Occupational lung diseases: from old and novel exposures to effective preventive strategies

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Occupational exposure is an important, global cause of respiratory disease. Unlike many other non-communicable lung diseases, the proximal causes of many occupational lung diseases are well understood and they should be amenable to control with use of established and effective approaches. Therefore, the risks arising from exposure to silica and asbestos are well known, as are the means of their prevention. Although the incidence of occupational lung disease has decreased in many countries, in parts of the world undergoing rapid economic transition and population growth—often with large informal and unregulated workforces—occupational exposures continue to impose a heavy burden of disease. The incidence of interstitial and malignant lung diseases remains unacceptably high because control measures are not implemented or exposures arise in novel ways. With the advent of innovative technologies, new threats are continually introduced to the workplace (eg, indium compounds and vicinal diketones). In developed countries, work-related asthma is the commonest occupational lung disease of short latency. Although generic control measures to reduce the risk of developing or exacerbating asthma are well recognised, there is still uncertainty, for example, with regards to the management of workers who develop asthma but remain in the same job. In this Review, we provide recommendations for research, surveillance, and other action for reducing the burden of occupational lung diseases.

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Introduction

Occupational lung diseases are difficult to enumerate with accuracy but are undoubtedly a substantial global health issue. With worldwide increases in production and consumption on a background of a rapidly increasing global population, the extent of the problem is greater now than ever, and no more so than in parts of the world undergoing rapid economic transformation. The International Labour Organization estimates that 2 million of the world's 2·5 billion workers die each year from occupational accidents or diseases; a third of these occupational diseases consisted of respiratory cancers and interstitial lung disease. The table summarises the findings from the Global Burden of Disease project[1] for occupational cancers, asthma, and COPD. Because many occupational lung diseases are not systematically recorded, the figures are undoubtedly underestimates of the true burden but they suggest that up to 25% of all lung cancer deaths are attributable to causes of occupational exposure.

Many workers are still confronted with substantial exposures whose risks are well known and for which there are established and effective means of control. In India, for example, an estimated 11·5 million workers are exposed to silica dust with, in some reports, extraordinarily high prevalence of silicosis and attendant tuberculosis.[2] In China, more than half a million cases of silicosis and more than 24 000 annual deaths due to silicosis were recorded between 1991 and 1995;[3] and in South Africa, the prevalence of silicosis in gold miners rose rapidly between 1975 and 2007, a trend that could be explained only in part by increasing length of employment.[4] The development of progressive massive fibrosis in coal miners is solely due to excessive inhalation of coal mine dust, therefore, such increase can only be the result of overexposures or increased toxicity caused by changes in dust composition, or both. The re-emergence of debilitating coal workers' pneumoconiosis in the USA (figure 1) shows that such cases are not confined to developing countries.[5] A particularly disheartening example of a new application of a long-recognised hazard was the high incidence of severe silicosis in Turkish men employed to sandblast denim jeans for wealthy consumers.[6]

Apart from these classic forms of hazardous exposure, reports have emerged from non-conventional or newly identified exposure sources, many of which have not yet

Key messages

- Occupational exposures remain important contributors to the global burden of respiratory disease, as economic pressures and technological developments create new hazardous exposures or hinder the control of well established exposures, or both.
- Modern occupational epidemiological research in large populations has increasingly shown quantitative relationships between exposure and disease burden, thus providing a rationale for risk reduction.
- Disease burden is subject to geographical shifts to areas of the world with large populations, accelerated economic growth, or underdeveloped regulatory environments. Even when disease mechanisms remain unclear, occupational respiratory diseases are preventable through well established approaches ranging from hazard substitution to local ventilation, while personal protection equipment should be the last resort. These preventive approaches rely on regulation and education.
- Physician awareness and diligent disease investigation, surveillance and reporting, and epidemiological research remain important in the identification and monitoring of occupational diseases, and their effective prevention.

	Number of deaths			DALYs (1000s)		
	Men	Women	Total	Men	Women	Total
Total occupational lung cancer	92 154	25 943	118 097	2087	594	2681
Asbestos	26 563	7047	33 610	521	132	653
Arsenic	1915	747	2662	45	18	63
Beryllium	114	49	163	3	1	4
Cadmium	410	145	555	10	3	13
Chromium	1361	570	1931	32	13	45
Diesel engine exhaust	18 773	3413	22 186	442	81	523
Second-hand smoke	17 189	7046	24 235	405	167	572
Nickel	6443	2702	9145	151	64	215
Polycyclic aromatic hydrocarbons	3092	993	4085	73	23	96
Silica	14 205	2072	16 277	333	49	382
Sulphuric acid	2606	239	2845	66	6	72
Asthmagens	25 364	8352	33 716	1359	661	2020
Particulate matter, gases, and fumes	171 553	47 311	218 864	6682	2460	9142
All occupational lung diseases	381 742	106 629	488 371	12 209	4272	16 481

DALYs=disability adjusted life-years. Table has been adapted from Lim and colleagues.[1]

Table: **Global estimates of deaths and DALYs due to occupational lung cancer, asthma, and COPD in 2010**

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been systematically studied. Many of these exposure sources are observed in developing countries and affect a large number of workers daily, particularly in the large informal employment sector, where regulation is lax. An area of increasing attention is the methodological challenge of an integrated view of all occupational and environmental exposures (known as exposome) in the context of increasing knowledge about genetic disease susceptibility and behavioural risk factors. The purpose of this Review is to summarise the causal perspectives of the predominant lung diseases caused by a wide range of hazards in the workplace, and to discuss possible avenues for their recognition and prevention.

