Occupational lung disease: when should I think of it and why is it important?

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Occupational lung diseases are often missed. Pulmonologists should assess occupational and environmental exposures as causes or contributors to virtually all cases of major respiratory diseases to ensure the best outcomes for their patients. https://bit.ly/3Uy8qQe

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Abstract

Exposure to toxic inhalants in the workplace has the potential to cause (in susceptible individuals) almost any major type of lung disease, such as asthma, COPD and interstitial lung diseases. Patients with occupational lung disease will often present to or will be managed by respiratory specialists without training in occupational respiratory medicine, and patients (or their clinicians) may not identify a link between their disease and their current or a past job. Without an awareness of the range of different occupational lung diseases that exist, their similarity to their non-occupational counterparts, and without directed questioning, these conditions may go unidentified. Patients with occupational lung diseases are often in lower paid work and are disproportionally affected by health inequality. Both clinical and socioeconomic outcomes generally improve if cases are identified early. This allows appropriate advice to be given about the risks of ongoing exposure, clinical management, occupational mobility and, in some cases, eligibility for legal compensation. As respiratory professionals, it is important that these cases are not missed, and if needed, are discussed with a physician with specialised expertise. Here we describe some of the most common occupational lung diseases and outline the diagnostic and treatment approach.

Educational aims

Readers should be able to:

- Describe the general approach to the assessment of occupational exposures as causative or aggravating factors for respiratory disease in their patients.
- Appraise the role that occupational and environmental exposures can play in causing almost any major respiratory disease pattern, including the most frequent ones, in the general population.
- Identify suspicion of occupational asthma and understand differences between sensitiser- and irritant-induced asthma.
- Understand key clinical features of occupational interstitial lung diseases.

Introduction

The structure and function of the lung, with its extensive surface area, high vascularity, and thin barrier between air and blood, make it an important contact site for environmental agents, many of which have local and/or systemic or immunological toxic effects. Pulmonologists must always review a differential diagnosis for every major pattern of respiratory illness that includes occupational and environmental exposures [1]. As summarised by Redlich and Balmes [1], toxicant exposures may cause virtually every major clinical form of respiratory disease, which implies that almost any defined lung disease may have an

environmental or occupational cause. Few occupational lung diseases will present with obvious pathognomonic features, some occupational agents can cause both acute and chronic effects which may be completely different clinically, and the acute effects of a given exposure may not predict its chronic sequelae. While for acute diseases there is a short and predictable interval between exposure and resultant clinical manifestations that should suggest an association, for chronic diseases, long latency between first exposure and subsequent clinical manifestations is common. Clinicians need to assess, as best as possible, the possible exposure dose (in terms of exposure duration, measured levels and subjective intensity), the latter may determine the severity of disease in an affected individual, the incidence of disease among the exposed, or the rapidity of onset, but not necessarily all three. All occupational lung diseases are preventable, as exposure elimination will lead to future disease elimination. However, many chronic diseases, particularly the interstitial lung diseases (ILDs), once established may progress despite curtailment of exposure to the offending agent. Finally, as with tobacco smoke, not all occupationally exposed individuals will develop disease, and susceptibility may be determined by factors that remain for the most part unclear.

To diagnose occupational respiratory diseases, it is necessary to obtain a complete occupational history (jobs held since actively employed), with any associated exposure to chemicals, biological products, vapours, gases, dust and/or fumes, ascertaining as much as possible the intensity and the duration of the exposure. It may be necessary to seek expert advice, and to access specialised and/or multidisciplinary investigations to have the best outcome for patients. Diagnosing the occupational cause of a lung disease may affect treatment and prognosis of the disease, have legal, vocational and financial implications for the individual patient, possibly help identify a larger population at risk, and also contribute to research into the disease type.

To exemplify the above principles, we selected for this review a mix of classically occupational respiratory disease (such as silicosis), and work-related common diseases (such as asthma and COPD), which have disease specific widely accepted guidelines with scarce mention or guidance on occupational factors for their diagnosis and treatment.

Occupational asthma

When should one suspect occupational asthma?

Work-related asthma is not uncommon but is probably under-recognised. There may be many explanations for this. First, the relationship between asthma symptoms and work may not be evident to the patient. Secondly, the clinician may not think to enquire specifically about any work-related symptoms. Thirdly, the clinician may not be confident in making an assessment of work-related asthma. Finally, there is only limited information about occupational asthma (OA) and its causes in international asthma guidelines [2].

There are two main types of work-related asthma. OA is caused by airborne exposures in the working environment [3], while in work-exacerbated asthma a variety of nonspecific factors in the workplace can worsen asthma symptoms, but the asthma is not caused by work. The features of these two conditions are not easily distinguishable from each other. Work-exacerbated asthma is common and is estimated to affect one fifth of working asthmatic patients [4].

