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Other respiratory diseases review

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Occupation has been recognised as a cause of respiratory disease for many centuries, and this link is a constantly evolving field as workplaces and exposures change, and new manufacturing processes and materials are introduced. With enhanced communication and reporting schemes, it has become easier to identify new causes and outbreaks of disease. Whilst asthma and COPD remain common in both the general population and the workplace, it is essential to ensure that developments in the less common diseases are not overlooked. This is especially so as whilst these rarer diseases are featured in the literature, they do not occur often in reporting schemes, suggesting that they may be under-recognised clinically. The aim of this report is to review the current evidence base in relation to the less well known occupational lung disorders, specifically to identify any new or emerging causes of occupational respiratory disease.

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EXECUTIVE SUMMARY

Objectives

Occupation has been recognised as a cause of respiratory disease for many centuries, and this link is a constantly evolving field as workplaces and exposures change, and new manufacturing processes and materials are introduced. With enhanced communication and reporting schemes, it has become easier to identify new causes and outbreaks of disease. Whilst asthma and COPD remain common in both the general population and the workplace, it is essential to ensure that developments in the less common diseases are not overlooked. This is especially so as whilst these rarer diseases are featured in the literature, they do not occur often in reporting schemes, suggesting that they may be under-recognised clinically. The aim of this report is to review the current evidence base in relation to the less well known occupational lung disorders, specifically to identify any new or emerging causes of occupational respiratory disease.

Main Findings

The broad search terms used for this review identified more than 9000 articles in the last four years, although a proportion of these were irrelevant or duplicated in different databases. This indicates that there is a substantial recent evidence base in relation to occupational lung disease. This review has identified various emerging issues related to established, or perhaps more traditional occupational lung diseases, but has also highlighted potentially new occupational respiratory diseases. The findings have been divided into specific disease categories;

Silica; exposure to crystalline silica in the workplace is still commonplace, and these exposures are potentially able to cause a range of respiratory (and other) diseases. It is important to focus not just on the risk of exposure causing chronic silicosis, but to be aware that acute and accelerated silicosis still occurs.

Recent guidance has been produced relating to health surveillance for silica exposed workers. For example, ACOEM have formulated such guidance designed to assist in the development of appropriate surveillance programmes.

Similarly, recent modelling data published from the Netherlands suggests an approach to health surveillance for silica-exposed workers that may allow a careful and evidence based judgement to be made concerning the need for chest X-ray examination.

Endotoxin/Organic dusts; it is evident that endotoxin and organic dust exposure continue to be associated with respiratory ill health. The highest exposures to endotoxin are generally seen with animal breeding, handling and during cleaning activities. The levels are variable with the type of work undertaken, although there are only a few working facilities with continuous exposures likely to exceed 50 EU/m^3.

However, the health effects associated with endotoxin exposure are often non-specific in nature, and may be associated with reduced FEV_1. Again, these effects are often difficult to interpret, as endotoxin levels in the workplace are variable according to work task.

Whilst a “safe” or recommended level of workplace endotoxin exposure may be adopted in the future, in the interim vigilance appears sensible from all those responsible for the health of exposed workers.

Metal fume fever/Pneumonia; whilst there does seem to be an accepted increase in susceptibility to pneumonia in welders, the mechanism behind this remains unclear, and the size of this potential problem is not accurately known. Further research would seem appropriate to identify the strength of this association and its potential mechanism.

Pulmonary fibrosis; the potential contribution of workplace exposures to the development of pulmonary fibrosis continues to attract research attention. Potential identified causes for this type of host response are varied, and include hard metal lung disease (cobalt and tungsten carbide in particular) and wood dusts.

Often, cases of pulmonary fibrosis present to health care professionals many years after potential occupational exposures have occurred. The long latency nature of these conditions makes it more difficult for practicing respiratory health care workers to identify cases where occupation may be relevant, let alone confirm this in an individual case. Interestingly, recent data have shown that scanning electron microscopy applied to induced sputum (or lung biopsy) can potentially assist in differentiating cause in this condition.

EAA; extrinsic allergic alveolitis is a traditional, established occupational lung disease, although new issues are emerging in the UK. A series of outbreaks of EAA has occurred in workers exposed to contaminated metal working fluids, and although recent literature addresses certain relevant issues, the evidence base requires further development in order to improve understanding of the natural history and prevention of this illness.

Other novel lung diseases characterised as EAA are recently reported, ranging from mushroom workers related EAA (with potential health effects also identified for complementary therapy workers) to lung diseases associated with both glass fibre-reinforced plastic (GRP) and chicory.

Bronchiolitis obliterans (OB); whilst ordinarily regarded as an uncommon disease, occupational causes of OB are identified. The most recent publication data relate to food flavouring inhalation and in particular the link between diacetyl exposure and the subsequent development of OB. The relationship between exposure levels and OB development is not fully understood, and at present there are no known safe exposure limits for diacetyl. Until this issue is resolved, it seems sensible that workplaces using diacetyl adopt a cautious approach. For example, it has been recently suggested that workplaces should institute mandatory respiratory protection for all exposed workers.

The likely impact of this condition in the UK is not known, as the current extent of diacetyl usage is not known, although a survey and site visits by HSL/HSE are ongoing to address this specific issue. The results of this exercise may benchmark the size of the at risk worker population, and identify further research needs.

Pneumoconioses; other than the typical established pneumoconioses, dental workers have recently been highlighted as a potential risk group, as new materials are constantly being introduced into this type of work practice. Recent work is also

suggests a potential genetic susceptibility to the development of various pneumoconioses.

Chronic beryllium disease; the development of lymphocyte proliferation testing to identify subclinical beryllium disease has recently revolutionised this field. However, it is evident from this review (and a more detailed review of health surveillance needs for beryllium exposed workers recently carried out at HSL) that there remain uncertainties about the best use of this test. Evidence is continually being produced in this area, and in particular in relation to the best application and clinical interpretation of the BeLPT test.

