Occupational Exposome and Lung Health

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Introduction

The average employed adult will spend between 60 and 90,000 hours at work throughout their lifetime [1]. Where and how you work impacts the exposome you inhabit, and has significant implications for respiratory health. Occupational lung disease remains a significant contributor to global respiratory morbidity and mortality. Patterns of globalization have altered the prevalence of occupational lung disease and shifted much of the burden of chronic occupational lung disease to the developing world. Meanwhile new technologies and production methods have resulted in new occupational lung diseases. Despite advances in technology, worker protections remain limited in many settings across both the developed and developing world.

Occupational safety and health directly impact respiratory health. Occupational exposures can result in a diverse range of respiratory conditions, from airways disease to interstitial lung diseases (Table 1). In this chapter, we will highlight a range of potential occupational lung diseases associated with specific industries focusing on non-infectious and non-malignant disease.

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Table 1 Examples of occupational lung disease by selected industries

Airways disease
Asthma (see Table 2)
Work related asthma
Irritant induced asthma
Sensitizer induced asthma
COPD
Smelter workers, machine operators, cleaners, coalminers, cotton workers, construction workers and bus drivers [23–25].
Interstitial lung and small airways disease
Pneumoconioses
Coal dust
Silica- (Benchtop fabricator, ceramics worker, miner, quarry worker, stonemason, sandblaster, tunneller)
Asbestos (Construction worker, electrician, mechanic, miner, railway worker, shipyard worker, carpenter)
Hypersensitivity pneumonitis
Bacteria (farmer, machinist, compost worker, swimming pool/spa);
Fungi (cheese worker, mushroom worker, tobacco grower, woodworker; animal proteins (birds, lab worker, textile worker)
Low molecular weight chemicals (polyurethane foam worker, painter)
Granulomatous lung disease
Chronic beryllium disease (aerospace machining and fabrication, nuclear industry, construction work, automotive fabricators)
World Trade Center Sarcoid-Like Granulomatous Disease
Cobalt (tool sharpeners, diamond polishers)
Aluminum (metal recycler, aircraft industry)
Obliterative bronchiolitis
Diacetyl induced (flavoring manufacturer, microwave popcorn manufacturers)
Constrictive bronchiolitis due to military deployment
Fiberglass reinforced plastics (boat builders)
Malignancy of the lungs
Lung cancer
Asbestos exposure, silica, radon, arsenic, PAH, diesel exhaust, cadmium, steel, nickel, chromium VI
Mesothelioma
Asbestos

Occupational Asthma

Occupational asthma is the most commonly diagnosed occupational lung disease globally and is generally underappreciated. An estimated 10–15% of adult asthma cases are related to occupational exposures, and approximately 20% of asthmatics report asthma symptom exacerbated by workplace exposures [2]. Occupational asthma can be sub-divided into three major categories- occupational asthma, work exacerbated asthma and acute reactive airway disease, also known as irritant induced asthma [2, 4].

Table 2 Occupational exposures and antigens associated with occupational asthma [2]

Sensitizer induced asthma	High molecular weight antigens	Cereals, flour, seafood proteins, animal antigens, detergent enzymes, latex, coffee beans
	Low molecular weight antigens	Isocyanates, red cedar dust, formaldehyde, persulfates, platinum, chromium, copper, acrylates, reactive dyes
Irritant induced asthma	Inhaled irritant	Cleaning agents, bleaching agents, acids, ammonia, sulfur dioxide, formaldehyde

Occupational asthma is characterized by a variety of respiratory symptoms including episodic cough, wheeze and dyspnea. The majority of occupational asthma develops as a result of exposure to an immune mediating sensitizer [2, 4–6]. The average latency between initial exposure to the sensitizing agent and development of clinical asthma is variable, but can occur as late as 10 years after first exposure to the agent [6].

Sensitizers can be categorized as high molecular weight (HMW) antigens (such as plant and animal antigens) or low molecular weight (LMW) antigens (such as wood-dusts and isocyanates) [2] (Table 2).

The majority of HMW antigens appear to induce asthma through an IgE mediated process. Patients with HMW antigen induced occupational asthma characteristically have detectable serum antibodies to the offending antigen, and describe acute onset of wheezing and dyspnea within minutes to hours of exposure [7]. By contrast, the process through which LMW antigens induce occupational asthma remains poorly understood. Some appear to act as a hapten — facilitating the binding of self-protein and generating airway inflammation. Others, particularly platinum and chromium, appear to induce asthma through an IgE mediated pathway [4, 7]. The asthma symptoms associated with LMW antigen occupational asthma are typically delayed, developing 4–8 h following initial exposure. Understanding the timing between exposure and symptom onset for these antigen groups is key to making a diagnosis of occupational asthma.

Globally, isocyanates remain one of the largest contributors to occupational asthma, with 1–30% of isocyanate exposed workers developing occupational asthma during employment [8, 9]. Isocyanates are widely utilized in automobile and aerospace manufacturing, as well as in commercial and residential remodeling. Car body shop mechanics and industrial painters are at particularly high risk due to use of polyurethane spray paints [10, 11]. While the risk of developing occupational asthma appears to be higher with higher concentrations and longer durations of exposure, isocyanate induced occupational asthma can occur at any level of exposure [2, 8].

In areas with significant forestry, exposure to western red cedar is also a major risk factor for the development of occupational asthma asthma [12, 13]. Cases of occupational asthma have also been reported among snow-crab, prawn and oyster processers [7, 14].

Irritant induced asthma is a non-immunologic form of asthma that follows exposure to irritants. First described in the 1980's, irritant induced asthma (also known as reactive airways syndrome) was classically characterized by the onset of asthma like symptoms within 24 h of exposure to an inhaled irritant [3]. A variant of this irritant induced asthma was seen among first responders following the World Trade Center disaster [15]. It is increasingly recognized the irritant induced asthma may present more gradually (within days to weeks of the initial exposure) [3]. Irritant induced asthma may also develop as a result of chronic lower level exposures to inhaled irritants, particularly cleaning products [16]. Exposure to bleach and ammonia based cleaning products has been associated with an increased risk of irritant induced asthma. Cleaners, who have persistent exposure to these chemicals are at high risk for irritant induced asthma syndromes [16].

Identifying occupational asthma early in the clinical course is key. A history of asthma symptoms that improve over the weekend or on vacation should prompt a high degree of clinical suspicion. In the early stages of disease, full recovery may be possible with removal from exposure. However, with prolonged ongoing exposure chronic pulmonary inflammation may develop, leading to persistent difficult to control asthma symptoms and significant asthma related morbidity [5, 13]. Due to the low level of antigen needed to trigger ongoing symptoms, removal from exposure typically requires removal from the workplace. Given this, the diagnosis should be made carefully and thoroughly. In contrast, triggers for patients with irritant induced asthma, unlike sensitizer induced asthma, are not specific to the causative agent.

As in all occupational respiratory diseases, history and a high index of clinical suspicion is the critical first step (Fig. 1). Temporal associations between exposures and respiratory symptoms are often uncovered, with many individuals reporting improvement away from work [2, 17] History and clinical judgment are sufficient to make the diagnosis. In the office setting, spirometry with evidence of a positive bronchodilator response can also support the diagnosis. Broncho-provocation testing can be considered, particularly to rule out the diagnosis in the setting of a negative test [2].

Unfortunately, asthmatics may demonstrate completely normal lung function away from exposure. Documenting the presence of airflow limitations at work can be quite informative. Serial workplace peak expiratory flow measurements are a useful alternative, and have relatively high sensitivity and specificity for occupational asthma [2, 18]. Ideally this testing should be performed for at least 4 weeks, with a period of time capturing data away from suspected exposure [2, 4]. Evidence of a clear difference in peak flows, or loss of diurnal peak flow variation are suggestive of an occupational trigger [2].

Industry Associated Occupational Lung Disease

The majority of patients will not present with a pre-specified diagnosis of occupational lung disease. Instead, identification of an underlying occupational lung disease is most commonly made through a thorough occupational history, and

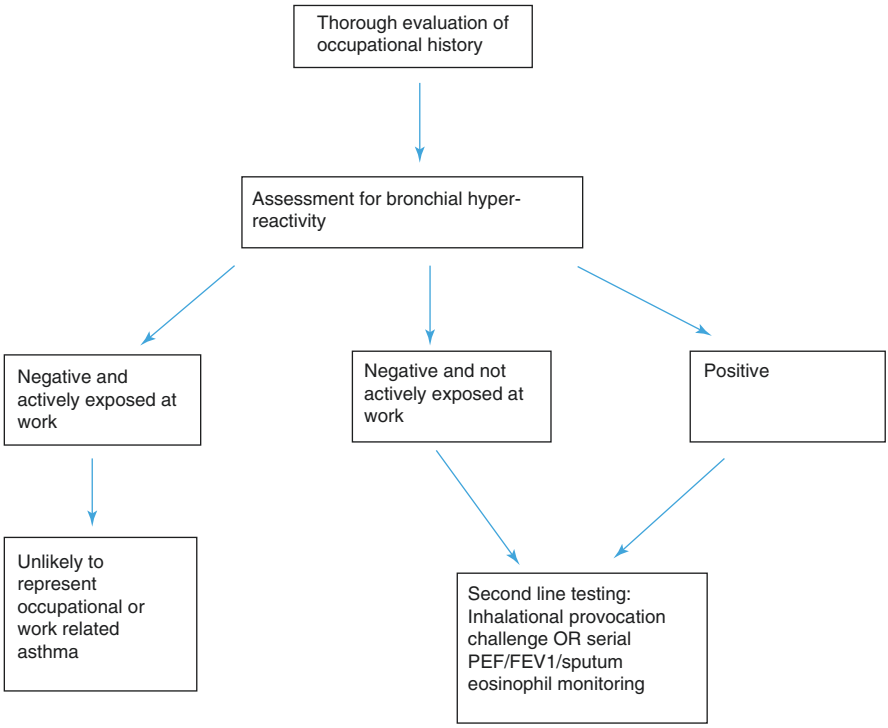

Fig. 1 Diagnostic pathway for evaluation of occupational/work related asthma [16]

identification of relevant occupational exposures. In the following sections, we will highlight occupational lung diseases associated with specific industries and provide a framework for evaluation of these conditions.