Recognising OA is challenging in many ways. For example, the observation that symptoms may worsen at work (or improve away from it) may not be made. In addition, factors relating to work can both cause asthma (either *de novo* or on a background of asthma) or can exacerbate pre-existing asthma symptoms. The clinician should consider the possibility of a diagnosis of OA in patients of working age who have new asthma symptoms, reappearance of childhood asthma, worsening of asthma control or when an airflow obstruction without explanation is detected (table 1) [3]. The suspicion should be even greater if the patient is working in high-risk jobs or is exposed to asthma-causing agents at work (table 2). Based on the underlying mechanisms there are two types of OA with differing clinical features which are summarised in the following sections and in table 3.

Sensitiser-induced OA

Sensitiser-induced OA is considered the most common type of OA and is induced by high-molecular-weight (HMW) or low-molecular-weight (LMW) agents. HMW agents are (glyco)proteins of animal, plant or microbial origin, which have ability to cause immunoglobulin (Ig) E mediated sensitisation. LMW agents are synthetic chemicals, metals and other natural agents that are considered to cause immunological reactions, but specific IgE antibodies are often not detected (table 2). Sensitiser-induced OA always requires a period of repeated allergen exposure before the onset of symptoms. During this "latent period" the sensitisation and immunological response develop [3, 6]. The latent period can vary from weeks to years, but the risk is highest for asthma development within the first 2 years of the relevant exposure.

TABLE 1 Clinical findings that should give rise to a suspicion of occupational asthma

When should one suspect occupational asthma?	
1)	Patients of working age present with:
	New symptoms suggestive of asthma OR
	Reappearance of childhood asthma OR
	Deteriorating asthma control OR
	Unexplained airflow obstruction
2)	Patients are employed (or have been during the onset of asthma symptoms) and:
	Are working in high-risk jobs[#] OR
	Are exposed at work to sensitising or irritant agents[#] OR
	Have asthma symptoms which are better away from work or during holidays

[#]: see table 2. Information from Barber *et al.* [3] and Bernstein *et al.* [5].

Asthma symptoms which improve away from work also increase the diagnostic probability of OA, but the relationship between symptoms and work is not always obvious [6]. Some patients with OA may report that their symptoms occur in the workplace or when performing certain tasks, while others may have more pronounced symptoms in the evening or at night, *i.e.* outside the workplace. Additionally, non-occupational triggers, like cigarette smoke, exercise and cold air, may worsen the symptoms. Any clear work-related pattern to symptoms generally declines the longer the duration of asthma. These features highlight the importance of considering the possibility of OA, even when the patient is experiencing few symptoms at work and most symptoms outside the workplace. OA caused by HMW agents is more

TABLE 2 Common causes of occupational asthma

Type of agent	Examples of agents	Workers/occupations at risk
Sensitising high-molecular-weight agents		
Cereal grain and flour	Wheat, rye, barley, buckwheat	Bakers, cooks, pizza and pastry makers, grain storage handlers, farmers, millers
Animals	Mice, rats, cows, fish, insects and mites, fish, seafood	Laboratory workers, farmers, greenhouse workers, veterinarians, fish and seafood processors
Other animal and plant-derived causes	Milk and egg proteins, beans (green coffee, soy), spices, gums (acacia, guar), plant-based hair colours (henna), pollen (tomato, bell pepper)	Food producers and processors, bakers, cooks, pharmaceutical industry, hairdressers, greenhouse workers
Enzymes	Amylase, protease, lipase	Bakers, pastry makers, food process workers, detergent and enzyme manufacturers
Natural rubber latex		Healthcare workers, rubber glove makers
Sensitising low-molecular-weight agents		
Isocyanates	Toluene diisocyanate (TDI), methylene diphenyl diisocyanate (MDI), hexamethylene diisocyanate (HDI)	Spray painters, polyurethane production, plastic industry, moulding, insulation installers
Persulphate salts	Ammonium and potassium persulphate	Hairdressers using hair bleach
Metals	Platinum, chromium, nickel, cobalt	Refinery workers, welders, metal platers, hard metal manufacturing, CNC grinders, lathe operators
Acrylic monomers	Cyanoacrylates, methacrylates	Adhesive work, dental professionals, aestheticians, printing industry workers
Acid anhydrides	Phthalic anhydride, trimellitic anhydride, maleic anhydride	Workers handling heat-cured epoxy resins
Drugs	Opiates, penicillins, other antibiotics	Pharmaceutical manufacture, healthcare workers
Wood dusts	Red cedar, iroko, obeche	Carpenters, sawmill workers, cabinet and furniture makers
Biocides	Aldehydes, quaternary ammonium compounds	Healthcare workers, cleaners
Irritant agents		
Inorganic acids	Sulphuric acid (H_2SO_4), hydrochloric acid (HCl), nitric acid (HNO_3)	Machine operators, mechanics and maintenance workers in pulp mills, mines, metal, chemical and other heavy industry, animal farm workers, cleaners, construction workers, truck drivers
Inorganic alkalis	Sodium hydroxide (NaOH), ammonia (NH_3), potassium hydroxide (KOH)	
Irritant gases	Chlorine (Cl_2), hydrogen sulphide (H_2S), sulphur dioxide (SO_2), detergents, fire smoke, isocyanates	
Inorganic dusts	Raw cement, calcium oxide, other alkaline or acidic dust	