High particulate load; both health and organisational related issues have emerged from the evidence published in the aftermath of the collapse of the twin towers of the World Trade Centre. In terms of health issues, affected workers (mostly emergency workers) suffered from a combination of rhino sinusitis, persistent cough, airways dysfunction syndrome (or acute irritant-induced asthma), COPD, pulmonary fibrosis, bronchiolitis obliterans, and cancers of the lung and pleura. In addition, a sarcoid like illness has been described.

It was also suggested that the lessons learned from such responses to disaster should guide future similar responses, particularly in regard to environmental controls and effective respiratory protection for emergency workers during the first days of harmful exposure.

Other; other important emerging areas identified within the review related to the health risks associated with refractory ceramic fibres, and the rapidly expanding area of nanotechnology.

1 INTRODUCTION

Occupation has been recognised to cause respiratory disease for many centuries, and as workplaces and exposures have changed, so have the diseases. As new manufacturing processes are developed and new materials introduced, different patterns of disease can emerge. Also, with enhanced communication and access to medical literature, coupled with reporting schemes, it has become easier to identify particular outbreaks of disease.

As an example of the global burden of occupational disease, an assessment has been made of worldwide morbidity and mortality due to exposures to selected occupational hazards using the methodology of the Comparative Risk Assessment (CRA) project of the World Health Organization (WHO). These risk factors were responsible for 37% of back pain, 16% of hearing loss, 13% of chronic obstructive pulmonary disease (COPD), 11% of asthma, 8% of injuries, 9% of lung cancer, 2% of leukaemia, and about 100% of pneumoconioses and mesothelioma. In total this resulted in the loss of about 24 million years of healthy life and caused 850,000 deaths in the year 2000 (1, 2).

For the same time period, looking specifically at workers exposed to airborne particulates and dusts using workforce data and the CAREX (CARcinogen EXposure) database, there were an estimated 386,000 deaths (asthma: 38,000; COPD: 318,000; pneumoconioses: 30,000) and nearly 6.6 million disability adjusted life years (DALYS) (asthma: 1,621,000; COPD: 3,733,000, pneumoconioses: 1,288,000) due to exposure to occupational airborne particulates (3).

In the UK, the SWORD (Surveillance of Work-related and Occupational Respiratory Disease) reporting system estimates the number of occupational cases of respiratory disease each year through a network of physicians. Whilst the majority of cases reported reflect asthma and asbestos related diseases, many other differing types of reports are still seen, including rarer occupational respiratory disorders such as extrinsic allergic alveolitis.

Whilst the range of occupational lung diseases seen in the UK is diverse, and whilst asthma and COPD remain common in both the general population and at work, it is essential to ensure that developments in and emergence of less common diseases are not overlooked. This is especially important, as whilst these rarer diseases are discussed in the scientific literature, they do not occur often in reporting schemes, suggesting that they may be under-recognised clinically.

The contents of this review, therefore, report findings relating to recent research relevant to occupational lung diseases other than asthma and COPD.

2 AIMS

The aim of this report is to review the current evidence base in relation to the less well known occupational lung disorders, in an attempt to identify any new causes or emerging relevant issues.

Diseases specifically included in the remit of this work, and consequently reviewed in detail, are; obliterative bronchiolitis, extrinsic allergic alveolitis (also termed hypersensitivity pneumonitis), endotoxin related lung disease, chronic beryllium disease and diseases related to metal fume exposure.

A priori, asthma, COPD, eosinophilic bronchitis [the focus of a recent HSL report – Review of Chronic Cough (4)], and cancer have been excluded from the remit of this work, as have isolated industrial accidents involving potentially harmful inhalation, and occupational infections contracted primarily by health care workers.

3 METHODS

A matrix of key words and phrases (shown in Appendix 1) was devised for searching the major health related databases. A compromise was sought in order to be as broad reaching as possible, whilst limiting the number of abstracts for review to a realistic number.

Key words used for search terms were devised by the project team and also reviewed by an independent international expert (Professor Paul Blanc, University of San Francisco), to ensure that no significant search strategies were excluded.

A Medline search was performed by HSL and then several different databases were searched by the HSE infocentre (shown in Appendix 2). The combination used was based on the National Institute for Clinical Excellence guidelines, the Scottish Intercollegiate Guidelines Network recommendations and also following discussion with the HSE info centre. In addition to formal database searching, grey literature was assessed using an internet search engine.

Abstracts from relevant scientific occupational sessions at the main respiratory meetings were also searched; from the ATS (American Thoracic Society), BTS (British Thoracic Society) and ERS (European Respiratory Society), between 2005 and 2008.

Finally, the Group of Occupational Respiratory Disease Specialists (GORDS) group in the UK were asked to comment on potentially emerging occupational respiratory diseases, and relevant comments have been incorporated into this work (www.hsl.gov.uk/cwh/gords.html).

In general, all identified articles that referred to occupation playing a causative role in respiratory disease were considered for assessment, and all relevant abstracts were entered into Endnote software (to facilitate organisation of the literature). Due to the broad nature of the search, and the range of databases reviewed, duplication occurred. Where recent comprehensive reviews have been conducted in an area, those were reviewed and cited first, and other references used to provide an update where appropriate.

As the scope of this work was to comment on new and emerging occupational lung diseases, the literature search was confined to the period from January 2005 to current, although a degree of flexibility was adopted. For example, if an established disease (with good previous systematic review evidence available) was thought to have emerging issues, articles before 2005 were assessed and cited where appropriate.

Full articles in languages other than English were assessed only by using the English written abstract.

4 RESULTS

The Medline search identified 7802 articles, although due to the broad scope of the search terms many articles were of no relevance. The search by HSE infocentre identified 1244 articles. In total 447 were considered worthy of further review i.e. related to a review article, an update or an emerging theme and entered into Endnote software.

