's constituent properties in different mines.

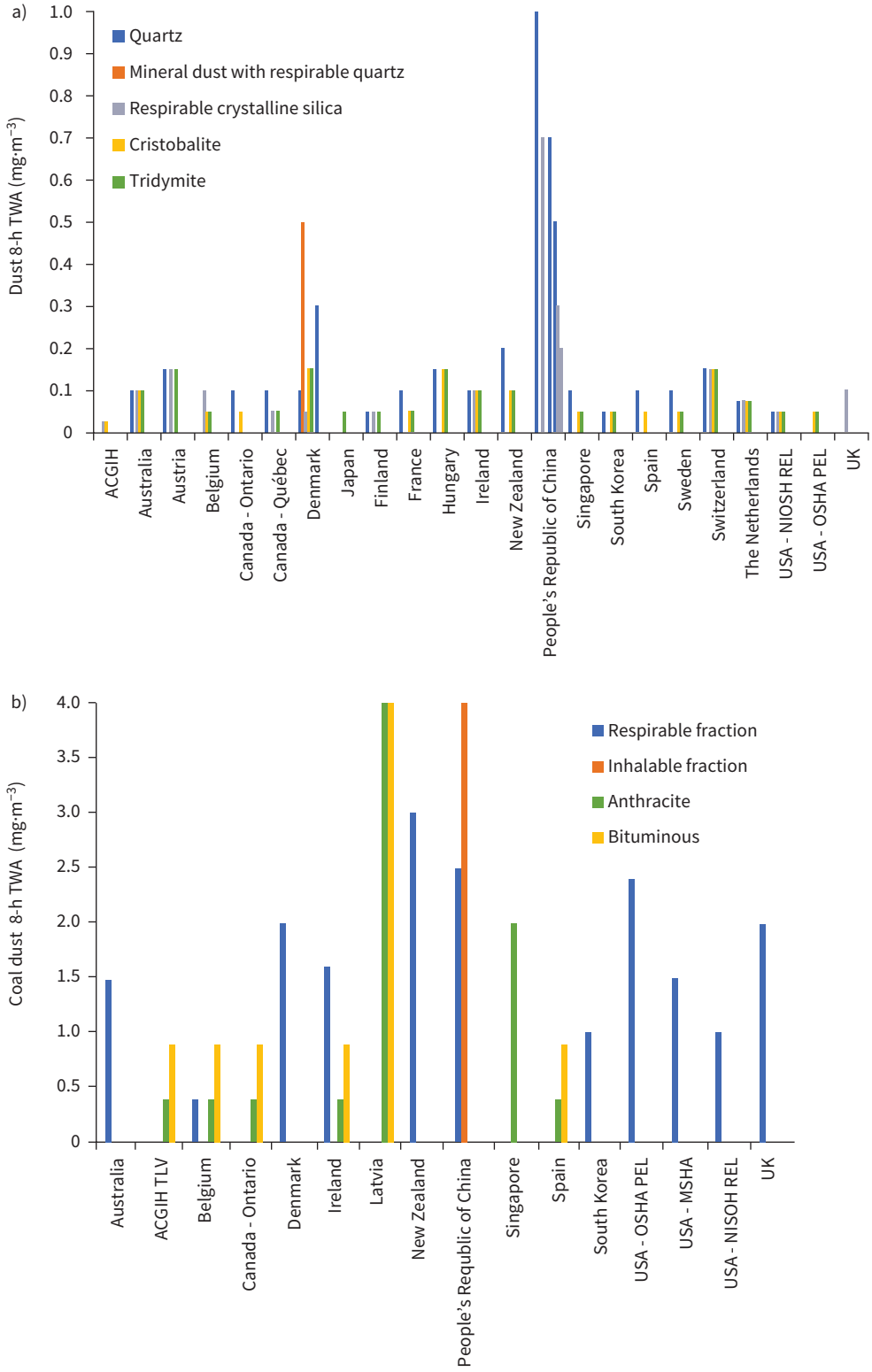


**FIGURE 4** Occupational exposure limits (OELs) of a) silica (quartz) and b) coal dust particulate matter (PM). The graphs show that the OEL or safe dust exposure limits of respirable and inhalable fractions of silica and coal dust PM vary significantly among different coal-producing countries. These limits are set primarily on particle size. TWA: time-weighted average; ACGIH: American Conference of Governmental Industrial Hygienists; NIOSH REL: National Institute for Occupational Safety and Health recommended exposure limit; OSHA PEL: Occupational Safety and Health Administration permissible exposure limit; TLV: threshold limit value; MSHA: Mine Safety and Health Administration.