Occupational respiratory diseases

Asbestos-related and silica-related respiratory diseases

Asbestos-related diseases remain some of the commonest causes of mortality and morbidity of workers exposed to occupational hazards worldwide. Asbestos, a building material used widely in low-income countries, is the most important occupational cause of respiratory tract cancers; is effectively the sole cause of malignant mesothelioma; is an important, and probably under-recognised,[7] cause of pulmonary fibrosis (asbestosis); and is sometimes the cause of debilitating pleural disease. Despite its well known toxic effects, approximately 125 million people in the world are currently exposed to asbestos at work.[8] An even larger number of people have had substantial exposure in the past and continue to be at risk of one of the several, long latency, asbestos-related respiratory diseases.

Although more than 50 countries, including those of the European Union, Australia, South Africa, and Japan, have completely banned the use of asbestos,[9] and some countries such as the USA, New Zealand, and Canada have restricted its use, asbestos continues to be mined and used in industrially developing countries (mostly in Russia, China, Brazil, and Kazakhstan), largely in the manufacture of roofing material and pipes for sanitation and irrigation and often with lax controls on exposure. However, Europeans and others born after the ban of asbestos in 2005 still continue to carry a heavy burden for the development of asbestos-related disease from the tonnes of asbestos put in place before the ban. In the USA, for example, there are some 25 million tonnes of asbestos in place from previous use although there is little continued use. There is increasing recognition of disease arising from the use before the ban.[10,11] Meanwhile, there is increasing recognition of cases arising from environmental exposure from homes in areas where industrial processes took place for many years before the ban.[12] Tackling the legacy of asbestos in the built, urban environment is a task that will probably take decades. Presumably, and depressingly, these patterns will be repeated in countries where the use of asbestos continues, although their recognition might be long delayed. Despite one cancer hospital in Mumbai identifying 32 cases of malignant mesothelioma in 1 year, India has not officially recorded any cases of the disease.

Silica, another abundant occupational hazard, has been studied for more than 100 years and, despite regulations and strategies for controlled exposure, new cases of silicosis continue to emerge, partly because of non-conventional sources of exposure. Silica is the leading cause of occupational respiratory disease worldwide, and is now recognised as a lung carcinogen.[13] Construction workers and workers engaged in building demolition or refurbishment are the largest occupational group exposed to crystalline silica. The infamous Hawk's nest incident, in which hundreds of men developed acute silicosis in the USA, highlighted the extreme hazards of rock drilling in the 1930s,[14] but that risk still exists with, for example, red rock mining in Rajasthan, India, or the building of the Washington, DC, subway system in the USA, where accelerated silicosis occurred in the 1980s. Engineered quartz conglomerates, such as caesarstone, are being used extensively in kitchen countertops and bathroom fixtures. These new materials can generate substantial concentrations of airborne crystalline silica during manufacture or installation with high risks of silicosis, silica-related autoimmune disease, pulmonary alveolar proteinosis, and other complex structural changes of the lungs (figure 2).[15–17] In low-income countries, many cases of silicosis are acute or accelerated, reflecting poorly regulated exposures; however, these more rapidly developing forms continue to be seen in wealthier countries with better developed health and safety systems.[16,18] Silicosis and silica exposure

are well known risk factors for pulmonary tuberculosis, particularly in areas of the world with high prevalence of HIV infection. The importance of controlling exposures to each of these three synergistic health hazards has been exemplified by the worrisome trends observed in South African miners.[19,20] The prevention of silica-related diseases is based on the control of exposure to inhalable dust. Although statutory occupational exposure concentrations—generally at 0·05–0·10 mg/m³—are commonly applied, they do not entirely eliminate the risk of either silicosis or silica-related lung cancer because most statutory exposure concentrations result from a compromise between disease risk and economic viability.[21] Engineering controls are claimed to be cost-effective both in economically developed and developing countries;[22] although some such measures are complex and require the expertise of experienced engineers and hygienists, simple techniques such as water suppression can be effective in reducing silica exposure.[23] The use of respiratory personal protection is suitable only for tasks of short duration for which it is difficult to devise methods of satisfactory control.

Regulations for the use of both asbestos and silica have been in place for decades. In the USA, more stringent rules are still required for silica exposure and are now under consideration by the US Government. The Canadian Government is considering banning further use of asbestos now that its mines are closed. Data collection regarding pneumoconiosis related to these exposures is problematic worldwide, but especially in low-income countries. Multidisciplinary ways forward are urgently needed globally. For example, many countries have inadequate health systems that make correct diagnosis of occupational respiratory conditions difficult. The importance of occupational history taking should be emphasised, and high-quality clinical, pathological, and radiological support might be assessed for the countries in need. Policy makers and regulators, health charities, and perhaps most importantly global health organisations, such as WHO and the International Labour Organization, have a crucial role to ensure that these diseases are, once and for all, committed to the past. This is likely to be achieved by cessation of the use of asbestos and improved control of silica exposure.