TABLE 3 Typical features of sensitiser- and irritant-induced occupational asthma (OA)

Sensitiser-induced OA	Irritant-induced OA (IIA)
Latency from weeks to years	No latency in acute/definite IIA Asthma develops after multiple symptomatic high-level exposures in subacute/probable IIA
OA may develop related to low-level exposure	The initiation of symptoms is related to high-level exposure
Rhinitis and conjunctivitis may precede or coincide with asthma symptoms (HMW agents)	Rhinitis, conjunctivitis, corneal ulcers, and pharyngeal erythema may relate to high-level exposure
Atopy is a risk factor (HMW agents)	No association with atopy
Reversible obstruction	Less reversible obstruction Restrictive pattern

HMW: high-molecular-weight. Information from Barber *et al.* [3] and Bernstein *et al.* [5].

common in people with atopy and almost invariably occurs in conjunction with work-related rhinitis and conjunctivitis. These symptoms may start before, or at the same time as, asthma symptoms. Therefore, any patient with both upper and lower respiratory symptoms associated with work should raise clinical suspicion. LMW agent-induced OA occurs less often with rhinitis, and typically has late asthmatic reactions, when compared with HMW agent-induced asthma [6].

When enquiring about potential airborne causal agents, it is important not only to ask about the patient's occupation, but also about their work tasks and other processes at their workplace. The workers may have "second-hand" or bystander exposure to the asthma-causing agent even if they do not handle the agent themselves. Over 400 sensitising agents are known to cause OA [7]. However, only a few agents cause the majority of OA cases, most commonly flour dust and isocyanates. Types of industry, with their associated causative agents, vary by geographical area and so it is useful to have an understanding of the local area and the common asthmagens to which the local population might be exposed. Table 2 presents common sensitising agents and occupations with a high risk for OA. Safety data sheets (SDS) provided for hazardous chemicals by the manufacturer, distributor or importer, are useful in identifying chemicals that can cause asthma *via* respiratory sensitisation. In the European Union (EU), respiratory sensitisation is marked with hazard statement EUH334. However, these SDS are not always comprehensive and so in some cases the statement can be missing even if the product contains sensitising agents.

Irritant-induced OA

Irritant-induced OA (IIA) accounts for 4–14% of cases in series and develops after exposures to high concentrations of airborne agents with corrosive or oxidative (irritant) properties, *e.g.* strong acids and bases (table 2) [3, 8]. The mechanisms of IIA are less well known, but irritants have been demonstrated to induce direct epithelial cell damage and mostly neutrophilic inflammation. IIA may develop after a single massive exposure to irritants (table 2), which usually occur in chemical accidents, fires or other hazardous events. The clinical features are distinctive. There is no latency and respiratory symptoms (*e.g.* dyspnoea, cough, wheezing, chest tightness) occur within 24 h of exposure. Coughing is typically the most prominent symptom. Patients may experience a burning sensation in the throat or nose and eye irritation in addition to respiratory symptoms [8]. This classical type of irritant-induced asthma was originally labelled as reactive airways dysfunction syndrome (RADS), but latterly, the terms acute or definite irritant-induced asthma have been used [5, 8]. It is unlikely that this diagnosis would be missed as patients would report a clear exposure history. However, it is important that appropriate diagnostic tests are performed to confirm objective evidence of airways disease rather than other sequalae such as breathing pattern dysfunction.

IIA can also develop after repeated symptomatic exposures to a high level of irritants (subacute or probable irritant-induced asthma) [9]. The symptoms experienced are the same as for acute IIA. It may be more common than acute IIA but is likely under-recognised because the relationship between multiple exposures and the onset of symptoms is more difficult to establish [8, 10]. Additionally, in epidemiological studies, chronic or repeated exposure to low-to-moderate levels of irritant substances had increased asthma risk (low-dose or possible irritant-induced asthma) [9]. It is not possible to diagnose this type of irritant-induced asthma with certainty at an individual level, because the association between exposure and the onset of asthma symptoms is difficult to establish [8]. In irritant-induced asthma airway obstruction is generally less reversible than in allergic asthma and a restrictive spirometric pattern, probably representing a manifestation of a small airway disease, may also be observed [8, 11, 12].