## Animal models

Experimental animal models have long been an important and valuable part of biological research in studying and developing novel treatments for human diseases. Among these, rodents such as mice and rats are widely used because of the close resemblance of their physiology with that of human physiology, their sequenced genome and the availability of extensive immunological and molecular tools. For example, several novel mice and rat models have been developed to study occupational dust-associated respiratory (CWP, silicosis, mixed-dust pneumoconiosis, COPD, chronic bronchitis) and cardiovascular diseases [101]. Such models can assess the effects of different types of dust exposures, including the effects of different levels of exposure and modelling exposures to dusts that are physicochemically different, on pathophysiological and immunobiological responses in a whole organism. These models not only provide insight into which types of exposures are likely to be harmful, but also identify biomarkers and therapeutic targets for different stages of disease. Here we describe animal model studies that have been conducted, highlight the need to conduct animal studies that are representative of different real-world worker exposures and recapitulate clinical disease to address the knowledge gaps in occupational lung disease and improve worker outcomes.

### *Rodent models for coal and silica dust*

To evaluate the effects of dust, mice and rats can be challenged with different levels and types of dust through intra-tracheal, intranasal and whole-body exposure. Each route of administration has its own merits and drawbacks. For instance, by using intra-tracheal installation/inhalation, larger volumes of dust particles (insoluble and soluble) can be deposited directly into the lower respiratory tract, allowing researchers to study dose-dependent responses to acute dust exposures in the lower respiratory tract more accurately. However, this route of exposure does not mimic natural exposures that occur in humans. Intranasal and whole-body exposures allow researchers to study the natural route of inhalation (*i.e.* inhalation through the upper respiratory to lower respiratory tracts); however, these routes of administration also have drawbacks. Whole-body exposure results in the entrapment of dust particles in rodent fur. Because rodents groom themselves, exposure results in potential unwanted side-effects from ingesting dust. Intranasal inhalation techniques overcome this issue by directly administering doses of dust to the rodent airways. In both cases, the concentration of administered dust that penetrates into the lower respiratory tract is difficult to ascertain, which complicates the interpretation of histopathological and pathophysiological findings. Nevertheless, findings from inhalation studies have been used to show the potential effects of different levels and types of coal mining dust exposure on lung disease. Mu *et al.* [102] intranasally challenged C57BL/6 male mice with coal dust for different durations of time (3, 6 and 9 months) and showed that mice challenged with dust showed structural destruction of lung parenchyma with increased inflammation and upregulation of necrotic, autophagic and apoptotic pathways, which led to cell death and eventually lung fibrosis. These results show that coal dust inhalation in mice can be used to recapitulate key pathological features of CWP and thus is an appropriate platform for understanding the mechanisms of disease pathogenesis. Other studies have shown that coal dust can drive these pathological responses by perturbing key physiological and immunological processes in the lungs. For example, coal dust exposure was found to increase the expression of apoptosis regulator bcl-2 like protein 4 (Bax) in the lungs, leading to cellular apoptosis [103]. Other studies show that coal dust induces oxidative stress *via* increased production of ROS, RNS and other markers of oxidative stress, including malondialdehyde, nitric oxide and xanthine oxide, and the subsequent downregulation of antioxidant genes, including *Sod1*, *Scd1*, *Nqo1*, *Mt1*, *Mt2* and *Ddit3* [68, 104–106]. The disruption of redox equilibrium in lung cells can lead to cellular, protein and DNA damage, activating the apoptotic signalling cascade and compromising overall lung function. Rodent models may also be used to investigate the effects of coal dust exposure in at-risk populations, such as obese coal mine workers. A study showed that coal dust exposure increased oxidative stress and cellular inflammation several-fold in obese rats compared to non-obese controls [50]. Exposure to coal dust increases lipid peroxidation and the peroxidative index with increased macrophage influx [107] and upregulation of inflammatory cytokines, especially IL-6, TNF-α and IL-1β [108]. Lung macrophages are the predominant inflammatory cell type associated with coal dust exposure [107]; however, delivery of high concentrations of coal dust impairs the function of alveolar macrophages and triggers chronic inflammation with granulocyte influx and increased production of inflammatory cytokines, leading to lung fibrosis and tumours [109, 110]. Wild mice collected from near mining sites have increased concentrations of the inorganic metals cadmium, copper and zinc, along with an increased expression of the antioxidant genes *Nqo1*, *Mt1*, *Mt2*, *Sod1* and *Ddit3*, confirming the potential of coal dust to affect other organs systematically [105]. These observations show how coal dust exposure from mining activities could affect nearby communities in addition to coal mine workers.