Work-related asthma

The term work-related asthma refers to patients whose disease is either caused or exacerbated by agents present in their workplace.[24] When the relationship is directly causal, the condition is termed occupational asthma. Occupational asthma can result from an allergic response to a specific workplace sensitiser (known as immunological occupational asthma) or from exposure to a toxic concentration of an irritant agent (known as irritant-induced occupational asthma or reactive airways dysfunction syndrome).[25,26] There is increasing interest in whether persistent exposure to low concentrations of respiratory irritants might also induce occupational asthma.[27] When a workplace exposure aggravates pre-existing or concomitant non-occupational asthma, the condition is termed work-exacerbated asthma.[28] Work-related asthma is among the commonest of occupational respiratory diseases reported in countries with effective surveillance schemes, but is undoubtedly under-recognised worldwide.

The distinction between occupational asthma and work-exacerbated asthma is important, both in devising effective strategies for prevention and in managing individual patients, because continued exposure in cases of occupational asthma (but not work-exacerbated asthma) is believed to worsen prognosis of the disease. Because most cases of irritant-induced occupational asthma are due to accidental exposure, primary prevention should include measures that ensure the safety of workers in

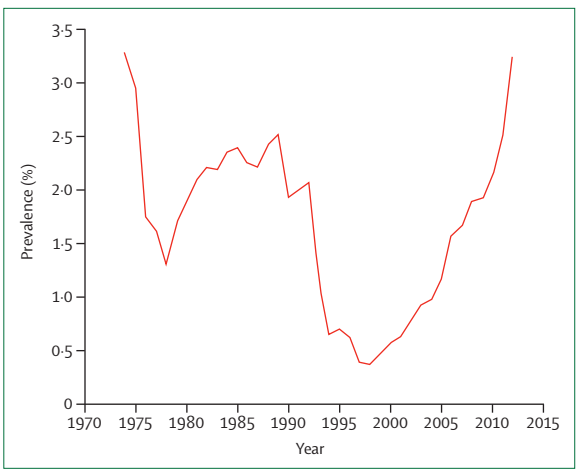

Figure 1: **Prevalence of progressive massive fibrosis in underground coal miners with 25 years or more of exposure in three states of the USA**
Reproduced from Blackley and colleagues,[5] by permission of the American Thoracic Society.

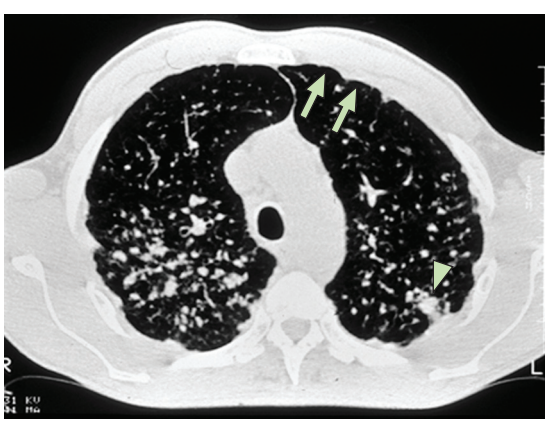

Figure 2: **CT scan showing silicosis in a man from the UK who dug tunnels for a living**
The scan shows pleural involvement (arrows) and confluence of opacity (arrow head).

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environments where major spills and accidental exposure to irritants is possible. In immunological occupational asthma, the primary objective is to prevent sensitisation to the causal agent. Specifically, this approach could entail the reduction of the occupational exposure—ie, reduction to known sensitisers, irritants, and exacerbating factors using the principles of occupational hygiene.[29]

Complete elimination of exposure is the most effective way to reduce the risk of occupational asthma; a good example is the replacement of natural rubber latex gloves with nitrile gloves.[30] Many agents, however, cannot be replaced, and in these instances exposure control is required. There is good evidence that the risk of occupational asthma increases with higher exposures to sensitising agents,[31,32] but there is considerable debate over thresholds below which risk of disease is absent because sensitisation depends on individual susceptibility.[33] Three systematic reviews[34–36] have questioned whether current data are sufficient to establish exposure avoidance as the best clinical management option. A 2014 study[37] concluded that approximately 10–15% of patients with occupational asthma deteriorate, whether or not they are moved from their place of work. Indeed, delay in diagnosis seems to be the main factor in determining prognosis,[34,37] reinforcing the need for prompt recognition of the disease.

In animal models, dermal exposure to chemical allergens increases asthma risk,[38] but the relevance of this observation to occupational asthma in people is unknown. In work-exacerbated asthma, appropriate exposure controls should be accompanied by optimal therapeutic management of the underlying asthma. Because the mechanisms that determine whether an individual's asthma will worsen in the workplace are unknown, implementation of prevention measures becomes particularly difficult.[39] An individualised approach is necessary, and, in severe cases, relocation might be the only option. The prevention of work-exacerbated asthma might be complicated by the fact that, in most countries, employers are seldom held to account and the condition receives little attention from regulators.

Secondary prevention includes early identification and appropriate management of patients with possible occupational asthma or work-exacerbated asthma. It is usually achieved through surveillance programmes of workers at risk, ensuring that health-care providers have adequate knowledge of the conditions, and education of workers about the early symptoms of disease. In individuals with work-exacerbated asthma, the disease can usually be controlled with adjustments to treatment and by minimising environmental exposures.