Several reports mentioned non-specific irritant respiratory and eye symptoms that were also excluded, as were articles relating to non-specific FEV_1 and lung function changes, where it was felt these could be attributed to COPD or asthma.

In general, several review articles were summarised for each section, with cross-checking of references where required, and then up to date evidence from more recent publications was added. Diseases felt to be generally of relevance to developing countries rather than the UK were also excluded, e.g. sisal workers in Tanzania..

The following broad categories of occupational respiratory diseases emerged; (i) silica related problems, (ii) pulmonary alveolar proteinosis, (iii) endotoxin/organic dust related disease, (iv) metal fume fever/pneumonia, (v) hard metal lung disease, (vi) pulmonary fibrosis, (vii) extrinsic allergic alveolitis (EAA), (viii) bronchiolitis obliterans, (ix) pneumoconiosis, (x) chronic beryllium disease, (xi) world trade centre collapse as a model for high particulate exposure, (xii) asbestos/ceramic fibres, (xiii) nanotechnology and carbon nanotubes, (xiv) miscellaneous.

These categories will be dealt with below in turn, allowing for the fact that there was some element of overlap between categories. In order to contextualise the comments relating to recent literature, each section will be prefixed by a short summary of each disease type.

4.1 SILICA EXPOSURE

Whilst silicosis is an established and well-documented occupational respiratory disease, it is included within the scope of this review as various issues related to the risk associated with exposure to silica emerged in the reviewed literature. This section, therefore, does not represent a full appraisal of the literature related to silica exposure, and the associated risks, but highlights the recent relevant literature.

By way of background, silica is composed of silicon and oxygen (SiO_2) and usually occurs in a crystalline form, the most common type being quartz. Quartz is abundant in soil and rocks, and consequently many workers are at risk of potential exposure to silica dust or respirable crystalline silica (5) (Appendix 3).

Silica exposure is still commonplace globally, with estimates of at least 1.7 million workers in the USA being potentially exposed, with more than 100,000 in high-risk occupations (6), and approximately 3.6% of workers being overexposed to airborne silica above the OSHA-calculated Personal Exposure Limit (7). Worldwide, many millions of workers are exposed to crystalline silica, particularly in low and middle income countries such as India, China and Brazil (8).

An estimate from the UK of exposure from 1990 - 1993 suggested 600,000 workers, of which three quarters worked in the construction industry (9), were currently exposed. An Italian review looking from 2000 - 2004 suggested the number of workers potentially at high risk of silica exposure was 28,712, the most important sectors being construction, mining and quarrying, metal working, and manufacturing of non-metallic products (10).

Silica exposure is classically associated with the development of silicosis, a fibrotic lung condition characterised initially by small nodule formation, and subsequently with the potential to develop more coalescent fibrosis and scarring. This condition is caused by the inhalation of large quantities of crystalline silica, normally over a prolonged period of time (11, 12).

There are three main types of silicosis, acute, accelerated, or chronic disease (11, 12).

Acute silicosis, also known as alveolar lipoproteinosis, normally develops after short-term high level exposure to silica. This is ordinarily after exposure to a fine dust with high silica content. The alveolar space fills with an eosinophilic lipoproteinaceous material, causing immediate shortness of breath. The condition has a significant mortality rate.

Chronic silicosis is a potentially progressive lung disease with a long latent period, typically occurring after 10 to 20 years of exposure and characterized by fibrotic nodules. These are initially found within the hilar lymph nodes, although as the disease progresses, they also develop within the pulmonary parenchyma and tend to predominate early in the upper lobes of each lung. These can eventually affect the visceral pleura overlying the lung surface.

With increasing silica exposure, the typical silicotic nodules coalesce, leading to progressive massive fibrosis (PMF), in a similar manner to that seen in coal worker's pneumoconiosis.

The accelerated form of this disease occurs typically following between three and ten years of exposure, and is associated with similar, but not identical, pathological changes (8, 13).

The rate of disease progression potentially depends upon the duration and intensity of exposure, the total amount of crystalline silica retained in lung tissue, particle size and individual susceptibility to develop fibrosis for a given fixed exposure (8, 12).

Silicosis can progress following complete cessation of exposure, and may even present for the first time after exposure has ceased (8).

Clinically, chronic silicosis is not normally associated with any respiratory symptoms (such as shortness of breath) until progression to PMF occurs, when exertional breathlessness becomes a central feature. Hence chronic silicosis may often present as an incidental radiological finding, with chest x-ray nodules, for which the International Labour Organisation (ILO) has developed radiological reading guidelines (14).

As there are no effective treatments for any of the typical forms of silicosis (8), and acute silicosis is often fatal over only a few years (15), prevention is absolutely key.

This should ideally be affected by early detection through a suitable surveillance programme of exposed workers. Whilst the exact and detailed content of health surveillance programmes will be subject to local context, modelling analysis of recent data with symptom questionnaires, physical examination, chest x-rays and spirometry in silica exposed workers identified potential methods for health surveillance that may reduce the requirement for radiological examination (16).

Specifically, this study identified various factors that were associated with radiological abnormalities consistent with silicosis, and were baled together to define a predictive model to assess whether workers should undergo x-ray examination. 1291 Dutch natural stone and construction workers with potentially high quartz dust exposure were evaluated using a combination of questionnaire, spirometry and chest radiograph. A subsequent multivariable logistic regression model was developed using the ILO profusion category of small nodules >1/1 as the reference standard. Being aged over 40 years, being a current smoker, working in a high risk job, working 15 years or longer in the construction industry, ''feeling unhealthy'' and having a reduced FEV_1 were independent predictors in the diagnostic model for the presence of silicosis. Furthermore, this study noted that by using a cut off in the questionnaire derived score (with a high negative predictive value) the occupational physician could efficiently detect a large proportion of workers with a low probability of having pneumoconiosis and then exclude them from unnecessary x-ray investigations.