Agricultural Associated Respiratory Disease

"Farming" is a broad term for what can encompass a range of occupations and exposure patterns. The specific animals or crops farmed, the type of farm equipment utilized and the surrounding climate all impact risk of developing farming associated occupational lung disease.

That farming is not just an occupation, but a lifestyle cannot be under-emphasized. The majority of farmers will work and live in the agricultural environment-posing significant challenges in management where exposure limitation is necessary. Spouses of farmers, even when working off the farm, are exposed to many of the same risk factors as farmers themselves. Agriculture creates a unique exposome of exposure. The variety of potential antigens associated with agricultural work leads to a range of occupational lung diseases, due to both immune mediated and non-immune mediated processes.

Farmers Lung

Farmer's lung is a hypersensitivity pneumonitis syndrome, caused by an immune reaction to bacterial and fungal spores in damp hay and livestock feed. While a number of bacterial and fungal spores have been associated with the condition, sensitivity to aspergillus or Thermophilic actinomyces species is most commonly identified [19].

The prevalence of farmer's lung varies widely. In large cohort studies of agricultural workers, between 0.1% and 4.4% of farmers had clinical evidence of farmer's lung [19–22]. A further 5–20% of farm workers have detectable serum antibodies against aspergillus and Thermoactinomyces, suggesting risk for hypersensitivity development [20]. Conditions that promote microbial growth increase the risk of developing farmer's lung (FHP). Livestock farmers who are required to handle feed are at increased risk, as are those faming in damper northern climates [20, 22]. Conversely rapidly drying hay has been associated with decreased spore development [20, 22].

FHP is described as occurring in three phases- acute, subacute and chronic FHP. In clinical practice, distinguishing between sub-acute and chronic FHP may prove challenging. Even patients with chronic FHP may experience symptom "flares" which mimic acute HP, further confounding clear separation.

The acute phase of FHP is primarily driven by a type III hypersensitivity reaction. Exposure to large volumes of small inhaled antigens in a previously sensitized individual leads to activation of the pulmonary immune response, characterized by acute onset of dyspnea, fevers, cough, and malaise [23, 24]. Symptoms and imaging findings generally resolve with removal from exposure.

While acute FHP is commonly described in the literature, many patients experience a more sub-acute course, particularly in the setting of ongoing antigen exposure. Patients may report similar symptoms of dyspnea, cough and low grade fevers, occurring during work and resolving during weekends or with prolonged absence from the exposure. These chronic symptoms may be interspersed with occasional "flares" related to higher level antigen exposure. With prolonged exposure, chronic FHP develops. This is characterized by ongoing low level TH-2 lymphocyte activity and chronic inflammation, which progresses to widespread fibrosis.

Workup for FHP should begin with a clinical history. FHP should be considered in any worker exposed to hay, wheat or livestock who presents with acute or progressive dyspnea. Physical examination is frequently normal, though in some cases inspiratory crackles may be audible; inspiratory squeaks or "squawks" favor hypersensitivity pneumonitis over IPF. Spirometry may be variable, though restrictive defects are commonly seen [23–25]. Chest imaging findings vary depending on whether patients present with an acute or chronic phenotype. The CXR in acute FHP may mimic pulmonary edema, with HRCT confirming the presence of diffuse ground glass infiltrates and poorly defined centrilobular nodularity [23]. In patients with sub-acute or chronic FHP reticulation, honeycombing and traction bronchiectasis may be prominent on CT imaging, and can easily be mistaken for idiopathic

pulmonary fibrosis [23, 24]. Air trapping representing small airways disease may be noted, and can help to distinguish between the two conditions.

Specific IgG antibody testing or precipitins for a variety of putative antigens such as Aspergillus species, Micropolyspora faeni and Thermoactinomyces actinomyces may be performed. False negatives may occur due to time away from exposure or due to the fact that the particular assay does not specifically identified the causative antigen [25, 26]. False positives may simply reflect exposure, as studies have demonstrated high levels of positivity amongst asymptomatic farmers [27].

While in many cases an HP diagnosis may be made confidently on the basis of imaging and history, certain cases may require invasive sampling. Bronchoalveolar lavage can be performed, and is characterized by a strong lymphocyte predominance (typically greater than 20%) [28]. While commonly cited, a low lymphocyte CD4/CD8 ratio is neither sensitive nor specific, and routine use in diagnosis is not recommended [28]. Transbronchial biopsy can be performed. Classically biopsies will demonstrate lymphocytic interstitial pneumonia, peribronchiolar infiltrates and poorly formed granulomas [23]. Surgical lung biopsy may also be considered. For a full discussion of the histopathologic findings in HP, see Chap. 5.

Once diagnosed, the primary treatment for both acute and chronic FHP is antigen avoidance. Removal from exposure has been associated with an improvement in short term survival, and a decrease in the rate of DLCO decline. This benefit is less pronounced in those with fibrotic FHP [29]. However, especially in the context of farming, where antigen avoidance typically involves both a loss of income and a loss of housing full antigen avoidance may prove challenging, and create significant financial hardship.

In patients for whom those for whom antigen avoidance is not possible, or does not result in complete resolution of symptoms, a trial of corticosteroids should be considered. While dosing varies, a 4–8 week course of 40–60 mg of prednisone daily followed by a gradual taper is recommended, and has shown some evidence of improved FVC in patients without fibrotic lung disease [23, 25, 29]. In patients with chronic FHP, steroid sparing agents such as mycophenolate, leflunomide or azathioprine may slow disease progression and improve DLCO [30]. Recent evidence suggests that nintedanib may slow lung function decline in patients with progressive fibrotic HP [31]. For those patients who fail to respond to immunosuppressive therapy, referral for lung transplantation evaluation should be considered.

While farmer's lung remains the most common cause of HP in agricultural workers, outbreaks of hypersensitivity pneumonitis have been described among a number of other worker groups. For a description of high risk occupational exposures and their associated antigen, see Table 1.

Primary and secondary prevention should be recommended to farmers. Individuals should be encouraged to use PPE during handling of hay and feed though practically this may prove challenging. While full-face masks may be adequate in some cases, for those with severe FHP, self-contained pressure demand respirators may be required [20].

Drying wet hay and grain prior to storage is effective in reducing the risk of fungal spore exposure- however this may often be expensive and impractical. If

possible, hay with a high risk of spoilage should be stored in silage rather than in bales. Additionally, attention should be paid to ventilation in areas where large amounts of dusty material will be stored. Farm chores which involve handling hay or feed should be mechanized where able—though again this may prove cost prohibitive, especially for smaller farms. Finally, wetting down of dust prior to cleaning barns and stables may be effective as a measure to reduce aerosolization of fungal spores.

Organic Dust Toxic Syndrome

Organic dust toxic syndrome (ODTS) is an acute non-immune mediated syndrome triggered by exposure to high levels of organic dust. While typically not life-threatening, ODTS is extremely common among agricultural workers. Between 30% and 40% of workers exposed to agricultural organic dust will experience at least once episode of ODTS during their employment [32]. Workers in hoggeries are particularly at risk, with up to 70% of swine workers reporting at least one episode of work related respiratory distress [33]. Case clusters have also been reported among shrimp processing workers, and even in fraternities where large volumes of hay were utilized for decoration [32, 34, 35].

The presentation of ODTS is similar to that of acute hypersensitivity pneumonitis, with acute onset of dyspnea, fever, myalgias and cough 4–8 hours following organic dust exposure. While the clinical presentation is similar to HP, unlike acute HP, ODTS is not antibody mediated [20, 32]. Instead, inhalation of large volumes of bacterial endotoxin contained within these organic dusts triggers an acute inflammatory response [20, 32]. Imaging and physical examination are typically unremarkable, and symptoms will resolve within 24–48 hours of initial exposure [36].

To date, there is no evidence of long term pulmonary complications associated with ODTS [20, 33]. Given the acute nature of symptom onset and the fairly rapid resolution, it is likely that ODTS is significantly under-reported. Utilization of appropriate PPE when high levels of organic dust are anticipated effectively prevents ODTS, and should be recommended in all at risk workers [32].

Silo Fillers Disease

Silo fillers disease is a non-immune mediated complication of occupational exposure to nitrogen dioxide (NO_2) produced by silage (livestock feed produced by fermenting green forage) [37]. First reported in the early 1950s, silo fillers disease occurs across a spectrum of severity, ranging from mild dyspnea to death [38, 39].

Silage, the end product of fermenting a high moisture crop used for feeding livestock is stored in silos- large, vertical storage devices made of cement or steel.