A wide variety of inhaled gases, fumes, aerosols and dusts have been associated with irritant-induced asthma (table 2) [8, 10]. Typically, acute irritant-induced asthma is caused by spills of irritating volatile compounds, overheating of materials, accidental fire and mixing of cleaning products. Subacute irritant-induced asthma is most common in industrial operators and maintenance workers performing their usual tasks under poor hygiene conditions. A confined space with reduced ventilation often amplifies the effects of irritant agents. In SDS, chemicals classified as corrosive (Skin Corr 1A or 1 B) or oxidative (Ox Gas, Ox Liq) and hazard statements EUH314 ("causes severe skin burns and eye damage") and EUH071 ("Corrosive respiratory tract") may help to identify the causal agent. Occasionally, high-level exposure to isocyanates or other sensitising chemicals may also cause irritant-induced asthma. Incidentally, dusts and fumes with less irritative properties (*e.g.* dusts in building sites and welding fumes) may cause work-exacerbated asthma but are not considered to cause irritant-induced asthma.

Diagnostic tests for OA

In addition to detailed clinical and occupational history, diagnostic tests of asthma including spirometry with bronchodilator and nonspecific bronchial hyperresponsiveness tests (*e.g.* methacholine and histamine challenge tests) are useful in the diagnosis of both sensitiser- and irritant-induced OA [2]. When sensitiser-induced OA is suspected, a few specific tests are available to confirm the diagnosis. These tests are most sensitive if they are performed early, before starting maintenance asthma therapy and while the worker is still in the job suspected to cause asthma [6]. Serial peak expiratory flow recording at work and off work can be used to assess airway response to inhaled agents at work if the patient is still exposed to the suspected causal agent at work [13]. Recordings every 2 hours during waking hours for at least 3 weeks are recommended, and specific software can be used in the interpretation. Immunological testing is useful with HMW agents and some LMW agents. Positive skin prick test or elevated specific IgE level to a workplace agent confirms sensitisation. Also, specific inhalation and workplace challenge tests can be used to confirm OA. The diagnosis of IIA is based on suggestive exposure history, time course of symptom onset with respect to the occurrence of exposure and evidence of reversible airflow limitation and/or nonspecific bronchial hyperresponsiveness.

Why is it important?

Early diagnosis of sensitiser-induced OA is important for several reasons. The longer the duration of exposure the poorer the asthma outcomes. Persistent exposure results in greater degree of airflow obstruction, increased nonspecific bronchial hyperresponsiveness and faster decline in forced expiratory volume in 1 s compared with avoidance of exposure [6]. The prognosis is better if OA is identified earlier and the patient is able to avoid further exposure to the causal agent. Every OA case is an illustration of the presence of workplace hazards to health and measures should therefore be considered to protect other workers.

Occupational COPD

COPD is the ultimate environmental respiratory disease: its main causative determinant being inhalation of tobacco smoke, a powerful and complex mixture of respiratory toxicants with what has proven to be an efficient delivery system. While pulmonologists know this association well, only continued research to the present day has brought to light and emphasised the considerable proportion of patients with COPD (25–35%) who were never-smokers and unveiled several exposures and risk factors for the development of the disease, which may in many cases act jointly with cigarette smoke. In the mid-19th century, John Hutchinson, the inventor of the spirometer, had already noted different vital capacity according to height, age and occupation, and encouraged public health and statistics experts to conduct studies to ascertain the influence of both trade and locality on respiratory health [14]. Subsequent landmark publications [15–17] established the role of occupational exposures to dust, gases, and fumes in the causation of "focal emphysema", COPD, and industrial (chronic nonobstructive) bronchitis, respectively. In 2019, a joint statement of the American Thoracic Society and the European Respiratory Society [18] estimated the pooled smoking-adjusted population attributable fraction (PAF; *i.e.* the proportional reduction in COPD in the population that would result from exposure elimination) for the occupational contribution to COPD at 14% (95% CI 10–18%), and 31% (95% CI 18–43%) if restricting studies to non-smokers. For chronic bronchitis, the PAF was 13% (95% CI 6–21%) [18].

The occupational exposures with stronger evidence of association with COPD include coal mine dust, silica, grains and textiles, and less strongly with agricultural dusts, asbestos, cadmium, carbon black, refractory ceramic fibres, endotoxin, flour, isocyanates, welding fumes, coke oven emissions, diesel exhaust, and tunnelling dust and fumes [19, 20]. The dose–response relationship, interaction with cigarette smoking (it seems to be additive), the individual contribution of different agents, and other mechanistic aspects remain poorly understood in occupational COPD, and further research is clearly needed.

Besides occupational exposures, investigations have established the causative role of other environmental exposures, such as indoor air pollution from biomass burning [21] or second-hand smoke, or outdoor air pollution [22], as well as likely genetically determined susceptibility factors, factors or events affecting lung development in early life, possibly including dysanapsis (airway calibre underdevelopment in relation to that of the lung alveoli), accelerated ageing or senescence, or lung diseases throughout life, such as asthma (more so, perhaps, in individuals with work-related asthma [23]), tuberculosis, rheumatoid arthritis, HIV and other viral and nonviral infections [20]. These investigations have solidified the belief that COPD is a heterogeneous disease, and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) is beginning to propose a subclassification of the disease based on some of the major exposures or risk factors (including non-tobacco environmental exposures) [24], acknowledging the contribution of risk factors.