Coal workers' pneumoconiosis

Coal workers' pneumoconiosis is still a major concern in industrially developing countries and in some long-industrialised countries such as the USA. As with silica—an important co-exposure in some coal mines—the prevention of diseases from coal mine dust is achieved through a comprehensive programme of dust control and health surveillance.[40] There is good evidence that the risks of pneumoconiosis in coal miners are determined by their cumulative exposure to coal mine dust, and are modified according to the composition of the dust.[41] Furthermore, coal miners are also exposed to hazards other than coal dust and silica—eg, diesel exhaust fume, which is an established lung carcinogen. In 1986, a group convened by WHO tentatively recommended exposure limits of 0·5–4·0 mg/m³ for respirable coal mine dust where the proportion of free silica is less than 7%;[41] limits more than 0·5 mg/m³ should be applied only in mines where there is epidemiological evidence of a low risk of coal workers' pneumoconiosis. These values are broadly in line with those set in many but not all parts of the world. In China for example, the legal limit for anthracite coal mine dust is 4·0 mg/m³, ten times higher than that in the USA.[42] As with other mine dusts, control of exposure is achieved through engineering solutions that include enclosure of processes, ventilation, and other dust suppressing technologies. Respiratory protective equipment should be used as a primary means of protection, although there is weak evidence that the use of facemasks by coal miners can be associated, in the short term, with a higher level of lung function.[43]

Prevention of respiratory disease in coal miners is complex. An analysis of disease rates in the USA, prompted by concerns over increasing rates of coal workers' pneumoconiosis, concluded that variations in incidence were determined not only by measured dust concentrations but also by low-seam mining, an increasingly prevalent activity in some parts of the USA, and by mine size; rates of coal workers' pneumoconiosis were higher in small mines where fewer resources could be applied to health prevention than in large mines.[44]

Hypersensitivity pneumonitis

A large and bewildering variety of occupational agents have been reported as potential antigens in hypersensitivity pneumonitis, and new occupational agents continue to be identified. Naturally, primary prevention requires the application of exposure control measures even in the absence of any meaningful data for exposure–response relationships for any of the recognised agents. The identification of an index case and sentinel case generally heralds the presence of other cases in the same workplace and indicates the need for a risk assessment and survey of other employees to identify further cases.[45] Historical cohort studies suggest a decline in the rate of hypersensitivity pneumonitis in farmers after the introduction of modern farming techniques,[46] and in metal workers after improvements in the maintenance of metal working fluids, changes in engineering, and increasing awareness of disease risk.[47] In affected cases, removal from the causal agent offers the best chance of a favourable clinical outcome.

Chronic beryllium disease

Chronic beryllium disease is a granulomatous pneumoconiosis induced by a delayed hypersensitivity to beryllium, and is clinically indistinguishable from sarcoidosis. The primary diagnostic tool for testing the cell-mediated immune response is the beryllium lymphocyte proliferation test.[48] The test has been used in workplace surveillance programmes to detect both beryllium sensitisation and workers who have chronic beryllium disease without clinical manifestations.[48] Health surveillance using this test alongside industrial hygiene measures has been effective in identifying sentinel cases of beryllium sensitisation and high-risk processes,[49] although the benefit of the test to asymptomatic workers has been questioned.[50] Comprehensive programmes that combine exposure reduction with workers' education have reduced rates of beryllium sensitisation and chronic beryllium disease.[51] In workers with either beryllium sensitisation or chronic beryllium disease, avoidance of further beryllium exposure is recommended,[52] although whether this approach improves the prognosis of either condition is unknown.

Occupational COPD

The epidemiological evidence supporting the occupational contribution of exposure to a wide variety of workplace dusts, fumes, or gases to the causation of COPD continues to accrue.[53] The extent of confounding by other socioeconomic determinants of lung function, the causal contribution of smoking, and the absence of any clear relationship between exposure and risk make it difficult to translate this evidence into a preventive strategy, beyond a call to minimise irritant exposures at work and initiatives to promote smoking cessation. There are some important specific exceptions—notably exposures to coal mine dust and silica—for which the risks are clearly established and, in the case of coal mine dust at least, are independent of smoking.[54] Additionally, obliterative bronchiolitis, which is often misdiagnosed as COPD, has been described in association with the inhalation of gases, toxic fumes, or irritants such as nitrogen dioxide, chlorine gas, and mustard gas.

On the basis of its clinical features, COPD related to occupation cannot, at an individual level, be distinguished from the same disease arising from other causes. This fact complicates workplace health surveillance; the potential benefits of lung function measurements in COPD surveillance, for example, should be balanced against the risks and costs of misattributing changes in lung function that are unrelated to work.

Respiratory infections

The risk of pneumococcal infection is increased in welders and probably others with occupational exposure to metal fumes;[55] the risk could extend to other respiratory infections.[56] A small decline in mortality rates from pneumococcal disease in British welders between 1991 and 2010 might reflect improvements in exposure control,[57] but does not necessarily detract from the argument that specific vaccination should be promoted in this workforce.

Other important respiratory infections acquired at work include those with a zoonotic (eg, anthrax, Q fever, and psittacosis) or environmental (eg, Legionnaires' disease, melioidosis, and leptospirosis) origin. It is also important to recognise that several respiratory viral pandemics (eg, H5N1 influenza) began as occupational diseases or posed occupational hazards to health-care workers caring for infected individuals, or both. Of the occupational infections acquired through human transmission, tuberculosis is most prominent, particularly among health-care and prison workers. Preventive methods, such as those discussed, have been well established.