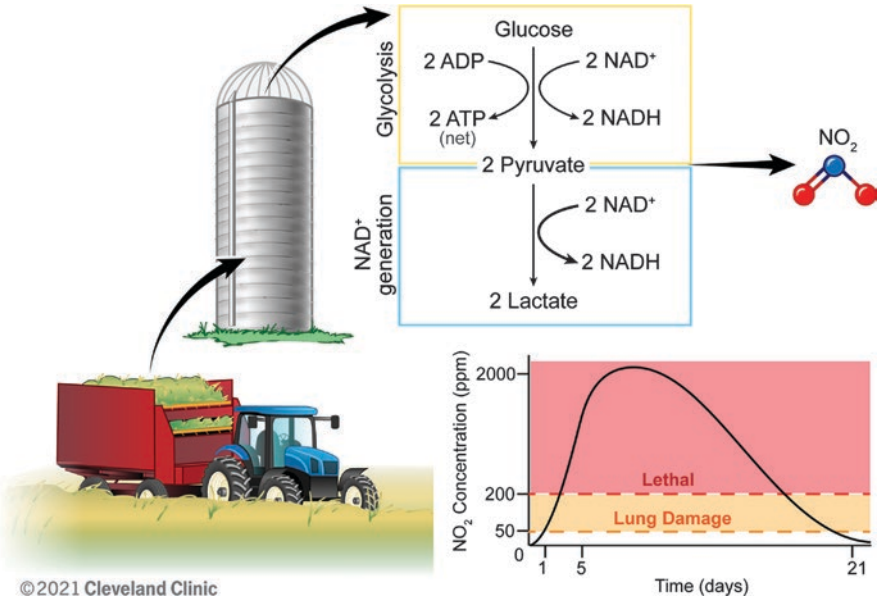

Fig. 2 Green materials are placed in the silo and undergo fermentation, resulting in the release of NO_2. Levels remain elevated in the 1–2 weeks post filling

Green materials such as oats, standing corn or alfalfa are placed within these silos and undergo fermentation [38]. Within a day of silo filling, concentrations of NO_2 rapidly reach toxic levels, often in excess of 200 ppm. Elevations in NO_2 persist for the first 1–2 weeks post-filling even in a well constructed silo, can remain elevated for as long as 6 weeks [38] (Fig. 2).

While the hazards of NO_2 are well known by most farmers, accidental exposure to elevated NO_2 remains relatively common [37]. Failure of unloading equipment or accidental loss of a tool in a freshly filled silo are the most commonly cited reasons for NO_2 exposure among cases [39]. Accidental exposure in temporary workers who are unaware of the potential for silo-fillers lung disease is also common [40, 41].

The severity of disease is determined by level and duration of exposure to NO_2 [38, 42–44]. Acute high level exposure to NO_2 is characterized by the immediate onset of dyspnea, wheeze and rapidly progressive encephalopathy. Loss of consciousness is common, leading to rapid death from asphyxiation in those who are not removed from exposure immediately [38, 42]. If exposure removal is achieved, initial pulmonary symptoms will rapidly resolve. Four to twelve hours post initial symptom resolution, rebound acute lung injury may develop. Characterized by profound hypoxic respiratory failure and diffuse bilateral pulmonary infiltrates, patients present in florid acute respiratory distress syndrome (ARDS) [38, 39, 44, 45]. Treatment of NO_2 associated ARDS with steroids is often initiated, though data are limited to case reports and animal studies [37, 38, 46]. In many cases, this secondary ARDS may prove fatal [37, 38, 46].

Prolonged, lower level exposure to NO_2 can result in a clinical picture more suggestive of bronchiolitis obliterans, with dyspnea, cough and diffuse bilateral nodular infiltrates [43]. Systemic symptoms may also be reported, including fever, chills and fatigue [43]. PFT testing in these patients may reveal evidence of obstructive physiology, with a decreased DLCO [38, 43]. Unlike the bronchiolitis obliterans reported with other occupational exposures, the majority of patients presenting with subacute silo fillers disease experience a gradual improvement in symptoms with removal from exposure. Cases of chronic bronchiolitis obliterans secondary to silo fillers disease have been reported, though they are relatively uncommon [38, 39].

Primary prevention of silo fillers lung focuses on training farmers to avoid entering upright or horizontal silos in the 2–3 week period following silo filling. If the silo must be entered during this time period, the silo should be ventilated for 30 min prior to entry, and a self-contained breathing apparatus should be utilized. Use of a buddy system during periods of silo entry should be strongly encouraged.

Manufacturing

Manufacturing evolves continuously. Some advances in technology have reduced the risk of occupational lung disease. Others have resulted in new exposures, and new clinical syndromes. With globalization, a significant burden of occupational lung disease related to manufacturing has been shifted to the developing world. The risk of occupational lung disease secondary to manufacturing is determined not only by the type of manufacturing, but by job specific exposures. Careful assessment of both duration and intensity of exposure is key in determining risk of disease.

Lung Disease Associated with Food Manufacturing

Flavoring Associated Bronchiolitis Obliterans

Diacetyl is utilized widely in food processing, giving foods an artificial butter flavor. While considered generally safe for human consumption, inhalation of diacetyl is associated with the development of severe bronchiolitis obliterans.

Pulmonary disease associated with diacetyl inhalation was first described in animal studies in the early 1990s [47, 48]. In 2000, “popcorn workers’ lung” was reported after a series of workers in a microwave popcorn production facility were found to have profound fixed obstructive ventilator defects due to bronchiolitis obliterans (BO) [47, 48]. Since these initial cases, additional clusters of diacetyl

induced lung disease have been reported among artificial flavor workers, including coffee bean roasters and cookie dough manufacturers. Additionally, a flavoring substitute for diacetyl, 2,3-pentanedione, has also been associated with BO. Workers directly involved in mixing flavorings are at highest risk, though in factories without adequate ventilator controls, all workers have the potential for exposure [47, 49, 50].

BO is a disease of the small airways, and presents initially with non-specific respiratory symptoms, including dyspnea, cough and reduced exercise tolerance [50, 51]. Timing from exposure to onset of disease is relatively rapid, with an average latency of 1.5 years [48, 52]. Patients with BO generally experience no improvement in symptoms with removal from exposure [47, 51].

Pulmonary function testing in the early stages of BO may be relatively unremarkable. As disease progresses, a profound ongoing decrease in FEV1 is noted, with the development of a fixed obstructive deficit over time [51]. A positive bronchodilator response may be seen in some patients, and misdiagnosis as asthma or emphysema is common in this patient population. Restrictive defects in PFTS have also been described in exposed workers, though are less common [50].

HRCT should be obtained in all patients with a concern for BO, and should include expiratory phase imaging to allow detection of air trapping and mosaic attenuation [51] In cases with a clear occupational history and PFTS suggestive of BO, biopsy is not recommended [50, 51]. Surgical lung biopsy may be performed in cases where the diagnosis is in question, though the potential for false negative biopsies is relatively high due to significant geographic and temporal heterogeneity of bronchiolar disease [51].

No treatment for BO exists with the exception of lung transplant. Trials of immunosuppression have been largely ineffective. Use of inhaled steroids and azithromycin have been described, it is recommended to discontinue these therapies if patients do not report significant benefit after a brief trial [51, 53].

In response to the growing body of evidence that diacetyl inhalation was associated with BO limits on allowable respirable diacetyl have been recommended by the National Institute for Occupational Health and Safety (NIOSH) [54]. Restrictions on respirable diacetyl outside of the US remain limited [49, 50, 52, 55, 56].

All workers with occupational exposure to diacetyl or other artificial butter flavorings are now recommended to undergo six monthly spirometry screening. A 15% fall in FEV1 over 12 months should raise concern for the development of BO and prompt formal assessment and possible reassignment, even if FEV1 remains within a “normal” range [50]. Removal from exposure prevents further decline in FEV1, but does not result in recovery of previous lung function.

While substitution or elimination of diacetyl containing products is the most effective mechanism for preventing BO, the potential pulmonary risk of exposure to substitute products is not yet known. Given that, engineering controls which ensure adequate ventilation and reduce worker exposure are recommended.

Lung Disease Associated with Textile Manufacturing

Byssinosis

Byssinosis is a occupational airway disease caused by inhalation of raw flax, hemp and cotton dust. In the US, cotton dust is the most common cause of byssinosis; it has been proposed that endotoxin from gram negative rods in the cotton dust contributes to disease pathogenesis [56].

Rates of byssinosis across the US and UK were significantly reduced with the introduction of a occupational standard for allowable respiratory cotton dust and enforcement of strict workplace controls [57]. Production of cotton has now shifted to the developing world, where byssinosis remains a significant health concern [58].

Acute byssinosis is characterized by acute onset of dyspnea, cough and wheezing following exposure to cotton dust [59, 60]. Also known as "Monday asthma" or "Monday Fever", acute byssinosis is typically most severe on the first day of return to work after the weekend due to transient removal from exposure. Acute byssinosis can be severe, resulting in high workforce turnover [59]. In workers with ongoing exposure, symptoms begin to occur consistently throughout the week. Over time, symptoms of dyspnea and cough persist even with removal of exposure—reflecting progression to chronic byssinosis [59].

The diagnosis of byssinosis is made on the basis of an occupational history and spirometric assessment, which reveals the presence of a fixed obstructive defect [60–62]. FEV1 continues to decline with ongoing exposure, and a serial decrease in FEV1 during workplace surveillance testing should prompt concern for the disorder. Imaging is variable, and classically mimics COPD.