COPD is currently defined by the presence of respiratory symptoms and fixed obstruction. In a few studies conducted in COPD associated with an environmental exposure (biomass smoke) relatively more proximal airway inflammation and less emphysema have been noted [25, 26], but more research is needed. The diagnosis and treatment of occupational COPD generally follows general recommendations [27]. Assessment of exposure is necessary to exclude an occupational contribution to COPD (see the introduction), but also as curtailment of hazardous exposures may need to be part of its management if appropriate. It is also very important to assess and grade impairment and/or disability, using accepted and applicable guidelines, and render appropriate public health and occupational surveillance reporting.

Occupational interstitial lung diseases

When should one suspect occupational interstitial lung disease?

ILDs are characterised by varying combinations of parenchymal inflammation and/or fibrosis. There are some inhalation exposures encountered in the workplace which are well-established causes of ILD, where both the exposure and disease are easily identified, *e.g.* coal dust exposure and pneumoconiosis. However, in other ILDs, the association between occupational exposures and disease may not be made, particularly if the clinical or radiological picture is nonspecific. This results in patients languishing in clinics without an identified aetiological cause of their ILD and without the appropriate clinical management and advice about employment. Here we outline some of the commonest occupational causes of ILD, with these summarised in table 4.

Idiopathic pulmonary fibrosis and asbestosis

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive disease characterised radiologically by basal predominant subpleural fibrosis and honeycombing, and histologically by scattered fibroblastic foci in alternating patches of normal and fibrosed lung, both described as usual interstitial pneumonia (UIP) pattern. By definition, IPF has no known cause, but does this just reflect that the underlying mechanisms are yet to be fully understood? A review of the burden of non-malignant respiratory disease found the PAF for occupational exposures in IPF to be greatest for exposures to vapours, gases, dusts and fumes at 26% (95% CI 10–41%), with a pooled odds ratio of 2.0 (95% CI 1.2–3.2). Statistically significant associations were also seen for metal dusts (8% (95% CI 4–13%)), wood dusts (4% (95% CI 2–6%)) and silica (3% (95% CI 2–5%)) [18].

IPF is commoner in men than women (ratio of 1.6) with a median age of 70 years at diagnosis and increased incidence in industrialised areas [28]. These observations, and other ecological variations have generated the hypothesis that a proportion of IPF may be due to unrecognised asbestos (and other) occupational exposures [29]. A multicentre, incident case–control study of men diagnosed with IPF and age-matched male hospital outpatient controls recently assessed lifetime occupational asbestos exposure applying a job exposure matrix. Occupational asbestos exposure was not associated with IPF; however, there was a significant interaction between smoking and exposure for carriers of the minor allele *MUC5B* rs35705950, highlighting the likely complex relationships between dual exposures and genetics [30].

Asbestosis often mimics IPF radiologically, presenting most commonly with a UIP pattern on high-resolution computed tomography but other ILD patterns are also seen (table 4). The key to diagnosing asbestos-related disease is a careful occupational and exposure history. An understanding of their jobs (including unpaid or part-time work) and the era in which they worked is important, as is a knowledge of the asbestos legislation (particularly whether asbestos was still being imported) in their country of work. Occupational groups at increased risk of asbestos exposure are listed in table 4. Some individuals, for example, construction workers carrying out refurbishment of commercial and domestic buildings may have, unknowingly, encountered asbestos exposure in their jobs. There is a dose response between asbestos exposure and risk of developing asbestosis and the latency is around 20–30 years. Quantification of exposure is challenging because it relies on a knowledge of concentration of exposure.