Byssinosis

The global textile and clothing industries employ more than 60 million labourers,[58] the majority working in economically developing countries. Exposure to cotton dust and endotoxins in these sectors is a major health issue with high rates of byssinosis—a progressive respiratory disease characterised by cough, shortness of breath, chest tightness, and airflow obstruction.[59] Although the first case of byssinosis was detected several centuries ago, this disease remains prevalent with up to 40% of textile industry workers affected in some surveys.[60,61]

The first legal measure against byssinosis was the Factories Act in the UK in 1937, subsequently modified by the American Conference of Governmental Industrial Hygienists in 1964, and the British Occupational Hygiene Society in 1973. In 1982, the UK Occupational Safety and Health Administration set the upper limit of dust concentration to 0·2 mg/m^3;[59] however, the dust concentrations in many factories often exceed this limit. In developing countries where industrial laws are absent or unenforced, safety measures can be recommended, including the cleaning of machines and floors by vacuum cleaners, the maintenance of humidity in spinning rooms, and the use of respiratory protection.

Other non-specific lung diseases due to novel exposures

New occupational risks—arising from new agents or new settings for established agents—continue to be recognised. An example of new settings for established agents is provided by the series of silicosis cases due to denim sandblasting.[6,62,63] These workers developed severe symptoms and impairment of lung function even after short exposure durations (average latency period ranges from 2 to 14 years).[64] Although many fabric industries have banned sandblasting, this process is still used in countries such as China, Bangladesh, and Pakistan and is not expected to be abandoned in the near future.

Exposure to nanoparticles has recently emerged as a novel occupational exposure, and several studies[65–67]

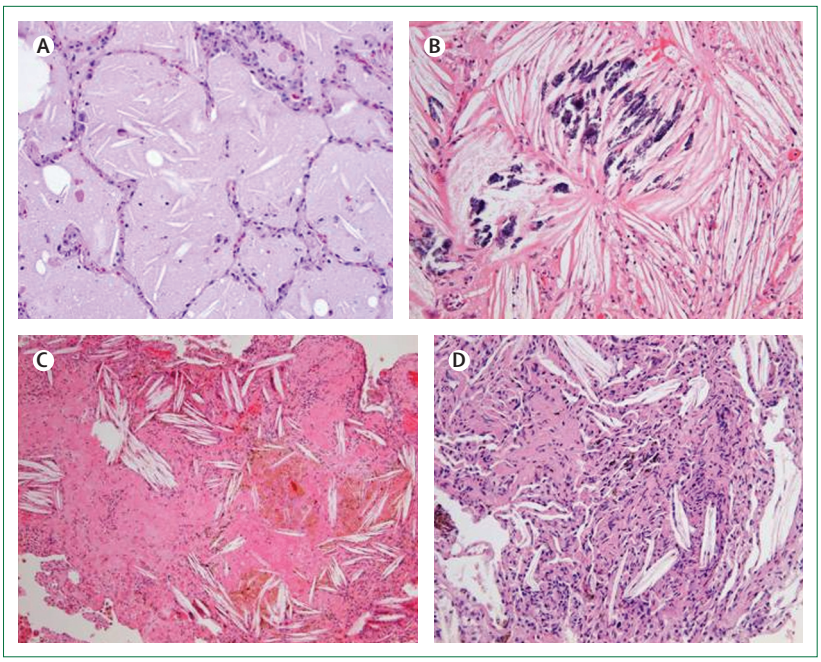

Figure 3: **Various histopathological features of indium lung disease through haematoxylin and eosin stains**
(A) Intra-alveolar exudate characteristic of alveolar proteinosis, with occasional cholesterol clefts; ×200 magnification. (B) Innumerable cholesterol clefts; ×200 magnification. (C) Intra-alveolar exudate characteristic of alveolar proteinosis, cholesterol clefts, and fibrosis; ×100 magnification. (D) Cholesterol clefts, associated multinucleated giant cells, interstitial fibrosis, and brown particles composed predominantly of indium; ×200 magnification. Reproduced from Cummings and colleagues,[89] by permission of Elsevier.

in people have concluded that inhaled nanoparticles contribute to cytotoxic reactions in the lungs. There is a growing demand for engineered nanomaterials of very small dimensions and diverse chemistry, making them strong candidates for agents of respiratory and systemic toxicity. Although studies of human health effects of engineered nanoparticles have been sparse, non-specific pulmonary inflammation with fibrotic changes and foreign body granulomas have been observed among workers occupationally exposed to polyacrylate nanoparticles.[65] Other studies[66,67] have also shown increased leukotriene concentrations in exhaled breath condensate and hypermethylation of the *DNMT1* gene in workers occupationally exposed to nanoparticles. Current approaches for risk control are limited by our rudimentary understanding of the toxic effects of these materials, the largely uncontrolled processes of their development and manufacture, and the considerable technical difficulties in measuring their airborne concentrations.