Relating to this need for regular health surveillance of silica exposed workers, the American College of Occupational and Environmental Medicine (ACOEM) have recently formulated useful guidance. Whilst the full report is freely available via its associated web link (26), an extract of this report is reproduced verbatim below (in italics).

Recommended Surveillance Program

A. Target Population

The pool of workers to be included consists of those individuals exposed to levels of crystalline silica that place them at risk for silicosis. Since the exact exposure-response relationship remains unclear, it is appropriate to make the inclusion criteria for this program conservative. Thus, inclusion of any workers exposed to a crystalline silica concentration > 0.05 mg/m^3 is recommended. This level is both the National Institute for Occupational Safety and Health's (NIOSH's) Recommended Exposure Limit (REL) and essentially one half of the current OSHA PEL for pure crystalline silica.

B. Components of the Evaluation

As specified in the OSHA Special Emphasis Program, components of the surveillance evaluation should include the following:

1. *Occupational and medical history (questionnaire)*
2. *Physical examination*
3. *Purified protein derivative (PPD) tuberculin skin test*
4. *Chest radiography*
5. *Spirometry*

The history can be obtained using a directed questionnaire focusing on characterization of risk and identification of symptoms related to silicosis, tuberculosis, obstructive pulmonary disease, connective tissue disease, and lung cancer. Important items regarding risk characterization include identification of likely onset and duration of silica exposure, intensity of silica exposure, description of all job titles associated with silica exposure, a review of types of respirators used and the quality of the respiratory protection program, and presence of other risk factors associated with the various silica-related adverse health effects (e.g., smoking, non-occupational risk factors for tuberculosis, etc.). If possible, exposure data from the worker should be supplemented by exposure data obtained by an industrial hygienist. Whenever possible, questions relating to symptoms should be validated questions and in as complete and concise a format as possible.

In addition to risk characterization, this questionnaire can be useful for the early detection of chronic obstructive pulmonary disease, active mycobacterial disease, and connective tissue disorders. The OSHA Asbestos Questionnaire could be used as a model for a silica questionnaire, but it would need significant revision and supplementation to make it useful to identify those risks and symptoms of particular concern for silica. For example, Question 22 of the Initial Questionnaire and Question 12 of the Periodic Questionnaire would need to be expanded to address silica-exposing work. Questions aimed at identifying extra-pulmonary aspects of silica exposure would need to be added.

The physical examination should be focused on the general condition and respiratory status of the worker. Depending on the questionnaire responses, additional parts of the examination, such as the musculoskeletal, can be added.

The baseline tuberculin skin test reactivity status of all silica-exposed workers should be established at job entry, by intradermal administration of purified protein derivative (PPD), using the Mantoux technique. The two-step technique for PPD skin test administration and interpretation of results (positive = > 10 mm induration) should be followed for this baseline determination, following current Centers for Disease Control and Prevention (CDC) guidelines for the detection and evaluation of tuberculosis. Periodic monitoring of PPD skin test reactivity is useful for the detection of both latent tuberculosis infection and active tuberculosis.

The chest radiograph has long been a cornerstone in the diagnosis of silicosis, and radiographic manifestations of this disease often precede the development of symptoms and clinically significant pulmonary function loss. It is felt that detection of simple silicosis, followed by removal from silica exposure, can decrease the risk of progression of the disease. Chest radiography is also useful for monitoring the progression of silicosis, as well as for identifying the appearance of treatable complications, such as mycobacterial disease. Consequently, a chest radiograph should be considered a fundamental tool in the medical surveillance of silica-exposed workers. It is essential that interpretations be based on films meeting high-quality standards. The interpretation should be performed by a physician knowledgeable about the radiographic manifestations of occupational lung diseases, and in accordance with the 2000 International Labor Office (ILO) International Classification of Radiographs and Pneumoconioses.

Although clinically significant decrements in spirometry are not typically observed in the early stages of simple silicosis, previous studies have shown that the prevalence of obstructive ventilatory defects is higher in silica-exposed workers, even in the absence of silicosis and after accounting for smoking. Therefore, spirometry is useful in this worker population. Spirometry should be performed in accordance with accepted standards for quality assurance and interpretation. ACOEM has authored position statements on Spirometry in the Occupational Setting and Evaluating Pulmonary Function Change over Time in the Occupational Setting to provide additional practical guidance in these areas. Forced vital capacity (FVC), forced expiratory volume in one second (FEV 1) and FEV 1/FVC ratio should be evaluated cross-sectionally relative to predicted values. FVC and FEV 1 can also be evaluated longitudinally, to determine whether a worker's change over time is excessive. Although measurement of diffusing capacity has been suggested for inclusion in medical surveillance, at present it is not practical because of limited availability near the worksite, cost, and inter-laboratory variability in results and reference ranges. Several other tests were considered as part of this surveillance evaluation but not included because of lack of value as screening tools. A high-resolution chest CT scan may be more sensitive in identifying the parenchymal opacities of silicosis than a plain chest radiograph. However, the increased radiation dose, as well as the added expense and time involved, do not justify its use as a surveillance tool. In addition, the standard method of diagnosing silicosis is by history and chest X-ray.

Serum immunological markers for connective tissue diseases, such as ANA and rheumatoid factor, have not been included, because of their low predictive value for these diseases in the absence of compatible symptoms or signs. More recent techniques such as studies of silica-induced DNA changes in lymphocytes, in serum and urine levels of neopterin, and in the release of reactive oxygen and nitrogen species, cytokines and specific transforming factors by alveolar macrophages have been studied only in small groups or in silica-exposed animal models thus far. Their place in medical surveillance remains to be established. The feasibility of using induced sputum rather than bronchoalveolar lavage to assess the effects of silica exposure has been reported by some investigators. The role of urinary screening to detect renal injury is yet to be determined. The cost-effectiveness of these new approaches also needs to be investigated.