TABLE 4 Common occupational interstitial lung diseases

Disease	Occupational exposure	Types of industries exposed	CT features	Histological features
Asbestosis	Asbestos	Carpenters, boiler room workers, construction workers, ship-yard workers, maintenance and insulation workers, vehicle brake mechanics, asbestos cement workers, tiles, shingles and textiles workers, certified asbestos handlers	Parenchymal bands, traction bronchiectasis, rounded atelectasis, honeycombing, intralobular thickening, subpleural curvilinear lines, GGO	Diffuse interstitial fibrosis, asbestos bodies, asbestos fibres
Hypersensitivity pneumonitis (HP)	Many exposures, including *Aspergillus* and other microorganisms, plant matter, animal proteins, and less commonly certain chemicals (*e.g.* isocyanates)	Agricultural workers, animal-related workers, food industry (processing and foodstuff), metal workers, manufacturing	Non-fibrotic HP: GGO, mosaic attenuation, centrilobular nodules, air trapping Fibrotic HP: irregular linear opacities, reticulation, traction bronchiectasis, mid/upper-zone predominant, with some features of non-fibrotic HP	Alveolar septal thickening, inflammatory infiltrate predominantly of lymphocytes with occasional multinucleated giant cells, poorly defined granulomas, small foci of organising pneumonia
Silicosis	Respirable crystalline silica	Construction and quarry work, tunnelling, stonemasonry, mining, ceramic and pottery industry, kitchen worktop fitters, stone-washing	Vary depending on type of silicosis (acute, chronic, accelerated); includes upper lobe predominant small pulmonary nodules in perilymphatic distribution and hilar and mediastinal lymphadenopathy with or without calcification	Small fibroblastic nodules and histiocytes becoming increasingly hyalinised over time; silicotic nodule; occasionally granulomas
Chronic beryllium disease	Beryllium	Electronics, aerospace, telecommunication, nuclear industry	Pulmonary nodules with upper lobe fibrosis, traction bronchiectasis and interlobular septal thickening; mediastinal lymphadenopathy may be present	Peri-bronchial non-necrotising granuloma
Hard metal lung disease	Tungsten carbide/cobalt	Tool manufacturing, hard metal tool use, diamond polishing, dental technician	Multifocal consolidation, GGO, upper zone predominant reticulation and interlobular septal thickenings, pulmonary nodules	Giant cell interstitial pneumonitis; airspace filling with alveolar macrophages and cannibalistic multinucleated giant cells
Metal dust-induced granulomatosis	Aluminium Titanium Zirconium	Aluminium plants, welding, grinding, polishing, smelting, foundries, automotive industry Milling, grinding, paint production Aircraft, aerospace, nuclear industries	GGO, patchy consolidation, reticulation, traction bronchiectasis, pulmonary nodules	Non-caseating granulomas with birefringent material on polarised light; granulomatous pneumonitis or fibrosis

CT: computed tomography; GGO: ground-glass opacities.

Whilst 25 fibre·mL^{-1}-years (for example, 1 year of exposure at 25 fibres per mL or 5 years of exposure at 5 fibres per mL) has been proposed as a threshold for a greater risk of asbestosis or lung cancer in the Helsinki criteria [31], the reality is that this is difficult to ascertain in practice and not generally of use.

Whilst the presence of pleural plaques indicates asbestos exposure, relatively low exposures are thought to be required to develop plaques. Therefore, it is important not to automatically attribute all ILD in patients with pleural plaques to asbestosis. Conversely, asbestosis can occur in isolation and so a diagnosis of asbestosis should not be excluded based on the absence of plaques alone. The diagnosis of asbestosis is almost always based on history of exposure and compatible radiological and physiological findings. However, very rarely, a biopsy is undertaken and a number of histological features to determine significant asbestos exposure in a patient with interstitial fibrosis based on the Helsinki criteria have been proposed. These include use of electron or light microscopy to identify the presence of asbestos bodies or asbestos

fibres in tissue and in bronchoalveolar fluid [31]. There are caveats to such criteria as the distribution of asbestos bodies is not uniform throughout the lung and thus multiple sampling sites may be required to identify their presence. Finally, cigarette smoking is known to increase the risk of asbestosis.

Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (HP) is an inflammatory and/or fibrotic ILD arising in susceptible individuals after exposure to inciting antigens, many of which can occur in occupational settings. HP is not always straightforward to diagnose, with no inciting antigen identified in ∼50% of cases. It is estimated that the occupational burden of all HP cases is 19% [18]; therefore, in any case of HP, an occupational aetiological agent should be considered. HP is probably under-recognised due to the challenges of diagnosis, and this, coupled with the marked geographical variation in cases, means the epidemiology can be difficult to describe. More than 300 different agents have been associated with HP and can be broadly defined as microbial agents (bacteria, fungus), animal antigens, and less commonly, chemicals. All of these exposures can occur in occupational settings. Historically, exposure to avian antigens ("bird fancier's lung") and moulds on hay ("farmer's lung") were the commonest causes of HP; however, with more recent changes in workplace practices and industrialisation, metalworking fluids used in engineering have emerged as an increasingly common aetiological agent for occupational HP with outbreaks reported [32].

Identification of an occupational cause of HP often requires direct questioning about specific agents known to cause HP. Key features include exposure to a known occupational cause of HP, and a temporal relationship with worsening of symptoms at work and improvement at weekends, on holiday or when working in areas where they are unexposed. Improvement away from work may take several weeks to become evident. The exception to this is cases of acute HP, which occur less frequently but here the symptoms start within a few hours of exposure to the putative agent and a clear exposure pattern is usually evident. Acute HP may be difficult to differentiate from acute bronchitis or pneumonia.