Treatment of byssinosis should focus on exposure removal to prevent further decline. Patients with ongoing symptoms may benefit from inhaled therapies, similar to those utilized in chronic asthma.

Prevention of byssinosis is primarily focused on dust control- both through ensuring adequate ventilation through engineering controls in high dust exposure areas, providing appropriate PPE during high dust exposure activities, and utilizing washed cotton to reduce dust release [57].

Nylon Flock Workers Lung

Nylon Flock Workers Lung is an interstitial lung disease caused by exposure to flocking—a process in which nylon cut to an extremely fine level to create a velvet texture. Originally, it was believed that the nylon particles created by the flocking process were too large to be respirable. However, changes in the process of flocking production to increase efficiency and decrease cost resulted in the move towards the use of rotary cutting devices [63]. Unlike traditional guillotine cutting devices, these can easily become blunted- resulting in the release of smaller, respirable nylon particles.

Respiratory symptoms in flocking workers were first noted in Ontario in the 1990s after a cluster of workers within a single factory developed severe dyspnea, hypoxia and diffuse pulmonary infiltrates [64]. Initially symptoms were attributed to an unidentified fungal exposure. Reports of similar cases in nylon flockers across Rhode Island and Massachusetts, triggered a formal investigation by NIOSH [65, 66]. The use of rotary cutters leading to high levels of respirable nylon particles was identified in all factories.

Nylon Flock Workers' Lung Disease is characterized by the development of progressive dyspnea and cough following exposure to nylon flocking [66]. Symptoms are persistent, and continue even after removal from initial exposure. PFT patterns within patient cohorts are variable, with the majority showing evidence of a restrictive process. Overlying reversible airway obstruction has also been reported [66]. Imaging is characterized by ground glass opacities in a peripheral distribution, with or without associated fibrosis [67].

Biopsy in Nylon Flock Workers' Lung disease classically shows a pattern of lymphocytic bronchiolitis and peribronchiolitis with lymphoid hyperplasia [68]. However, significant variation on biopsy has been reported, leading some experts to suggest that rather than a strict pathologic criteria, a diagnosis should be made on the basis of respiratory symptoms, a clear occupational exposure, and pathology suggestive of ILD which is not clearly explained by an alternate cause [63, 69].

The majority of patients will recover with removal from exposure, though the process of recovery is slow [63]. Return of symptoms with return of exposure has been reported. Even with removal from exposure, some patients will continue to experience symptom progression and PFT decline [63]. Steroid treatment has been attempted in this population but has proved largely ineffective [63–65].

Mining and Heavy Industry

The lung disease associated with mining represents some of the oldest documented occupational respiratory conditions. The pneumoconioses are a group of interstitial lung diseases caused by inhalation of dust. While a number of exposures can result in the development of pneumoconiosis, asbestos, silica, and coal dust are among the most commonly reported.

Occupational lung disease associated with mining and heavy industry continues to cause significant morbidity and mortality, in both the developed and developing world. For example, over the past decade, rates of coal and silica associated lung disease have risen dramatically, reflecting changes in mining technique, and new occupational exposures [70–72]. In addition to the risk of pneumoconiosis development, exposures in these industries have been associated with chronic lung diseases such as COPD, diffuse dust fibrosis and lung cancer. Availability of screening, and options for treatment for workers diagnosed with mining related lung disease remain pressing issues.

Coal Dust Associated Lung Disease

Inhalational exposure to coal dust is associated with a spectrum of diseases, ranging from coal workers pneumoconiosis, COPD and dust related diffuse fibrosis. Patients with pneumoconiosis can present with either simple coal workers pneumoconiosis or complicated coal workers pneumoconiosis, also known as progressive massive fibrosis. (Table 3).

Coal mine dust contains a mix of carbon, crystalline silica and other trace minerals. Inhalation results in deposition in the terminal bronchioles, where it is engulfed by alveolar macrophages, resulting in the formation of localized nodules, and the release of pro-inflammatory cytokines, leading to scarring and fibrosis (Fig. 3) [70]. Coal rank- a quality of the coal seam which ranges from low rank, sub-bituminous coal, to higher ranking anthracitic coal, determines the relative concentrations of carbon, crystalline silica and trace minerals within coal dust [71]. Mining of higher ranked, anthracitic coal has been associated with a higher risk of pneumoconiosis in historical analyses, though the relevance of rank for risk of CWP is controversial.

The diagnosis of coal workers pneumoconiosis (CWP) is made on the basis of imaging findings, and is guided by the international labor office (ILO) classification throughout most of the world, with the exception of China, which uses the Chinese Roentgenodiagnostic Criteria of Pneumoconioses system [72, 73]. Imaging is classified according to the presence or absence of nodularity, nodule size, and nodule distribution.

Simple CWP is characterized by small (<1 cm) nodular opacities on chest x-ray. While classically these nodules have been described as having an upper lobe predominance, more recent research suggests that a large percentage of patients with simple CWP may have significant lower lobar nodularity [74]. Patients with simple CWP may be symptom free, or may report dyspnea, productive cough and wheeze. Again, while classic teaching states that pulmonary function testing is normal in patients with simple CWP, evidence globally suggests that even simple CWP may be associated with persistent PFT abnormalities [75, 76]. Abnormally low FEV1

Table 3 Spectrum of coal dust associated lung disease

	Imaging	Symptoms	Latency
Simple coal workers pneumoconiosis	<1 cm nodules	Asymptomatic, rare dyspnea, decreased exercise tolerance	5–15 years
Complicated coal workers pneumoconiosis	>1 cm nodules, irregular. Localized emphysema, fibrosis.	Dyspnea, cough, decreased exercise tolerance	5–15 years
Diffuse dust related fibrosis	Reticulation, traction bronchiectasis? Honeycombing	Slowly progressive dyspnea, cough, fatigue	10–20 years

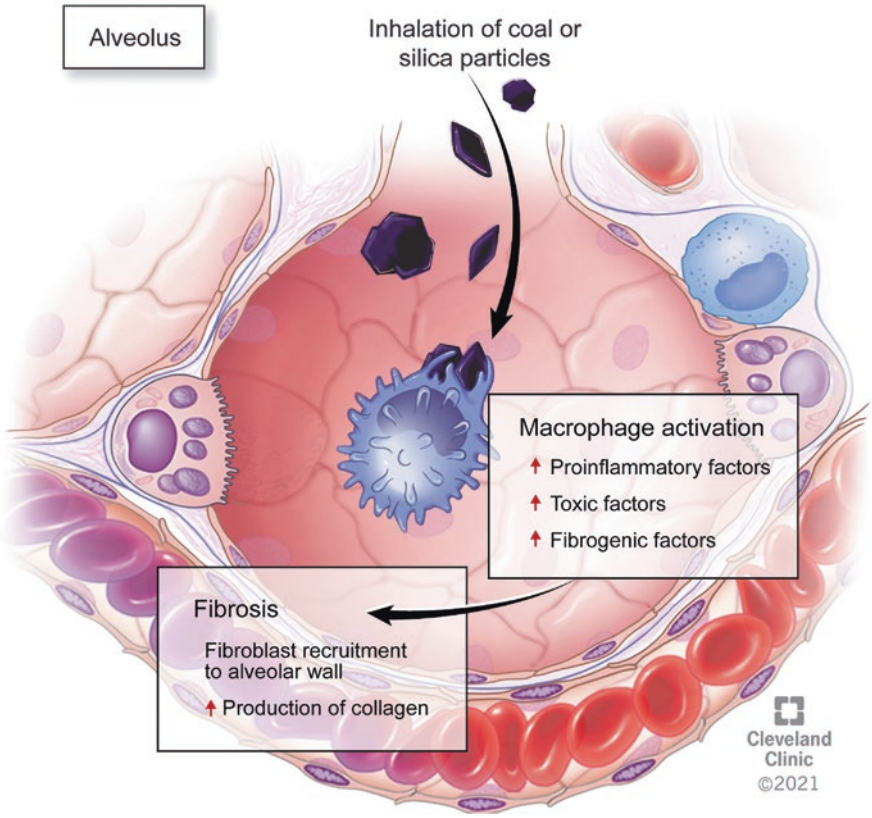

Fig. 3 Inhaled coal particles are deposited in the alveoli, resulting in macrophage activation and release of pro-inflammatory cytokines

measurements are common, and appear to correlate with increasing nodular proliferation [75, 76].

By comparison, complicated coal workers pneumoconiosis is characterized by coalescence of small pulmonary nodules into large (>1 cm), irregular nodules. While upper lobe distribution is typically described, nodularity can be seen throughout the lung fields, and may be accompanied by evidence of localized emphysema and fibrotic change. Patients are often significantly symptomatic, and may have substantial abnormalities in FEV1 and FVC, with evidence of focal obstruction or air trapping [77].

Also referred to as progressive massive fibrosis (PMF), rates of complicated CWP across the Unites States have steadily increased over the past decade. New diagnoses of complicated CWP among active miners have climbed to rates prior to the passage of the Federal Mine Health and Safety Act (FMHSA) in 1977 [74]. Reasons underlying this rapid rise in cases are likely multifactorial, including an

increase in slope mining, a move towards increased mining of high rank coal, a transition to thin seam mining and decreased compliance with FMHSA regulations [70].