Aggressive techniques to look for lung cancer, such as chest CT, cytology, and bronchoscopy, are not indicated in medical surveillance for silica-related diseases, although they may play a role in individual clinical evaluations, when guided by history, physical examination, and radiographic abnormalities.

C. Frequency of Surveillance Evaluations

1. Baseline Evaluation

An evaluation should be done on each worker, when he/she accepts a position involving exposure to a work site where silica is present and the concentration is either unknown or above 0.05 mg/m^3. Such an evaluation would both establish baseline lung function and TB skin status plus identify the presence of pre-existing lung disease. All findings should be discussed and explained to the worker promptly. Copies of pertinent results should be provided to the worker. Information provided to the employer should be limited to whether the worker is

medically fit to perform the job and whether work restrictions are indicated. Such an evaluation may be combined with an employer's standard post-offer evaluation. Ideally, the same provider would perform the baseline evaluation and follow-up surveillance evaluations to maximize continuity in the surveillance program. The ACOEM longitudinal spirometry statement, Evaluating Pulmonary Function Change over Time in the Occupational Setting, addresses the pitfalls to be avoided when serial measurements of spirometry are considered.

2. *Follow-up Evaluations*

   The initial follow-up examination should be performed within 12 months since acute silicosis and tuberculosis can occur in a relatively short period of time. The one-year follow-up evaluation allows the health care providers performing the medical surveillance evaluations to estimate the actual exposure the worker faces at a time when intervention might have significant benefits. It also provides an opportunity to reinforce to the worker the importance of preventive measures. Repeating the chest radiograph after one year should be at the discretion of the health care provider, but under most circumstances would not be needed unless local circumstances so indicate.

For workers with exposures < 0.05 mg/m^3, the frequency of follow-up can be reduced, based on questionnaire responses and documented exposure data. For workers with < 10 years of work experience with silica, frequency of follow-up evaluation should be every three years. For workers with > 10 years work experience with silica, follow-up evaluation should be every two years since workers with longer duration of exposure and time from initial exposure are at higher risk for silica-related abnormalities. Those workers who are more heavily exposed may warrant closer medical supervision. When a worker changes from one job involving exposure to silica to another, the health care provider should re-evaluate the need for an additional medical surveillance evaluation for that worker based on the new job tasks and level of silica exposure.

If a worker is suspected as having silicosis during the surveillance evaluation, he/she should be immediately removed from further exposure and promptly referred to a physician knowledgeable in the diagnosis and management of silicosis. If the diagnosis is confirmed, further management should be provided promptly. The management plan will necessarily depend on the specifics of each case.

3. *Exit Evaluation*

   A worker leaving a job with potential for silica exposure should be offered an exit medical evaluation. The components of the evaluation should be based on the results of the previous evaluations, time from initial exposure and duration and level of silica exposure, and change in symptoms from previous evaluations. For those workers with > 10 years of work experience with silica, a complete medical surveillance evaluation is indicated if the last evaluation occurred more than 12 months previously. If the worker is moving into a different job working with silica, the exit evaluation can also serve as the baseline evaluation for the next job.

Steps should also be taken to minimize smoking as there is a potential additive effect (5) and to watch for and treat tuberculosis (TB) and lung cancer both of which have increased prevalence in silica exposed workers (8).

Future developments in the field of silicosis are likely to include biomarkers to detect either high exposure to silica or susceptibility to silicosis, and further studies are planned in this area (17). There is also now increasing evidence that immunological and molecular factors play a role in the development of silicosis, and this is being investigated in order to potentially develop new therapeutic targets and strategies (18, 19).

Mortality from silicosis has decreased over recent decades, from approximately 1000 deaths per year in the 1920s and 1930s, to between 200 and 300 deaths per year in the US in the late 1990s, of whom approximately 30 were of working age (13, 20), although worldwide estimates are much higher (approximately 8,800 per year (3)). Due to the hazards of inhaling silica, many countries have enforced exposure limits. In the UK, for example, the Control of Substances Hazardous to Health Regulations (COSHH) 2002 have assigned respirable crystalline silica a maximum exposure limit of 0.1 mg/m^3 expressed as an eight hour time weighted average. Any worker exposed to levels greater than this should undergo periodic health surveillance, including a combination of a symptom questionnaire, lung function testing and a chest radiograph (21, 22).

In the US, the National Institute for Occupational Safety and Health (NIOSH) has recommended an exposure limit of half this value at 0.05 mg/m^3 (23), and the American Conference of Governmental Industrial Hygienists (ACGIH) reduced their limit in 2006 to 0.025 mg/m^3 (24), these reductions occurring due to concern that the previous level was not protective enough both for silicosis and lung cancer (25). With this in mind, the ACOEM recommend health surveillance for anyone exposed to more than 0.05 mg/m^3 of respirable crystalline silica (26).

Despite the well-documented harm caused by silica exposure, case reports of silicosis are ongoing, often in new occupational environments. For example, 18 people were recently diagnosed with *accelerated silicosis* after sandblasting and dyeing at Turkish denim factories, two of whom died from the disease (27-29). Workers in the jewellery trade, where chalk molds containing a high percentage of silica are used in casting, have been found to have silicosis on chest x-ray and CT scanning (30). A study of 624 South African gold-miners who had recently left employment found a 24.6% prevalence rate of silicosis (31).

Silica exposure and silicosis are also associated with other diseases, in particular COPD, chronic bronchitis, tuberculosis, lung cancer, usual interstitial pneumonia type pulmonary fibrosis (UIP) and pleural effects such as pleural effusions and pleural thickening. These diseases can overlap, and so cause a spectrum of symptoms. There are also suggestions that silica causes renal disease, arthritis and other auto-immune diseases (13, 25, 32-34).