Chemical byproducts, such as volatile organic compounds generated during the combustion of petroleum products, can lead to various lung diseases. Petroleum forecourt attendants developed a restrictive type of lung disease attributed to exposure to petrol and diesel fumes in fuel refilling stations;[68] continuing exposure can result in a more mixed, obstructive or restrictive type lung disease.[69] Non-combusted liquid petroleum gas, used to refill small cigarette lighters, can be hazardous. In India, street vendors who refill gas lighters are systematically exposed to the mist of liquid petroleum gas released from the pressurised containers and readily inhaled; such exposure causes airflow limitation among these workers.[70] Diesel exhaust, a newly recognised lung carcinogen, is an unavoidable exposure for workers in many transport and mining occupations.[71]

In 2000, eight microwave popcorn workers from the US state of Missouri were diagnosed with obliterative bronchiolitis; diacetyl (2,3-butanedione), a hydrophilic volatile vicinal diketone used as a flavouring material, was identified as the culprit.[72,73] Several studies[74–76] have since supported the exposure–disease relationship between diacetyl (2,3-butanedione) and obliterative bronchiolitis. Diacetyl substitutes such as 2,3-pentanedione might also induce lung disease.[77] Similar exposures and consequent cases have been discovered in other industries such as a cereal manufacturing facility, a dry bakery mix production facility, and chocolate, potato chips, and cookie factories.[78–80] After newly introduced control measures, exposure concentrations decreased substantially as seen by the reduction of TWA (time-weighted average) diacetyl air concentrations from 57·2 to 2·24 parts per million between 2000 and 2001 in popcorn factories.[81] Newly hired workers had reduced symptoms whereas older workers reported reduced nasal, eye, and skin irritation but stable chest symptoms. Obliterative bronchiolitis has also been observed among workers involved in preparing fibreglass who were exposed to a range of chemicals including styrene.[82]

Hydraulic fracking to extract natural gas involves the insertion underground of pressurised sand, water, and other materials and could impose a serious threat to workers who are often exposed to silica, combusted byproducts of mineral oils, various other inhalable organic materials, and hydrogen sulphide, with the risk of developing a wide array of respiratory problems including asthma, COPD, silicosis, and lung cancer.[83] In a 2013 study,[84] investigators documented high concentrations of silica at fracking sites, posing a serious threat to the workers because reliance on respirators did not provide enough protection. Fracking also generates nitrogen oxides, ozone, and various other air pollutants to which nearby residents are exposed.[85] Any fracking operations require adequate risk assessments and the implementation of appropriate preventive measures.

Indium-tin oxide (ITO) has emerged as a new occupational hazard from its extensive use in the manufacture of liquid crystal display screens. The first case of ITO-associated interstitial pneumonitis was reported in 2003 in a 27-year-old Japanese worker;[86] it was followed by several case series[87–89] describing workers with interstitial lung disease or pulmonary alveolar proteinosis (figure 3).

Another emerging topic is that of occupational respiratory disease in responders to man-made disasters. The terrorist attack on Sept 11, 2001, and subsequent

rescue, recovery, and service restoration of the World Trade Center in New York City, NY, USA, created an unprecedented and unique occupational and environmental exposure that affected a large and diverse group of rescue workers and volunteers. A variety of acute and chronic respiratory illnesses have been reported in these firefighters and rescue workers, and is the subject of large-scale ongoing investigation and follow-up.[90,91] The predominant chronic lower airway disorders related to the attack have been clinically characterised as irritant-induced asthma, non-specific chronic bronchitis, chronic bronchiolitis, and aggravated pre-existent chronic airway disease.[92] In addition to these clinical characterisations, several single case reports have suggested other associated lung complications among these workers. Lung function surveillance (particularly among firefighters who most consistently had data predating Sept 11, 2001) showed an exaggerated one time expiratory flow loss (about 500 mL), followed by an average decline in subsequent years that seems to follow age-related rates (figure 4).[93] In addition to respiratory ailments, ongoing longitudinal surveillance and other studies[94] are investigating associations with systemic autoimmune diseases and other diseases, such as sarcoidosis. This disaster invited reflection on ideal control measures in similar circumstances, which pose particular challenges.

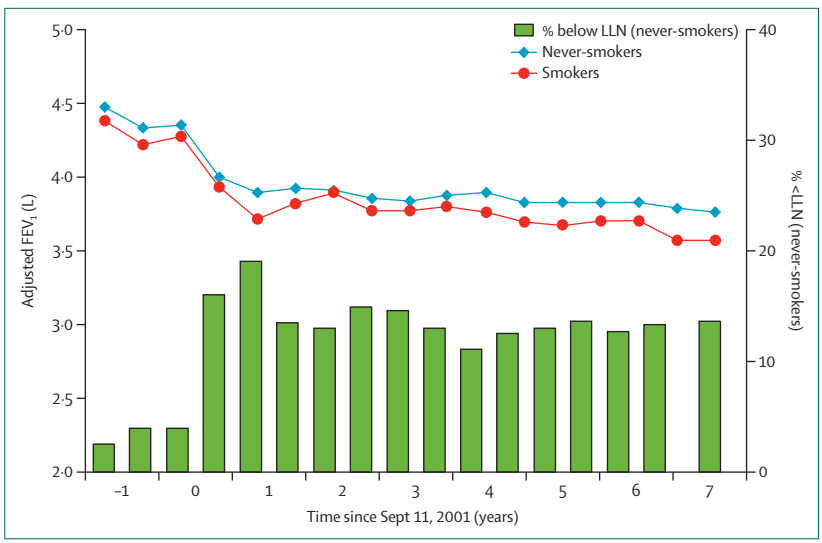

Figure 4: **Change of FEV_1 in never-smoking and continuously smoking male firefighters exposed to WTC dust for more than 7 years**
Bars represent the percentage of never-smokers at each time period that had FEV_1 below the LLN. FEV_1=forced expiratory volume in 1 s. WTC=World Trade Center. LLN=lower limit of normal. Data adapted from Aldrich and colleagues.[93]