The diagnosis of both simple and complicated CWP can be made on the basis of clinical presentation. Key features of the occupational history in the assessment of a patient with possible CWP include duration of mine work (typically CWP is seen after at least 10 years of exposure, though may occur earlier in the work course, particularly with higher levels of exposure), the type of mining performed (surface versus underground), job title and job duties. Particular jobs within mining are associated with higher volumes of inhaled dust exposure, particularly bolting and roof blasting.

In cases where the diagnosis is unclear, or atypical features are present, high resolution CT chest may be considered. HRCT is more sensitive for the detection of smaller nodules and air-trapping which may not be evident on CXR. In patients with consistent history and imaging, biopsy is rarely indicated.

While simple and complicated CWP are perhaps the most commonly recognized forms of coal dust associated lung disease, diffuse dust related fibrosis (DDF) is commonly reported on autopsy studies of miners [79]. Characterized by irregular consolidation, traction bronchiectasis and evidence of reticulation, DDF may be incorrectly diagnosed as interstitial pulmonary fibrosis (IPF) without a full occupational history. Patients with DDF have evidence of restrictive changes on PFTS, with reduced DLCO [79]. Biopsy if performed is significant for bridging fibrosis with interlobar septal pigmentation [78]. Nodular changes suggestive of CWP or silica exposure may be noted [78]. Compared with patients with IPF, patients with DDF appear to have a younger age of onset and somewhat more indolent course [78].

In addition to the spectrum of coal dust associated interstitial lung disease, inhalation of coal dust has been shown to result in chronic emphysematous changes and obstructive lung disease. Chronological studies of miners overtime shown that roughly 1 year of coal dust exposure is associated with a similar decline in FEV1 seen with 1 year of tobacco use [79, 80]. 35% of active coal miners report symptoms of chronic bronchitis, including productive cough, dyspnea and wheeze [81].

Limited treatment options exist for the spectrum of coal dust related lung disease. Further exposure should be limited if possible, though practically speaking this may prove challenging given the lack of alternative employment options in areas where coal mining is common. Lung transplant is indicated for those with severe, symptomatic disease, though rates of transplant for CWP remain relatively low.

The major mechanism of prevention for CWP is a reduction in exposure to respirable coal dust. In 2014, the Mine Health and Safety Administration released an updated final ruling on allowable respirable coal dust exposure, increasing the requirements for dust exposure monitoring, and reducing allowable dust concentrations to 1.5 mg/m [3] for underground and surface coal mines [82].

Silicosis

Silicosis is caused by exposure to crystalline silica. It can present as acute silicosis, chronic silicosis, or as accelerated chronic silicosis. First described among miners by Hippocrates, silicosis remains one of the most common causes of occupational lung disease on a global scale [83].

While mine workers are commonly perceived as being at highest risk for silicosis, exposure to silica is widespread in industries beyond mining. Workers are often unaware of their exposure to silica, and screening in these groups may be limited. A recent outbreak of silicosis among engineered stone fabricators across Australia, Belgium, Israel and the United States has highlighted the under-recognition of silica exposure in non-traditional industries [84–89]. Similarly, outbreaks of silicosis among diamond polishers across China and India highlight that across many industries, worker protections remain sub-optimal [90].

Silica exists in two forms. Amorphous silica is relatively inert, and is used widely in industry as a filler and anti-caking agent [91]. Crystalline silica, most commonly found in quartz, is responsible for the majority of respiratory complications associated with silica exposure [86]. Silica is present in various concentrations across many of the major rock types, ranging from granite and slate (which contain roughly 40% silica), to sandstone, which is comprised almost entirely of silica. Engineered stone, also known as Caesarstone or Silestone, is a mixture of composite quartz, and similar to sandstone, has an extremely high silica content.

When inhaled, crystalline silica lodges in the terminal bronchioles, where it is engulfed by respiratory macrophages. These respiratory macrophages trigger the release of IL-1 and TNF, initiating an inflammatory cascade [92, 93]. Over time, persistent inflammatory cytokine release results in the recruitment of type 2 pneumocytes and progression from inflammation to fibrosis [92].

Silicosis exists along a spectrum of disease severity that is primarily dictated by the degree and duration of exposure.

Acute silicoproteinosis develops in response to very high-level exposures to respirable crystalline silica. Now relatively rare, before the advent of respirable silica standards acute silicoproteinosis was a major driver of morbidity and mortality. Most infamously uncontrolled blasting of quartz containing rock in the construction of the Hawk's Nest Tunnel in West Virginia resulted in the deaths of between 500 and 1000 workers due to acute silicoproteinosis [94, 95].

The disease is characterized by the development of severe hypoxic respiratory failure in the days to weeks following exposure, with HRCT imaging characterized by lower lobe predominant infiltrates, ground glass opacities and centrilobar nodules [96, 97]. No treatment for acute silicoproteinosis exists, and mortality is high.

Simple silicosis is the most common form of the disease, and is characterized by the presence of small (<1 cm) silicotic nodules distributed throughout the lung fields, primarily in the upper lobes [98]. Simple silicosis typically develops after decades of exposure, and is frequently detected incidentally. In surveillance literature, between 30% and 50% of workers in high risk professions have evidence of

silicosis on initial screening [99–101]. Simple silicosis may not have a benign presentation. Workers may report cough, dyspnea and decreased exercise tolerance [102]. With increased burden of nodularity, evidence of obstructive or restrictive PFT changes may be noted [103].

Between 5% and 40% of workers with simple silicosis will progress to develop "complicated" silicosis, also known as progressive massive fibrosis (PMF) [86, 104]. This is characterized by coalescence of smaller silicotic nodules into large lesions greater than 2 cm in diameter, often with associated cavitation and significant fibrosis [102]. Patients with PMF are more likely to have significant respiratory symptom burden, and profound restriction, obstruction or mixed deficits on pulmonary function testing [86].

Rates of progression from simple to complicated silicosis vary, and are influenced by duration of exposure, frequency of high level exposures, exposure to tobacco products and host genetic factors [100, 105, 106].

Accelerated silicosis is characterized by a comparatively rapid progression from simple silicosis to PMF. Outbreaks of accelerated silicosis have been described in a number of worker groups, and are through to be due to more frequent exposure to high levels of respirable silica [87, 90]. Compared with traditional silicosis, patients with accelerated silicosis have rapid progression to significant disease burden, and are at increased risk of silica associated morbidity and mortality [85, 86, 90, 107].

In addition to the risk of developing silicosis, exposure to silica is associated with a number of other complications. Even when controlling for tobacco use, rates of COPD are higher in silica exposed workers [102]. Silica exposure, even in the absence of silicosis, is also associated with an increased risk of developing tuberculosis [109, 110]. This is thought to be related to suppression of the pulmonary immune system by inhaled silica. Particularly in countries where tuberculosis is endemic, the combined risk of tuberculosis and silicosis is of significant concern. Workers exposed to silica also have an increased risk of developing autoimmune diseases such as rheumatoid arthritis and may also develop chronic renal disease [108].

CXR has traditionally been used for silicosis screening, HRCT is more sensitive and specific for silicosis, particularly in the early stages of disease [109]. Classically, imaging in patients with silicosis is characterized by hilar lymphadenopathy with eggshell calcification, and diffuse nodules less than 1 cm in diameter. Pleural thickening is common, as is evidence of early fibrosis and distortion of the lung parenchyma [100, 106, 109].

In patients with a clear occupational history and classic imaging findings invasive testing is not necessary to confirm the diagnosis of silicosis. Bronchoalveolar lavage is typically non-diagnostic- the presence of silica in BAL fluid does not confirm the diagnosis of silicosis and may be seen in any silica exposed worker [98]. Biopsy may reveal silicotic nodules- characterized by concentric rings of fibrosis, resulting in an "onion skin" appearance [92].

With the exception of lung transplantation there is no treatment for silicosis. Even with removal from exposure, some workers will develop radiologic and symptomatic progression [99, 100]. Whole lung lavage has been attempted in a subgroup

of patients with acute and accelerated silicosis, but the usefulness of this is uncertain [110]. Prevention of silicosis is far more effective. Dust control measures, wet processing and personal protective equipment have all been shown to reduce respirable silica, and consequently the risk of silicosis.

Asbestosis

Asbestos exposure is associated with a range of pulmonary diseases, ranging in severity from benign pleural changes to rapidly progressive malignancy (Table 4). Utilization of asbestos in construction and manufacturing became widespread during the twenty-first century [111, 112]. A growing understanding of the harms associated with asbestos lead to widespread bans across the developed world. Despite this an estimated 125 million workers remain exposed to asbestos annually [112, 113]. Even in countries where use of asbestos is banned, demolition and remodeling of structures built with asbestosis results in an ongoing risk of exposure to workers.

Asbestos exists in two forms. Amphibole asbestos (which can be further subdivided into crocodolite, tremolite and amosite) is made up of straight, needle like fibers. In contrast, serpentine (christolyle) asbestosis consists of curved bundles of fibers. When these fibers are inhaled they become lodged in the terminal bronchioles, and are subsequently engulfed by alveolar macrophages [113, 114]. Macrophage phagocytosis of the asbestos fibers leads to macrophage death, triggering the release of reactive oxygen species, and initiating an inflammatory cascade [114]. These engulfed asbestos fibers are then either broken down, or remain in the terminal bronchiole, where they become covered in a layer of mucopolysaccharide and iron, forming asbestos bodies [113].