The relationship between silica and COPD has been the subject of debate and two recent review articles (35, 36) have highlighted new developments in this area. Epidemiological and pathological studies in smoking and non-smoking silica exposed workers have suggested that exposure to silica dust can be associated with airway obstruction in the absence of radiological silicosis. The studies have also demonstrated

an exposure-response relationship between silica dust exposure and airway obstruction and that silica dust concentrations between 0.1 and 0.2 mg/m^3 are sufficient to cause these changes. Smoking also likely potentiates this effect. The underlying pathological mechanism is not certain, but is postulated to occur either by inflammation in the alveoli and peripheral airways causing airways obstruction and emphysema, or by epithelial cell injury causing localised airway centred fibrosis. If silicosis is present, the annual decline in FEV_1 is increased, and in the absence of silicosis probably takes at least 20 years to develop disabling loss of lung function (35).

Similarly, silicatosis is a type of pneumoconiosis that is clinically and pathologically similar to silicosis, but usually less severe and less fibrotic (37). It is caused by silicates, which contain different elements than just pure silica and oxygen, and include mica, feldspar, talc and kaolin. A new occupation recently reported as a cause of silicatosis, is that of a carpet installer in the USA who had spent 15 years in this profession being exposed to talc (37).

From a disease prevention perspective, silica has the potential to cause a wide range of diseases, and is so universal that many workers are potentially exposed in a range of occupations. Exposure limits in some countries have been reduced in recent years, amid concerns that previous levels were not protective, and currently the COSHH limit in the UK is four times that recommended by some other institutions.

Whilst the long term harmful respiratory and other health effects of silica are not in doubt, attention needs to be given to emerging data on appropriate exposure levels. HSL will shortly be commencing work in the field of silica health surveillance.

4.2 PULMONARY ALVEOLAR PROTEINOSIS (PAP)

This rare condition was first described in 1958 (38) and is characterized by alveolar accumulation of a lipoproteinaceous material, whilst normal lung architecture is maintained (39). It has been estimated in an Israeli study to affect 0.37/100,000 people with an annual incidence of 0.36/million per year (40).

The main clinical features of this condition are shortness of breath (dyspnoea) and cough, with fever, weight loss, chest pain and haemoptysis also reported, especially if secondary infection is present (39, 41). A review of 410 published cases of PAP in 2002 found that more than 90% of acquired cases of PAP (rather than the congenital form) are thought to be idiopathic (41), although there have been some previously suggested occupational causes including aluminium dust (42), titanium (43), cement dust (44), and silica (45, 46).

Blanc and Golden (in a case report and review article in 1992) question the distinction between idiopathic and occupational PAP (15). Quoting one of the first review series of cases of PAP from 1969 (47), which involved 139 patients, at least 10 of these cases had been exposed to silica, and about half of these cases had been exposed to a range of dusts and fumes including asbestos, cadmium, wood dusts and tin.

In the last four years, the majority of published literature relating to PAP constitutes case reports and review articles. New developments are discussed, and focus around a postulated autoimmune element to this condition and new treatments (such as granulocyte/macrophage colony-stimulating factor). There have been two recent case reports related to occupational exposure, both relating again to silica (46, 48).

Whilst PAP has potentially been linked to occupation, the condition is extremely uncommon (a so-called orphan lung disease within the BTS scheme (49)). Such rarity inevitably makes the use of epidemiological information difficult to further assist identifying causes.

4.3 ENDOTOXINS/ORGANIC DUSTS

Endotoxins form part of the outer membrane of Gram negative bacteria, and are composed of proteins, lipids, and lipopolysaccharides (50, 51). Their toxicity is thought to relate to the lipid component, whereas the lipopolysaccharides are responsible for most of their biological properties (52). Consequently, the term lipopolysaccharide and endotoxin are often used interchangeably (53, 54). There is also speculation that peptidoglycans could play a contributing role in the inflammatory response seen from endotoxins (55). ß-glucans, usually found in the cell walls of fungi have also been implicated in causing adverse respiratory effects (55).

Exposure to endotoxin can occur in domestic environments, particularly from pets, carpets, damp areas and air conditioning, as well as in specific occupational exposures, mainly in environments with high exposure to organic dusts, such as during agricultural work.

Endotoxin exposure has been described in the following workplaces; agriculture work including poultry and pig work, dairy barns, animal feed, horse training, textile work, paper mills, wood work, cotton work, waste collection and processing, cigarette factories, fibreglass production, the potato industry, breweries, dental surgeries, sugar beet slicing, bio fuel plants, during plant breeding, and metal working. Water in ventilation or humidifier equipment may also be an occupational source of exposure, and associated health effects may contribute to “sick building syndrome” (51, 52, 56-65).

Whilst the term endotoxin was first used by Pfeiffer in the 19th Century (55), the first report potentially linking endotoxin with occupational disease was in 1942, in cotton workers (66). Since then, many airway challenges (human and animal based) have been conducted with exposure to pure endotoxin, both inhaled and intravenous, and have shown a consistent inflammatory response (55).

The evidence supports endotoxin exposure at work being linked to a variety of reported work related symptoms, such as fever, cough, shortness of breath, wheezing and chest tightness, headache, upper airways irritation, and acute airway obstruction and inflammation (52). It is not surprising, therefore, that organic dusts have been shown to cause a spectrum of respiratory disease, including asthma, allergy, EAA and organic dust toxic syndrome (ODTS) or toxic pneumonitis (55).

In addition to the harmful effects noted, certain epidemiological studies have also shown some protective effects from environmental endotoxin exposure with regard to atopic asthma and allergy development in early childhood (67, 68), the so-called “hygiene hypothesis”, and reduced risk of lung cancer in textile workers, agricultural workers, dairy farmers and machinists (69, 70). There may also be a genetic component to the individual susceptibility to endotoxin (71, 72).

Due to their nature and composition, endotoxins are widespread, although workplaces vary considerably in terms of levels encountered. A substantial historic evidence base identifies endotoxin as a cause of non-specific respiratory symptoms and reduced FEV_1, rather than causing a specific disease entity. A review article by Liebers in 2006 (52), has summarized 45 such studies dating back to 1984.