Silicosis

Silica is the earth's most abundant mineral, with respirable crystalline silica (RCS) generated in a wide variety of occupations, including those working in mining, tunnelling, construction, quarries and foundries, and in the manufacturing and cutting of artificial stone. Silicosis refers to a spectrum of diseases that result from RCS exposure, ranging from acute silicosis through to accelerated silicosis, chronic simple silicosis and progressive massive fibrosis (PMF). Acute and chronic silicosis vary both in the clinical presentation and the underlying pathological mechanisms of onset and histology. A dose relationship tends to exist, with acute silicosis occurring in people with high intensity exposure over a relatively short duration (typically within 10 years of exposure, but often within 1–2 years), and the converse applicable to chronic silicosis (exposure usually over more than 10 years). Specific occupational groups are at increased risk of acute silicosis, where grinding and cutting processes result in fractured or cleaved silica particulate release, such as silica flour processing, sandblasting and surface drilling. More recently, accelerated silicosis associated with a rapidly progressive disease amongst artificial stone workers, such as kitchen-fitters, has emerged [33]. Acute silicosis tends to present with fatigue, fevers, dyspnoea and weight loss, with the potential to develop rapidly progressive respiratory failure. Chronic simple silicosis tends to either be diagnosed in asymptomatic people through surveillance and incidental findings on chest radiography, or with mild respiratory symptoms such as cough or mild exertional dyspnoea. However, the concern is progression to PMF where more debilitating respiratory symptoms develop. Silica exposures are associated with tuberculous infection and silicosis is associated with a number of connective tissue diseases and renal disease [34].

Sarcoidosis

Sarcoidosis is a multisystem disease characterised by the presence of non-caseating granulomas. Whilst the underlying cause and mechanism of sarcoidosis remain unclear, it is likely the result of exposure to an environmental trigger in a genetically susceptible individual leading to immune dysfunction [35]. As more than 90% of cases of sarcoidosis involve the lungs (pulmonary sarcoidosis) [36], and seasonal and geographical variation in the onset of sarcoidosis have been recognised, inhalable environmental exposures or antigens are considered a potential underlying cause. It is estimated that ∼30% of the burden of sarcoidosis is occupational [18]. However, the quest for which exposures cause sarcoidosis is longstanding and unanswered, although many causal associations have been suggested, and continue to be investigated [37].

Many studies have described possible occupational associations with sarcoidosis and include silica, pesticide and mould and mildew exposures [37, 38]. The largest individual-level case–control study of lifetime occupational exposures in patients diagnosed with sarcoidosis was the ACCESS study [37], which found that occupational exposures to insecticides, mould and mildew and musty odours were more prevalent amongst sarcoidosis patients. Phenotypes of sarcoidosis are increasingly studied, and recently a

case–case study demonstrated that inorganic dusts were associated with pulmonary sarcoidosis, jobs with close human or livestock contact associated with liver and splenic involvement, and reactive chemicals or livestock contact with cardiac sarcoidosis [39].

Sarcoidosis is known as the "great mimic", meaning that it may behave like many other diseases, leading to diagnostic challenges in clinical practice. Silicosis [40] and chronic beryllium disease (CBD) [41] can present in an identical manner to sarcoidosis and cases may be missed if the occupational and exposure history is not considered. The recent British Thoracic Society clinical statement [42] and American Thoracic Society guidelines [43] recommend that alternative causes of granulomatous disease should be excluded in all new cases of sarcoidosis, including those related to occupation. This will primarily be done by taking a careful occupational history, whilst clinical manifestations of extrapulmonary disease may suggest an alternative underlying diagnosis.

Other granulomatous lung parenchymal diseases

CBD is a granulomatous disease caused by exposure to beryllium metal or its oxide (in the form of fumes or dusts), which are used widely in the aerospace, electronics and defence industries. Exposure can result in development of beryllium sensitisation, diagnosed using a beryllium lymphocyte proliferation test (BeLPT). The diagnosis of CBD requires evidence of non-caseating granulomatous inflammation in lung tissue, a positive BeLPT and radiological changes. The radiological features in the lung are essentially indistinguishable from those of sarcoidosis with lymphadenopathy and interstitial nodules; however, extrapulmonary manifestations such as uveitis and erythema nodosum are not seen. Genetic susceptibility to CBD is strongly linked to *HLA-DPB1* alleles possessing a glutamic acid at the 69th position of the β-chain (βGlu69) [44].

Hard metal lung disease (HMLD) or giant cell interstitial pneumonitis is another granulomatous ILD. It is caused by exposure to the extremely hard metal formed by compacting (or "sintering") tungsten carbide and cobalt together. The clinical picture, and latent period of HMLD, are variable with most commonly insidious onset. Radiologically, the appearances are nonspecific and are described in table 4. If a biopsy is obtained, the presence of multinucleated giant cells is diagnostic [45]. Like CBD, HMLD is associated with βGlu69-containing HLA-DP alleles. The prognosis may improve with removal from exposure.