Table 4 Spectrum of asbestos related pulmonary disease

	Imaging	Symptoms	Latency
Pleural plaques	Sharply demarcated, asymmetric lesions on pleural surface	Minimal	10–20 years
Benign asbestos pleural effusion	Unilateral small to moderate effusion. Costophrenic angle blunting	Minimal	10–20 years
Diffuse pleural thickening	Ill-defined/irregular pleural thickening. Costophrenic angle blunting	None to mild dyspnea, exercise intolerance	10–20 years
Asbestosis	Lower lobe predominant band like opacification, septal thickening, pleural thickening	Progressive dyspnea, cough and decreased exercise tolerance	5–40 years
Malignant mesothelioma	Irregular pleural thickening, pleural effusion, interlobar fissural thickening	Progressive dyspnea, chest wall discomfort, chest pain	10–20 years

Benign pleural plaques are the most common symptom of occupational exposure to asbestos- these present as sharply demarcated, raised, asymmetric lesions on the bilateral pleural surfaces [115]. Typically asymptomatic, the majority of pleural plaques are found incidentally. Between 20% and 60% of workers exposed to asbestos will develop pleural plaques with a latency of 10–20 years from initial exposure [113]. Histologically pleural plaques are characterized by bland bundles of collagen fibers in a basket weave pattern [115]. While symptoms associated with pleural plaques are rare, longitudinal studies suggest that the presence of pleural plaques is associated with a small but significant decrease in FVC [116].

Diffuse pleural thickening may also been seen in workers with a history of asbestos exposure. This is characterized by ill-defined and irregular thickening of the pleura, with blunting of the costophrenic angle evident on CXR [117]. The risk of developing diffuse pleural thickening is increased with longer durations of asbestos exposure [118]. The presence of diffuse pleural thickening is associated with a decrease in FEV1 and FVC, though the functional limitation associated with this is typically low [116].

Asbestosis — fibrosis of the lungs secondary to asbestos exposure, was first described among asbestos miners in ancient Greece [119]. The risk of developing asbestosis appears to be related to duration and level of exposure. While the average latency from exposure to disease development is 20–40 years, cases of asbestosis have been described in workers who experience rapid high level exposures after as little as 5–10 years [120, 121]. Classically, patients will endorse insidious onset of dyspnea, cough, progressive decline in exercise tolerance and fatigue. Following symptom onset, a fairly rapid decline in FEV1 and FVC is seen with development of significant restrictive physiology [116].

On CXR, asbestosis is characterized by irregular bilateral lower lobe opacification, usually accompanied by other evidence of asbestos exposure such as pleural plaques or pleural thickening [115]. Similar to the other occupational pneumoconiosis, the ILO score is used to describe severity of imaging findings. High resolution CT chest is significantly more sensitive for asbestosis, and is characterized lower lobe predominant band-like opacifications, honeycombing, septal thickening and evidence of pleural plaques/pleural thickening [115, 122].

Three major criteria are required to confirm a diagnosis of asbestosis- imaging or histology consistent with the diagnosis, evidence of prior asbestos exposure (either through occupational history, evidence of other asbestos related imaging findings, or the presence of asbestos bodies within a sample), and lack of another more likely diagnosis [118, 119]. Of note, biopsy is not required to confirm the diagnosis of asbestosis and with imaging findings suggestive of disease, a clear occupational exposure is sufficient [119]. No treatment exists for asbestosis, with the exception of lung transplantation.

In addition to the pulmonary and pleural disease related to asbestos exposure, the risk of malignancy is also significantly increased. A large population study on insulation workers revealed that asbestos exposure was associated with a 6.8 fold increase in the risk of death from lung cancer- similar findings have been reported among other worker groups exposed to asbestos [123–125].

Along with an increased risk of primary lung cancer, risk of pleural malignancy, specifically malignant pleural mesothelioma is significantly increased in workers exposed to asbestos [120, 126]. The risk of mesothelioma appears to be increased with even with comparatively low level asbestos exposure, with documented cases among spouses of asbestos exposed workers and clerical staff [114, 124, 126]. The latency period between exposure to asbestos and development of malignancy remains prolonged, and rates of malignant mesothelioma among workers previously exposed to asbestos are anticipated to peak between 2010 and 2020, reflecting changes to occupational safety standards made decades earlier [127].

Malignant mesothelioma may remain minimally symptomatic until significant disease has developed. Dyspnea secondary to the development of pleural effusion is common, as is chest pain and chest wall pain due to tumor infiltration [128]. The diagnosis of malignant mesothelioma can prove challenging. Imaging changes are characterized by irregular pleural thickening, peripheral parenchymal lesions, pleural effusion and interlobar fissural thickening, however sensitivity in early disease may be poor [128, 129]. Pleural fluid cytology has roughly a 30% sensitivity for the diagnosis of malignant mesothelioma, and pleural biopsy is recommended if the diagnosis is in question [128, 130].

The prognosis for malignant mesothelioma is bleak, with an average survival of 8–12 months. Chemotherapy has been shown to prolong survival in some patients with malignant mesothelioma [128, 131]. Radiation may be considered as a palliative measure [128, 131].

Chronic Beryllium Disease

Chronic beryllium disease (CBD), or berylliosis a chronic granulomatous disease often indistinguishable from sarcoidosis that predominantly affects the lungs. Beryllium is widely utilized across industries ranging from aerospace and weapons manufacture to dentistry due to its unique chemical properties. Similar to hard metal, beryllium is light, exceptionally strong, and highly heat resistant. It is also associated with significant respiratory disease.

In susceptible workers, exposure to beryllium results in the development of beryllium sensitization, characterized by activation of beryllium specific CD4+ T cells [132–134]. Workers who develop beryllium sensitization are at risk of progression to (CBD), an interstitial lung disease characterized by diffuse granulomatous inflammation, similar to that seen with sarcoidosis. The risk of developing beryllium sensitization and subsequent CBD appears to be multifactorial, related both to job specific exposure and underlying genetic factors. Machinists (those who directly cut and shape beryllium) appear to be at highest risk of sensitization, possibly due to higher task related exposures. Variation in the HLA-DPB1 E69 allele appears to be a significant contributor to the risk of developing beryllium sensitivity. The presence of any DPB1 E69 allele is associated with a significantly increased risk of developing beryllium sensitization, and of progressing to CBD [135–139].

The majority of beryllium sensitization is detected through workplace screening utilizing the blood beryllium lymphocyte proliferation test (BeLPT), which is required as part of routine medical surveillance in beryllium exposed workers [140]. Occasionally, workers may present with CBD prior to a diagnosis of beryllium sensitization, though this is relatively uncommon. CBD is characterized by dyspnea, exercise limitation, weight loss and cough, similar to the symptoms seem with pulmonary sarcoidosis [45, 143]. Unlike sarcoidosis, extra-pulmonary manifestations are uncommon [140].

Pulmonary function testing may be normal at the time of initial diagnosis, though over time the majority of patients will develop obstructive, restrictive or mixed defects [141]. Impaired gas exchange during cardiopulmonary exercise testing is one of the earliest clinical indications of chronic beryllium disease, and may be seen prior to the onset of clinical symptoms [142].

For a worker to receive a diagnosis of beryllium sensitization they must have either two positive BeLPTS, a positive BeLPT followed by a "borderline" "BeLPT" or three "borderline" BeLPTS. In workers for whom suspicion of beryllium sensitization is high, BAL BeLPT is more sensitive and specific. A single positive BAL BeLPT is sufficient to confirm beryllium sensitization.

For a beryllium sensitized worker in whom the diagnosis of CBD is suspected, transbronchial biopsy is recommended. The presence of non-necrotizing granulomatous inflammation confirms the diagnosis. Imaging showing diffuse granulomatous lung disease can also support a diagnosis of CBD, though is usually not sufficient to obtain workers compensation. Particularly in the early stages of disease, imaging findings may be highly variable.

Not all patients with CBD will experience significant disease progression, though the vast majority will experience decline in pulmonary function over time [143–145]. This pattern of decline varies widely, ranging from steady deterioration to periods of stability interspersed with rapid decline. The decision to initiate treatment for CBD is based on the rate and pattern of this decline and or presence of severe debilitating symptoms [146]. Data to support treatment is limited, however steroid therapy is conventionally used as first line therapy [147]. Prednisone is typically started at a dose of 20–40 mg, then slowly tapered, similar to initial treatment of sarcoidosis [147]. The majority of patients will experience short term improvement with steroid therapy, though long term response is more variable. Steroid sparing agents should be considered in patients with progressive disease, or those requiring high dose corticosteroid therapy [146–148].

Increased duration of beryllium exposure is associated with an increased risk of CBD, and avoidance of further exposure on diagnosis of CBD is highly recommended. However, CBD develops in response to an altered pattern of autoimmunity, triggered by beryllium exposure. Given this it is likely that many patients will experience progression, even if they have no further direct exposure.

Primary prevention of CBD focuses on reducing exposure to beryllium, through engineering controls and appropriate personal protective equipment. A recent update to the OSHA standard for allowable beryllium exposure reduced the permissible exposure limit for beryllium to 0.2 $\mu g/m^3$ over an 8 h period [149]. It is

recognized that even a small amount of beryllium exposure can trigger disease. Regular medical surveillance can detect beryllium sensitization, and facilitate early exposure removal.

Hard Metal Lung Disease

Hard metal induced lung disease, also known as 'Cobalt Lung', or "Giant Cell Pneumonitis" is a spectrum of interstitial lung disease which develops secondary to exposure to hard metal- alloys of cobalt and tungsten fused together through a process known as cementation or sinestration [150–152]. Hard metal alloys, also referred to as cemented carbides, are extremely strong and heat resistant and are used widely throughout industry for cutting, polishing and machining [153].