Certain more specific examples of risks associated with endotoxin exposure are dealt with below.

Pig farmers - Studies from Northern Europe have suggested that endotoxin exposure is related to symptoms and reduced lung function in pig farmers. Animal studies in rats have shown that multiple exposures to endotoxin-containing swine barn air induce airways hyper-responsiveness, and increase lung inflammation (73).

Poultry Workers - Previous studies have shown that poultry workers have an increased incidence of respiratory symptoms and reduced lung function. Recent data in this field comparing 42 non-smoking poultry workers and 40 controls not exposed to organic dusts showed significantly higher airway responsiveness among the workers compared to controls. The poultry workers had a higher prevalence of toxic pneumonitis, airways inflammation and chronic bronchitis compared to controls. Endotoxin levels in the poultry buildings exceeded suggested threshold value for airways inflammation (74). Another study comparing floor-housed poultry operations to caged facilities found that endotoxin concentration was a significant predictor of chronic phlegm production for all poultry workers, and that caged facilities had greater endotoxin concentration in conjunction with greater respiratory symptoms (75).

Food workers - A review of 150 workers occupationally exposed to herb dust, consisting of farmers and workers from the herb processing industry found that long-term exposure to dust from herbs caused work-related respiratory symptoms and lung function decline (76). A separate field study was performed at a food processing facility where workers were exposed to various fruit and vegetable dusts, during the grinding, sieving, mixing and packaging of freeze-dried or air-dried products. Whilst not specifically measuring endotoxins, the results did suggest an increased amount of general dust exposure (77).

Grain workers –The effects of grain dust on respiratory health are summarised in a recent review by Margaret Becklake (78), noting that grain can refer to wheat, barley, rye, oats or corn and that the dust consists of the grain itself, the associated epicarp hairs and the germ. As well as the plant itself, contamination can occur from weeds, fungi, rodents, as well as added chemicals. Workers can be exposed on farms, at grain elevators and in mills.

Grain dust has been shown in many studies since the 1970s to show a decline in lung function in exposed workers, an increase in respiratory symptoms, and also “grain fever” (a “toxic dust syndrome” like reaction), the cause of which may involve endotoxin exposure (52, 78). Dust control mechanisms have been effective in reducing respiratory symptoms (79).

A recent outbreak of work related health problems resembling organic dust toxic syndrome in workers of a grass seed laboratory prompted an assessment of exposure levels in the agricultural seed processing industry. Endotoxin concentrations in personal samples were high (mean 1800 EU/m^3) (endotoxin units, EU) in comparison

to the recommended health based endotoxin exposure limit of 50 EU/m^3. Indeed, this limit was exceeded in almost all personal samples and microbial infestation was found in most seed samples. The authors concluded that occupational exposure to inhalable agricultural seed dust can induce inflammatory responses, and is a potential cause of ODTS (80).

Cotton workers – Several recent studies have assessed the relationship between exposure to cotton dust (and endotoxins) and various health end points. Endotoxin, rather than dust itself, for example, has been implicated to cause a decrease in FEV_1 (55, 81). A prospective study of 157 newly exposed cotton workers was performed using a questionnaire, spirometry, and skin tests, and included personal dust sampling based endotoxin measurements. Smoking, endotoxin, and dust concentrations were found to be risk factors for all work-related symptoms. Acute airway responses were witnessed after immediate exposure. Across first shift and across week falls in FEV_1 reduced in size during the course of the study. This demonstrated that respiratory symptoms and acute airway responses develop early following first exposure, and a tolerance effect may develop in workers who have continued exposure (82). Cotton dust has also been implicated in acute and chronic byssinosis, COPD and pulmonary fibrosis (81, 83, 84).

Waste Workers – Waste collectors, workers and compost workers are exposed to a wide variety of respiratory irritants and sensitizers, such as moulds, bacteria, endotoxins, ß-glucan, mites, rodent allergens, and exposure to these agents has been considered a risk factor for respiratory symptoms (85). A study of 218 compost workers and 66 controls revealed high concentrations of thermo-tolerant/thermophilic actinomycetes and filamentous fungi in the bio-aerosols at composting sites. The compost workers reported a significantly higher prevalence of eye and upper airways irritation than control subjects, and had evidence of decreased spirometry (86). A study of 468 wastewater treatment workers from 67 sewage treatment plants with personal endotoxin exposure measurements found symptoms appeared to be more prevalent in workers exposed to endotoxin levels higher than 50 EU/m^3. A dose-response relationship was found for "lower respiratory and skin symptoms" and "flu-like and systemic symptoms" (87). A further study to investigate the relationship between exposure to hydrogen sulphide and endotoxin during specific jobs among wastewater treatment plant workers and water treatment plant workers found that statistically higher odds ratios of respiratory, eye and skin irritation, neurology, and gastrointestinal symptoms were shown among wastewater workers compared with water treatment plant workers (88).

Office work/Sick building syndrome - A population study of 1016 adults in South Finland identified that exposure to paper dust and fumes from printers and photocopiers was associated with upper respiratory and skin symptoms, breathlessness, tonsillitis and middle ear infections. Exposure to carbonless copy paper increased the risk of eye symptoms, chronic bronchitis and breathlessness and was also associated with increased occurrence of sinus and middle ear infections and diarrhoea (89). Office workers are also known to be at risk of humidifier fever, and recent evidence supports this (90). Similarly, recent evidence suggests that printer toner dust may implicated in adverse respiratory symptoms (91).

A recent investigation of workers in a water damaged building found significantly increased odds for lower respiratory symptoms, throat irritation, and rash/itchy skin with the highest fungal exposure group. Non-linear relationships were seen for many of

these symptoms and endotoxin levels in floor dust (92). Two recent literature reviews found evidence of an association between exposure to indoor damp and mould (and thereby fungi and endotoxin) and symptoms of wheeze and cough in asthmatic individuals, and a possible link with asthma development and breathlessness. The studies reviewed included the home as the source of exposure, but also damp workplaces, mainly office buildings and schools (93, 94).