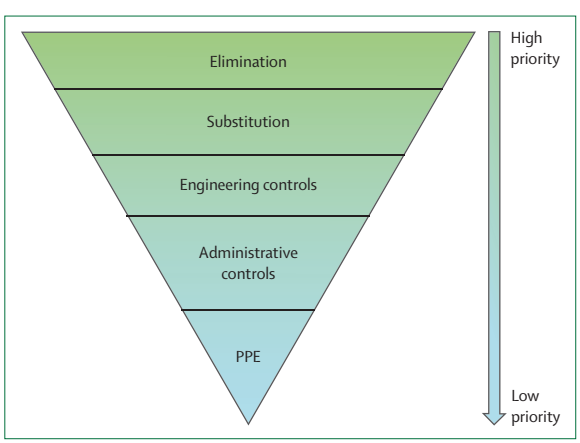

Figure 5: **The hierarchy of control used in managing hazardous exposures in the workplace**
PPE=personal protective equipment.

Principles of prevention and control

In principle, occupational lung diseases are preventable in three stages: primary prevention aims to reduce disease incidence, secondary prevention aims to reduce disease progression and severity, and tertiary prevention aims to reduce complications and consequences of the established disease. Primary prevention is desirable and usually comprises a hierarchy of controls (figure 5). Within this framework, elimination of the hazardous agent altogether is the preferred method. The replacement of asbestos in many parts of the world is an example; the use of asbestos in lagging has been largely substituted by less dangerous, although not necessarily risk-free, man-made mineral fibres such as rockwool. Industry is constantly developing new potentially hazardous agents, and evidence by analogy such as thorough analysis of quantitative structure–activity relationships,[95] although imperfect, can help to predict which novel agents could be associated with a pronounced hazard of occupational lung disease. Therefore, steps ranging from more stringent exposure control to searches for safer alternatives can be done prospectively to protect workers' health.

Frequently—as in the case of many mining and construction operations—elimination or substitution are impossible, and recourse is made to a variety of engineering controls designed to reduce the generation and inhalation of agents such as workplace dusts, vapours, gases, and fibres. These systems include methods to enclose processes and operations, or to extract their emissions away from the breathing zones of workers. In some cases, hazardous agents are reformulated to render them less inhalable, for example, the encapsulation of detergent enzymes used in the manufacture of biological detergents. The original enzyme formulations were finely powdered and readily inhalable, and their introduction was followed by high rates of occupational asthma in detergent manufacturers and subsequently in consumers. The problem was largely overcome by improved engineering controls and the use of enzymes coated in a polypropylene shell that was too large to be inhaled and largely resistant to crushing (figure 6). Engineering solutions can be accompanied by administrative controls, which include designing work schedules to reduce risks, prominent

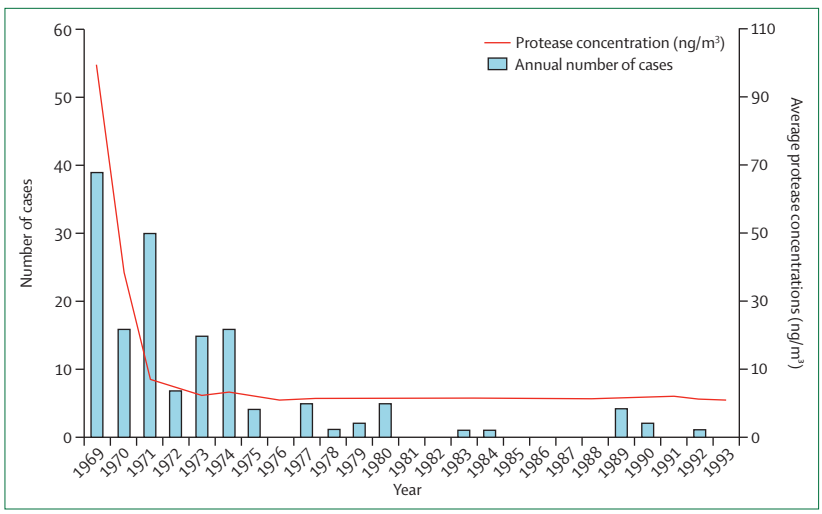

Figure 6: **Annual incidence of occupational asthma and average concentrations of protease exposure in factory air in 1969–93 in five UK detergent powder factories**
Data adapted from Cathcart and colleagues.[96]

Panel: priorities for future research and action

Public health strategies need to be better informed by epidemiological evidence of the population attributable fraction—as well as the attributable risk in specific exposures—in respect to occupational lung disease in general but especially in conditions with multiple or idiopathic causes (or both) such as chronic obstructive pulmonary disease (which is common) and idiopathic pulmonary fibrosis (which is less common but more severe). Where there is already a wealth of epidemiological evidence, such as for asbestos and silica, recommendations for exposure limits should be primarily based on principles of public health and health economic benefits. There is also a necessity to embrace modern methods of exposure and outcome measurement in occupational settings. Other considerations that are then applied to such limit setting, such as political or wider economic aspects, should be transparent and therefore open to scrutiny and debate. Lessons should be learnt from past mistakes by ensuring a research, regulation, and surveillance resource and infrastructure to pre-empt risks from novel technologies and exposures. Moreover, we need political and professional action to raise the profile of these diseases whose perceived importance has diminished in light of environmental and business agendas.

labelling of hazardous materials, and education and training of workers in safe practices. Contrary to popular belief, the use of personal protective equipment, such as various forms of respirator, occupies the lowest tier of the hierarchy and is reserved for situations in which other methods have failed adequately to control airborne exposures. Long-term wearing of respiratory personal protective equipment might be intolerable and difficult to enforce.