The syndrome of Hard Metal Lung Disease (HMLD) was first described in the early 1970s, after the discovery of unusual "cannibalistic" giant cells in the bronchoalveolar lavage fluid of patients with interstitial pneumonia [154]. While case reports of interstitial lung disease in workers exposed to hard metal had been described as early as the 1940s, the connection between these atypical "giant cells" and an occupational exposure to hard metal was not made until several years later, when the presence of tungsten was identified within BAL samples of patients with confirmed giant cell pneumonitis [155].

HMLD remains a fairly rare cause of occupational interstitial lung disease, though occupational cobalt exposure is highly associated with occupational asthma, and the development of contact dermatitis. HMLD may also be significantly underrecognized. Tool sharpeners, disc grinders, diamond polishers and employees working with diamond bonded tools are all at risk of developing HMLD [151]. Unlike more traditional pneumoconiosis, no formal screening program for HMLD exists, and much of the occupational exposure associated with HMLD is seen in smaller employers, or in self-employed workers [152, 156].

In one of the largest studies of workers at risk for HMLD, 2.6% of workers were found to have significant CXR abnormalities, and 10% reported work induced wheezing- an early warning symptom for both cobalt induced occupational asthma and subsequent HMLD [157]. Due to the highly soluble nature of cobalt, industrial processes such as wet cutting which are traditionally perceived as lower risk for respirable dust exposure are associated with a higher risk of cobalt exposure compared with "dry" cutting. Outbreaks of HMLD among workers exposed to these wet cutting processes have been reported even in settings where respirable cobalt measurements were significantly below the allowable limit [158].

The risk of developing HMLD appears to be largely related to host susceptibility, with some workers developing acute onset disease after minimal exposure, and others remaining disease free despite significant exposure [159]. The presence of an HLD-DPB1 glu-69 residue is associated with a significantly increased risk of developing HMLD among exposed workers [160]. Unlike chronic beryllium disease

however, lymphocyte proliferation testing has been largely ineffective in identifying sensitized workers at risk for developing respiratory disease [159].

The clinical presentation of HMLD typically begins with upper respiratory tract symptoms, including cough, throat pain, ocular irritation, and sinus drainage. With ongoing exposure, cough, dyspnea, and wheeze may develop. Systemic symptoms, including fever, weight loss and fatigue are common, and may be pronounced. Unlike the majority of other occupational interstitial lung diseases, in the early phases of HMLD, removal from exposure is associated with significant and immediate improvement. In patients for whom exposure cessation does not occur, chronic fibrotic pulmonary changes develop, similar to the clinical picture seen in chronic fibrotic hypersensitivity pneumonitis.

PFT testing in patients with early HMLD may be unremarkable, or may show evidence of obstructive physiology, with reduced DLCO [157]. Over time, restrictive changes typically develop, though patients with combined elements of occupational asthma may show a mixed PFT picture [151, 159].

Imaging patterns in early HMLD vary widely. Traction bronchiectasis, scattered ground glass opacities and air trapping are commonly reported [152]. Centrilobular and perilymphatic nodularity can also be seen, and may lead to misdiagnosis in the absence of a thorough occupational history [161].

Bronchoscopy may be performed to ascertain diagnosis. BAL fluid characteristically shows multinucleated giant cells, although the presence of these cells is not necessary to confirm the diagnosis of HMLD. Cobalt or tungsten may be identified within BAL fluid, though this is relatively rare.

Biopsy is characterized by lymphocytic interstitial infiltrate, alveolar epithelial hyperplasia and interstitial desquamation [151]. Emperipolesis, characterized by finding intact inflammatory cells within the cytoplasm of giant cells, is pathognomic for HMLD in the setting of exposure and consistent imaging findings. In advanced cases, biopsy findings may be indistinguishable from advanced fibrotic lung disease, with honeycombing and reticulation [162].

Treatment of HMLD begins with exposure removal. In patient's whose symptoms persist or worsen despite exposure removal, corticosteroid or other immunosuppressive therapy may be effective. Respirators and engineering controls should be utilized in areas where the potential for occupational cobalt exposure exists.

Potential Pulmonary Impact of Unconventional Natural Gas Development

Unconventional natural gas development (UNGD) has received increasing attention in the past decade. Also known as "fracking", UNGD is characterized by the use of hydraulic fracturing fluid to access natural gas deposits within seams of hard rock, primarily shale, coal-beds and tight sand.

The impact of UNGD on respiratory health remains largely unknown at this time, though all phases of UNGD are associated with potential exposures to

pulmonary irritants. The process of establishing a new hydraulic fracturing site begins with a pre-production period, where the land for the well-pad is cleared and transportation pathways developed [163]. This period has been associated with an increase in atmospheric $PM_{2.5}$ and PM_{10}, primarily related to diesel exhaust from heavy machinery, road dust and brake-pad debris [164]. Increased exposure to inhaled $PM_{2.5}$ and PM_{10} has previously been associated with an increased risk of respiratory symptoms and exacerbations of chronic airway disease in children and adults [165, 166].

Following pre-production, drilling begins. Once sufficient depth has been reached, the process of hydraulic fracking begins. During this process, large volumes of water, hydraulic fracturing fluid and proppant (material, usually sand, instilled to keep natural gas seams open) is injected at high pressures. Again, this process results in increased levels of atmospheric $PM_{2.5}$ and PM_{10}, along with the release of volatile organic compounds [163, 167]. The specific chemical contents of fracturing fluid varies between well developers. While mines are encouraged to disclose fracking fluid content, this disclosure is not currently mandated by law [168].

Exposure to silica contained within proppant sand is also of significant concern during the hydraulic fracturing stage. Previous studies have found that fracking workers are at risk for acute, high level silica exposure, which may not be prevented by traditional half-face mask personal protective equipment [169, 170]. Workers employed in UNGD should undergo regular silica screening, and silicosis should be considered in any patient with a history of hydraulic fracturing exposure presenting with interstitial lung disease features.

After hydraulic fracturing is completed, the process of gas venting begins. Output from UNGD wells typically slows after 2–3 years, and wells may undergo a "re-fracking" process multiple times during their lifecycle to boost production [163, 167]. During all phases of UNGD, exposure to $PM_{2.5}$, PM_{10}, volatile organic compounds (particularly benzene and toluene), and greenhouse gas emissions remains a concern.

Work into the health of residents surrounding UNGD sites is ongoing. Studies of residents in areas around UNGD sites show increased rates of self-reported respiratory and sinus symptoms [167, 171]. At a population level, periods of heavy UNGD activity are associated with an increased rate of asthma exacerbations [168]. Research into the respiratory health of UNGD workers is limited.

Occupational Lung Disease in Military Personnel and First Responders

Military personnel and first responders are at risk for a number of potential pulmonary exposures. Unlike traditional occupational lung disease evaluation, a single event may result in expected and unexpected exposures to a wide range of potentially damaging materials. Immediate environmental monitoring is rarely available,

making quantification of exposure challenging. Given this, it is important to consider a broad differential diagnosis when evaluating a symptomatic patient with an occupational history of deployment or emergency response.

Deployment Related Lung Disease

Since the early 2000s, more than 2.7 million United States service personal have been deployed to South Asia and the Middle East [172]. In addition to the potential for combat related injury, these deployments are characterized by exposure to a range of potential pulmonary irritants, including inhaled particulate matter, gas and fumes created by incineration of organic and inorganic waste [172].

Sixty-nine percent of deployed personnel report experiencing respiratory symptoms during deployment- the second most common non-combat related illness reported during deployment [173]. These respiratory symptoms are not limited to deployment- post-deployment, personnel who have been deployed continue to endorse significantly more dyspnea, wheeze and chronic cough compared to non-deployed personnel [174]. In addition to non-specific respiratory symptoms, a range of respiratory syndromes have described in personnel returning from deployment, including asthma, vocal cord dysfunction and constrictive bronchiolitis [172, 175]. Estimates of respiratory disease related to deployment are confounded by tobacco use among military personnel.

Exposure to open-air burning of waste, also known as "burn-pits" has been of particular concern. These large open air waste pits were utilized to dispose of industrial waste, plastic byproducts, human waste and solvents at a number of bases [176]. Due to the uncontrolled nature of burn-pit temperatures, breakdown of these waste products is often incomplete. Environmental air sampling in the areas surrounding a large burn-pit revealed elevated levels of atmospheric $PM_{2.5}$, PM_{10}, acrolein and benzene- all known pulmonary irritants [177]. Concern that burn-pit exposure could have long-term respiratory health impact is high among returning personnel [173]. To date, there has been no clear association between burn-pit exposure alone and risk of pulmonary disease, though there is concern that this may represent a risk factor for constrictive bronchiolitis development [173, 178].

Deployed personnel have a significantly higher risk of developing new onset asthma during deployment [179, 180]. This is theorized to be related to increased exposure to environmental $PM_{2.5}$ and other irritant particulate matter, though causal mechanisms remain not fully understood [172]. Rates of PTSD are also high within deployed personnel- exposure to increased allostatic load has also been shown to increase the risk of asthma among adolescents, and has been theorized as a potential driver of the high levels of asthma seen within this population [181]. Vocal cord dysfunction, which may mimic asthma symptoms, is also prevalent among deployed personnel- in one cohort, 6.6% of deployed personnel referred for evaluation of unexplained dyspnea were found to have vocal cord dysfunction [182].