Exposure to the dusts (or fumes) of other metals, such as aluminium, titanium and zirconium, also, very rarely, induces granulomatous lung disease. Following the World Trade Center disaster, an increase in the incidence and prevalence of sarcoid-like granulomatous lung disease was suggested amongst firefighters [46] and case series have described disease amongst exposed local residents [47]. Epidemiological studies of sarcoidosis are methodologically difficult and highly susceptible to detection bias, and no properly designed studies have validated or replicated the results of that initial study. Components of the dust-cloud generated from the World Trade Center may have been responsible, as it contained a complex but poorly characterised mix of calcium salt and metal dust, synthetic organic materials, combustion products, silica and chemicals [48].

Why is it important?

Correct identification of occupational ILD is critical for the patient. For example, traditional immunosuppressive regimes applied in sarcoidosis may be ineffective if used in silicosis and expose patients to unnecessary and potentially toxic side-effects [49]. There is good evidence that, in HP, removal from exposure to the inciting antigen results in a better prognosis [50]. Making a diagnosis of occupational HP is thus crucial both for the individual, so as to remove them from exposure and maximise the chance of a full recovery, and for the employer, so that they can identify other cases and put into place strategies to prevent further cases. However, in most cases of occupational ILD, removal from exposure will not result in disease resolution, for example, in asbestosis and silicosis and some cases of chronic HP. In addition to HP, CBD cases may benefit from immunosuppressive treatment. Currently, however, occupational respiratory specialists are not part of the multidisciplinary discussion teams that try to establish the diagnosis and best treatment options for ILD patients [51].

Finally, depending on the country, a diagnosis of occupational ILD may allow the patient to claim benefits and apply for legal compensation, and patients should be informed that these processes may need to be done within a certain timeframe.

Conclusion

Pulmonologists need to assess occupational and environmental exposures as causes or contributors to virtually any major respiratory disease pattern. Occupational and environmental exposures are also

important in considering the management of patients affected by non-occupational disease. An assessment of occupational and environmental exposures is thus part of the comprehensive management of respiratory diseases in most patients. In this article, we presented some of the most common disease patterns that occupational exposures cause or aggravate, to illustrate the approach to clinical investigation and management. Other important disease types with similar occupational considerations include lung [16] and pleural neoplasms, specifically mesothelioma, a variety of interstitial and granulomatous lung diseases, as well as occupational respiratory infections, as amply demonstrated by tuberculosis for centuries, and the recent coronavirus disease 2019 [17] and the preceding pandemics [19].

Key points

- Occupational exposures can cause almost any major respiratory disease pattern, and thus pulmonologists need to consider them in the differential diagnosis.
- Occupational exposures can also aggravate or interfere with adequate symptom control of several respiratory diseases, so they need to be assessed and possibly curtailed.
- Occupational asthma should be suspected in working-age patients who have new asthma symptoms, reappearance of childhood asthma, worsening of asthma control or when an airflow obstruction without explanation is detected.
- Many interstitial lung diseases are caused by occupational exposures that may be modifiable.
- The management of respiratory diseases caused by occupational exposures can vary and an awareness of these factors is important to ensure the best possible outcome for patients.

Self-evaluation questions

1. Please select the incorrect statement about occupational COPD:
    a) Occupational COPD is for the most part indistinguishable from its non-occupational counterpart.
    b) An occupational contribution to the causation of COPD cannot be considered in smokers.
    c) Limited studies have suggested that COPD caused by an environmental factor other than tobacco is associated with relatively less emphysema, and more airway inflammation.
    d) Identification of occupational COPD can be important as it may lead to investigation of a larger at-risk group (co-workers).
    e) An occupational history is important as exposures may have not contributed to causing COPD, but may affect the ability of the worker to perform his/her usual duties.
2. In what type(s) of asthma is a latent period (*i.e.* time between beginning of exposure and beginning of symptoms) always found?
    a) Sensitiser-induced occupational asthma related to high-molecular-weight agents.
    b) Sensitiser-induced asthma related to low-molecular-weight agents.
    c) Irritant-induced occupational asthma.
    d) Work-exacerbated asthma.
3. Which of the following statement(s) is/are false?
    a) Contaminated metal working fluid is a common cause of occupational HP.
    b) A biopsy is rarely required to diagnose asbestosis.
    c) Chronic beryllium disease is characterised by a positive beryllium lymphocyte proliferation test.
    d) The latent period for occupational interstitial lung diseases is 10 years.
    e) It is likely that occupational causes of interstitial lung diseases are under-recognised.

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Suggested answers

1. b. Cigarette smoking does not exclude a diagnosis of occupational COPD, although it makes it more difficult, and in any case, exposures, if relevant and appropriate, need to be managed.
2. a and b.
3. d. The latent period is very variable.