In some settings, pre-employment examinations are used to identify individuals believed to be at increased risk of developing occupational lung disease. For instance, identification of individuals who are atopic and those with pre-existing non-specific bronchial hyperresponsiveness has been proposed for occupational asthma prevention.[97] These traits, however, are highly prevalent and confer only a relatively small increase in risk; their use in selection of employees is highly inefficient even if it were morally justifiable. The evidence base was assessed as being generally of very poor quality by a 2016 Cochrane review[98] of pre-employment screening for the reduction or prevention of occupational injury, disease, and sickness absence, or to inform risk mitigation; additionally, the review did not provide any conclusive support for the use of pre-employment screening.

In places where exposure cannot be eliminated below a critical threshold and there is a residual risk of occupational disease—or when the exposure–risk relationship is poorly understood—health surveillance for early signs of disease might be appropriate. In well managed industries, health surveillance is organised alongside ongoing hazard surveillance, and failures in either surveillance systems are cross checked in a root cause analysis. In this way, surveillance becomes an important component of a preventive strategy. A successful, integrated programme of primary and secondary prevention of diisocyanates asthma in Ontario, Canada, for example, resulted in an eventual reduction in both the number and severity of new cases of occupational asthma.[99]

Workplace surveillance is generally organised and affected by an occupational health service, which is either internal or provided through an external contractor. The internal model, which is increasingly rare, more readily integrates surveillance with other elements of a primary preventive strategy. This integration might be more difficult when the occupational health service is provided externally. In an analysis of surveillance provided to the UK motor vehicle repair industry by an external contractor, Mackie[100] showed a clear example of how such a system is inadequate. Unfortunately, surveillance is often done simply to satisfy a regulatory requirement and merely becomes an instrument for identifying and replacing employees who develop occupational disease.

Legislative approaches

The law can contribute in several ways to reducing the risk of occupational lung disease, and these lend themselves to varying degrees of application and evaluation. At one end of the spectrum lie legislative measures banning the use of specific agents, such as the use of asbestos either absolutely or in more specific limited contexts. However, an absolute legal ban might not eliminate a risk completely, although it should reduce exposure substantially. Thus in the case of asbestos, its persistence in the fabric of buildings or in industrial plants can be associated with continuing

Search strategy and selection criteria

We searched PubMed and identified references that were published from Jan 1, 2000, to Sept 12, 2016, concentrating on publications from recent years. We used the search terms "lung", "respiratory", "prevention", and "control" with "occupational exposure" and, to identify publications relating to novel exposures, "artificial stone dust", "LPG", "hydraulic fracking", "diesel exhaust", "food flavouring agents", "indium-tin oxide", "World Trade Center dust exposure", "occupational asthma", and "occupational COPD". We gave particular attention to original research but also consulted reviews and commentaries. We considered papers published in English and those in other languages provided that their abstracts were available in English.

exposure especially when disturbed during building refurbishment. At the other end of the spectrum lies a less drastic but perhaps the most commonly adopted legal measure which is the establishment and enforcement of occupational exposure limits of various kinds. These limits are seldom set with reference to health risks alone, and often incorporate a consideration of what is technically and economically feasible. The benefit of these measures is often inferred from the counterfactual—ie, by studying exposure–response relationships before the determination of the limit, and hence estimating what benefit might arise after its application. Some notable examples of evidence[101] of their value exist, although other studies have reported mixed results.[102] In many countries, obligations exist for employers to undertake risk assessments, take steps to control risks as far as reasonably practicable, and educate workers in matters ranging from hazard and risk to the provision and use of personal protective equipment.

Legislative provisions for payment of damages and compensation can also contribute to secondary prevention, although alas not in the workers awarded the money. These legal awards can impose financial, reputational, and market pressure on employers, manufacturers, and their insurers to reduce risks.

Conclusion

Ironically, the exposure of many millions of workers to serious occupational hazards garners disproportionately less attention compared with lifestyle risks such as tobacco, salt, sugar, and alcohol overuse. The proximate causes of occupational diseases, after all, are known and in most cases well understood, and workplaces are, in principle, environments where it is relatively easy to exert control of occupational hazards. In practice, several competing interests, some more malign than others, make effective prevention more difficult than it might otherwise be. Better dissemination and awareness is needed among all those concerned from politicians to employers, workers, and physicians regarding the wealth of knowledge of occupational health risks and the means for their prevention (panel). Additionally, on-going efforts are needed to monitor trends in recognised occupational diseases, evaluate interventions, and develop methods for identifying and predicting new hazards.

Contributors

PC, REdlH, and SM conceived the design and drafted the manuscript along with RA and XM. All authors contributed to the literature search and preparation of this manuscript.

Declaration of interests

ALF testifies regularly in courts throughout the USA and has testified or provided written reports in several international settings (Canada, Australia, and India) about workers injured by asbestos. ALF advocates the banning of asbestos in various nations through scientific reports and lectures. All other authors declare no competing interests.

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