Constrictive bronchiolitis- a disease characterized by fibrosis, narrowing and destruction of small airways, has been reported in personnel presenting with unexplained dyspnea following deployment. The largest case series identified 38 cases of constrictive bronchiolitis in previously deployed personnel referred for evaluation of unexplained dyspnea [183]. While personnel within this case series had a number of unique exposures, the majority had been exposed to high levels of inhaled sulfur due to a large sulfur mine fire in the region during the time of deployment. Cases of constrictive bronchiolitis in patients exposed to sulfur mustard have previously been reported. However, many of the identified cases had no clear sulfur exposure. Similar cases of constrictive bronchiolitis have been reported in other centers among deployed personnel, the majority of whom also lacked a clear exposure to sulfur [172, 184].

Constrictive bronchiolitis can be challenging to diagnose. PFTS are often unremarkable in the early stages of disease, though with disease progression evidence of fixed obstruction or restriction may be present [185]. HRCT imaging is also often unremarkable, though can show evidence of mosaic attenuation due to air-trapping in the fibrotic small airways [186]. Diagnosis of chronic bronchiolitis is made by surgical lung biopsy, which classically shows areas of fibrotic sub-epithelial scarring, with narrowing and obliteration of the small airways [172]. This fibrotic scarring can have significant geographic heterogeneity however, and may be easily missed [172]. Over-diagnosis is also possible due to ex-vivo contraction of smooth muscle within the bronchial wall [187]. The true incidence of constrictive bronchiolitis among previously deployed personnel remains unknown.

Tobacco use remains an under-recognized contributor to respiratory and cardiovascular morbidity among deployed personnel. 30% of US army veterans, and 14% of active duty personnel endorse active tobacco use [188, 189]. Deployment is a significant risk factor for initiation of tobacco use, and of smoking recidivism [190].

In a patient with a history of deployment who presents with unexplained dyspnea, evaluation should begin with a thorough history, including deployment history and length, occupation while deployed, and history of exposure to burn pits, dust storms or other atypical exposures. Pulmonary function testing, including spirometry with bronchodilator testing, DLCO and lung volumes is recommended as part of initial evaluation, along with high resolution CT chest imaging [175]. Of note, because the deployed population is on average, healthier than the non-deployed population, PFT testing should be carefully interpreted. Pulmonary function testing was within normal limits in many of the patients subsequently diagnosed with constrictive bronchiolitis, though lower than the values seen in healthy deployed personnel [183].

If pulmonary function is within normal limits, provocation testing to evaluate for asthma should be performed. Given the high prevalence of vocal cord dysfunction, laryngoscopy is also often recommended [175, 182]. For those in whom initial evaluation is unremarkable, cardiopulmonary exercise testing may be considered.

Whether to proceed with surgical lung biopsy should be considered on a case-to-case basis. While this may have utility in diagnosing constrictive bronchiolitis, due

to challenges in making the diagnosis even with tissue sampling and lack of consensus into the relationship between constrictive bronchiolitis and deployment, overall benefit to the patient may be low [175].

World Trade Center Associated Lung Disease

While we commonly consider occupational lung diseases from the standpoint of ongoing long-term exposures, public health disasters or mass exposure events, such as the world trade center (WTC) disaster on September 11th 2001, have been associated with a wide range of occupational sequelae, spanning from reactive airway syndromes to chronic fibrotic lung disease.

The collapse of the WTC resulted in the release of large volumes of suspended dust and smoke, comprising of a mix of gypsum (a mix of silica, calcium carbonate and sulfates), asbestos from building insulation, and volatile organic compounds released from burning jet fuel [191, 192]. This initial dust cloud was strongly alkaline, and persisted for several days as a result of ongoing fires within the site of the initial collapse.

Multiple worker groups were exposed to the immediate and moderate term effects of the WTC collapse, including paramedics, firefighters and local disaster coordination teams [191]. Residents of the area surrounding the collapse, and nearby office workers also had significant exposure [15].

A range of health conditions have been associated with exposure to the WTC collapse, and more continued to be identified. From a respiratory standpoint, cough and upper respiratory tract symptoms were some of the most commonly reported symptoms immediately following the event, with approximately half of firefighters involved in the response to the WTC collapse reporting daily cough in the first year post event [192, 193]. Wheeze and dyspnea were also common, with a high incidence reactive airways disease diagnosed in the immediate aftermath of the event. Many first responders have evidence of chronic respiratory sequelae as a result of this exposure—a significant increase in the prevalence of asthma diagnoses among firefighters was noted in the years following the collapse [194, 195].

Granulomatous disease with the potential for multi-organ involvement has been reported in WTC responders [196, 197]. An increased risk of sarcoidosis has also been identified in residents surrounding the WTC collapse [15]. Cases of idiopathic pulmonary fibrosis (IPF) have also been identified among WTC responders [198].

Evaluating and Managing Occupational Exposures

Identifying a potential link between workplace exposure and disease requires a high index of suspicion. In patients presenting with symptoms that may have a link to the workplace, a thorough occupational history is essential to identify potential exposures.

Table 5 Key elements of the occupational history

Identifying exposure:	Detailed history of current and previous employment, including specific job duties and roles Detailed history of hobbies and other environmental exposures (housing, pets, etc.) History of known exposure to agents associated with occupational lung disease Participation in previous worksite screening or surveillance programs Clusters of illness among co-workers or community members
Quantifying exposure:	Duration of time in each job role/title Single exposure versus ongoing Percent of time exposed while at work Route of exposure (inhaled, ingested, dermal) Protective factors (PPE, engineering controls)
Timing of exposure:	Temporal relationship with exposure and onset of symptoms Improvement in symptoms with exposure removal

The history include an assessment of workplace, home, and recreational exposures. Current as well as past exposures should be assessed, with specific information collected regarding job titles and job tasks at each place of employment. The presence of respiratory symptoms among co-workers or individuals with similar exposures provides further evidence for disease. Many occupational lung diseases have a long lag time between exposure and development of symptoms- because of this, reliance should not be placed on descriptions of acute symptoms during initial exposure. Use of personal protective equipment and environmental controls such as local exhaust ventilation should be ascertained. (Table 5)

For some exposures including coal, beryllium, respirable crystalline silica and asbestos, OSHA mandates for exposure assessment in the workplace may already be in place. Exposure can be assessed in a multitude of ways, including average exposures over the work day such as an 8-hour period—referred to as permissible exposure limits (PEL) or short-term exposure limit. Quality of exposure monitoring may vary, and average exposure estimates may not capture short term, high level exposures. In addition to OSHA mandates, NIOSH also publishes exposure level recommendations, known as RELS or recommended exposure limits. The American Conference of Governmental Industrial Hygienists also publishes recommendations regarding threshold limit values, which offer detailed guidance into occupational safety measures. It is important to recognize that for some occupational exposures, a true "safe" exposure limit may not exist. For diseases such as occupational asthma and FHP which develop in response to exposure to a sensitizer, disease can occur even with low level exposures.

For exposures known to cause occupational lung disease, mandatory workplace surveillance may already be in effect. These mandatory surveillance programs may comprise of a mix of symptom screening, spirometry, and chest imaging. Workplace surveillance allows for early detection of disease- decreasing the risk of progression

for impacted workers and identifying risk for other workers. Worker participation is not compulsory however, and quality of workplace spirometry may vary.

The "healthy worker" effect is an important consideration when interpreting workplace spirometry surveillance data. Those in the workforce may have supernormal FEV1 and FVC values when compared with the overall population [199]. Evidence of a longitudinal decline in FEV1 or FVC should prompt concern for occupational lung disease, even if the values remain within a "normal" range. It is also important to recognize that workplace spirometry offers a snapshot of respiratory health. For diseases with a primarily restrictive process, full pulmonary function testing including DLCO and lung volumes may be necessary.

Many diseases of the workplace have a long latency. For that reason, ongoing medical surveillance should be considered even after retirement or change in occupation, though is not readily available. Former worker screening programs exist in some industries- for example, beryllium exposed workers who were employed by the Department of Energy are eligible for lifelong screening for beryllium related complications [199]. Similarly, retired miners are eligible for ongoing screening for CWP through the NIOSH Coal Workers Health Surveillance Program [200].

Occupational lung disease surveillance relies heavily on CXR imaging. The International Labor Organization produces a CXR classification system which is widely utilized in the diagnosis of pneumoconicosis [201]. HRCT is generally not part of routine surveillance, but may be indicated when concern for disease is high. It is important to highlight that biopsy is generally not required for the diagnosis of occupational lung disease, though may occasionally be required to confirm a diagnosis.

Evaluation of sentinel cases of occupational lung disease often requires a multidisciplinary collaboration between academia, industry and government agency. In patients presenting with symptoms and an unknown exposure, safety data sheets (SDS) can provide information about potential agents the worker may have been exposed to. If there is concern that multiple workers have been impacted, an employer, employee or union official can request a NIOSH Health Hazard evaluation of the workplace. For employers wishing to evaluate their own workplace safety practices, OSHA provides a free consultation service. OSHA consultation is not associated with OSHA enforcement and will work with an employer to identify and remediate potential hazards. It is critical to remember that regulatory limits do not exist for many exposures or sensitizers. Hence public health experts must remain cognizant of the potential for the presence of workplace toxicants and continue to advocate for exposure mitigation as well primary and secondary prevention through monitoring and surveillance programs.

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