In contrast to coal dust, silica dust is considered more toxic and potent in eliciting oxidative stress and cellular inflammation in the lungs [111]. Because of this toxic potential, silica dust has been of intense

research interest over the past few years. Recent reports using rodent models suggest that oxidative stress is one of the major driving forces of silica-induced disease. Zhao *et al*. [112] confirmed a role for oxidative stress in silica-induced lung disease using mice that overexpress the lipoic acid synthetase gene and therefore have increased antioxidant activity. This increased antioxidant capacity inhibited the oxidative stress usually induced by silica dust exposure and prevented the rise in inflammatory cytokines and NF-κB activation [112]. Inhaled silica dust also impairs efferocytosis efficacy of alveolar macrophages by regulating Rho/Rho-associated coiled-coil containing protein kinase (RhoA/ROCK) pathways [113]. Another study showed that silica exposure results in dysregulation of macrophage polarity in the lung. M1 macrophages were predominant in the initial stage, with increased inflammatory cytokines such as IL-6, IL-1β and TNF-α. However, in later stages, M1 macrophages were replaced with M2 macrophages, with increased levels of the anti-inflammatory cytokine IL-10 through signal transducer and activator of transcription (STAT) and interferon regulatory factor (IRF) pathways [114]. Upregulation of TGF-β is a key mediator in initiating silica-induced lung fibrogenesis [115]. Inhibiting the TGF-β–Smad signalling pathway using tanshinone IIA increased the expression of miR-411p3p and significantly lowered collagen deposition (I and II) and proliferation of fibroblasts [116, 117]. Smad3 phosphorylation is a major factor involved in fibrosis [118]. A recent study in Wistar rats showed increased expression of angiotensin-converting enzyme (ACE) and the AT1 receptor on silica exposure with a subsequent decrease in ACE2 in silicotic rat lungs [119]. This may influence susceptibility to infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and resulting COVID-19 [120]. Indeed, both coal and silica dust could promote other respiratory infections, as occurs with cigarette smoke [121, 122], and the lung and gut microbiomes that may also be involved in respiratory and other disease pathogenesis [123–125]. Furthermore, studies have highlighted that blocking the G-protein-coupled subfamily prototype P2Y12 using clopidogrel (receptor antagonist) effectively reduces cellular oxidative stress, inflammation and fibrosis after silica exposure, and increases lung function [126]. $SiO_2$ nanoparticles were also found to increase mucus production in the airways, with elevated activity of NLRP3 inflammasome resulting in asthma-like symptoms [127, 128]. Thus, targeting the TGF-β1 signalling pathway would be a potential treatment for silica-associated fibrosis. Finally, silica dust-induced disruption of macrophage function also contributes to the increased susceptibility to *M. tuberculosis* infection [129].

Together, these studies show that exposure to coal and silica dust in rodents can recapitulate key features of occupational lung disease seen in clinical disease. Importantly, these models may be used to identify factors that are induced in the earliest stages following exposure and drive the progression of disease. However, while these studies shed light on how dust inhalation affects the lungs, we now require studies that use these models as platforms for assessing the differential effects of different types and levels of PM encountered in real-world workplaces and compare findings from these models to clinical disease.

## Conclusion

Occupational lung diseases like CWP and silicosis are increasingly burdening miners and construction workers. The recent re-emergence of CWP and unacceptably high rates of silicosis in Australia and worldwide in the 21st century demonstrate our poor understanding of the chemico-biological nature of different occupation-associated dust types and their potential to elicit various disease phenotypes or exacerbate pre-existing respiratory conditions (figure 4). Though these diseases are ancient, the exact mechanisms underlying disease pathogenesis are still debatable. Moreover, the increasing incidence of CWP questions the current dust safe exposure levels and control measures followed at mining sites globally. Evidence indicates that dust PM toxicity and disease aetiology are determined by chemical makeup and exposure level/time. Thus, individual dust properties specific to mining operations/occupation need to be examined and better understood to devise appropriate allowed exposure standards and safety measures. In addition, there is still heavy reliance on radiological findings to identify and analyse disease progression. Such changes are often only present during the later stages of disease when effective treatment and management strategies do not exist. Factors that are associated with and drive disease during the early stages of exposure need to be determined so that diagnostic markers and therapeutic targets can be identified. However, such studies are difficult to conduct in workers with established disease. Studies have shown that dust inhalation can lead to key features of occupational lung disease in animal models. To identify which types and level of exposures are most harmful, we propose that complementary studies are needed to examine the effects of dust from different stages of mining from different mining operations, and to compare the pathophysiological effects of these different exposures with the physicochemical properties of different dusts, in both workers and animal models. Such translational studies that examine how different exposures differentially affect pathophysiological processes in the lungs and systemically, from the early stages of exposure and through disease progression, could also be used to identify novel biomarkers for diagnosis of early stage disease. Finally, clinically representative animal models not only

help identify the pathophysiological processes that underpin the progression of disease following exposure, they also allow for the testing of novel therapies that target these processes.

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