Currently in the UK there are no formal exposure limits set for endotoxin exposure (95), although guidance levels have been suggested in some other countries. For example, The Dutch Expert Committee on Occupational Standards of the National Health Council has proposed a guidance threshold value of 50 EU/m3 over an 8-hour period for endotoxin (96). In the conclusion to his recent review article, Liebers states “The implementation of a general health-based threshold limit value for endotoxins at workplaces seems to be not suitable at the moment. In agricultural workplaces, for example, compliance with such threshold limit values is technically impossible. In addition, it has to be considered that bioaerosols are very heterogeneous and differ from area to area. Therefore, if any control value is established it should be specific for industrial sectors, graded procedures of protection should be adopted”.

In addition to endotoxin level values, a recent publication also highlights problems with measurement techniques for endotoxin. The main assay method for endotoxin is the Limulus Amoebocyte Lysate (LAL) test, a highly sensitive assay based on the activation of a clotting enzyme present in the lysate of lymph of the Limulus polyphemus (horseshoe crab). In general, the LAL-test is the current internationally accepted method for measuring airborne endotoxin levels (being accepted by the US Food and Drug Administration in 1980); other tests to measure endotoxin are possible, but are still being evaluated at the present time. Whilst the LAL is the best test at present, problems such as standardization between labs, technical issues and costs may limit appropriate measurement in the workplace (52).

A further difficulty relates to the fact that inhaled organic dusts, as well as containing endotoxin, also contain other microbial cell wall agents and potentially bacteria and fungi, so assessing the true effects of each component is even more difficult.

4.4 METAL FUME FEVER/PNEUMONIA

Metal fume fever is a benign, self-limiting occupational respiratory disease that results from the inhalation of fine metal particles. Whilst the exact mechanism for this condition is not known, the primary cause is thought to relate to inhalation of zinc oxide fumes produced when zinc-coated steel or zinc-containing alloys (e.g. brass) are heated to high temperatures. A variety of other names for this condition have been used previously, including copper fever, brazier’s disease, welder’s ague, foundry fever, brass chills, and spelter shakes (97, 98).

Welders are the most commonly affected workers, with up to 20% of welders having experienced this disease by the age of 30 (97). Clinically, metal fume fever presents (like any of the other known inhalation fevers) with fever, muscles aches and pains (myalgia), headache, nausea, dry cough, chest tightness and breathlessness. Physical examination will often reveal fever, and crackles or wheeze on chest auscultation.

Laboratory tests may show an increased white cell count (leucocytosis), raised inflammatory markers and hypoxaemia. In general radiology and lung function testing are normal, although can occasionally show changes consistent with pneumonitis (99).

The clinical management of this condition is supportive, with removal from the exposure, and oxygen, fluids, rest and bronchodilation as required. In general there are not thought to be any longer term sequelae from repeated exposures, in contrast, for example, to cadmium fume exposure, which is associated with chronic lung disease (100, 101). Some workers can experience worsening symptoms with subsequent re-exposure to the offending causative exposure, for example on returning to work after a weekend off. This effect has been termed Monday morning fever.

Occasionally metal fume fever can present in an atypical fashion, and be associated with more serious health endpoints. For example, a recent case report is described of a 25-year-old male welder presenting with aseptic meningitis, pericarditis, pleuritis and pneumonitis, attributed to a systemic inflammatory response causing a multi-organ serositis (102).

Similarly, recent evidence supports a variety of differing potential health endpoints from a single type of welding process. Bridge welding, causing manganese exposure was recently shown to be associated with neurological, neuropsychological and pulmonary adverse health effects (103).

Further evidence has emerged recently relating to metal fume exposure and an increase in the risk of developing pneumonia. A UK study identified a population of 650,000 men aged between 20 and 64 in the West Midlands region from November 1996 until May 1999 (104). Pneumonia was found to be associated with reported occupational exposure to metal fume in the previous year (adjusted odds ratio 1.6), but not in time periods prior to this. The risks for pneumonia were highest for the lobar type, and for recent exposure to ferrous fumes (odds ratio 2.3). This association was not specific to any one particular microorganism as a documented cause of pneumonia.

To add to these findings, the same group went on to measure various markers of host defence function in welders and non-welders. Induced sputum and blood samples were collected from 27 welders with regular long-term exposure to ferrous metal fume and 31 unexposed matched controls, and analysed for a variety of inflammatory markers. The data suggests that chronic exposure to metal fume decreases the responsiveness to inhaled particulate matter, although the mechanism behind this finding remains unclear, and the authors suggest that further targeted research is needed (105).

Various other research outputs relating to welding and metal fume include animal data to support stainless-steel fumes causing impaired immune responses to bacterial infections (106), and human data to support the production of inflammatory reactions in the lung, such as cryptogenic organizing pneumonia or interstitial pneumonias (107), (108).

4.5 HARD METAL LUNG DISEASE

Hard metal lung disease is an interstitial lung disease (pulmonary fibrosis) usually associated with the inhalation of cemented tungsten carbide dust, either in the manufacture or use of high-speed drill or saw tips. In addition to tungsten carbide,

these tools usually contain cobalt, and a variety of other metals including tantalum, titanium, nickel, niobium and chromium.

The condition is rare and was first described in Germany in the 1950s. Typically, the exposure causes lung disease with a typical histological pattern of giant cell interstitial pneumonia (109-113). Debate remains about the exact aetiology, as whilst there is a strong association between this condition and exposure to tungsten carbide and cobalt, cases are reported with no obvious exposure to these materials (114).

There is also a potential hypersensitivity component to this disease (115), and hard metal has also been reported to cause a diffuse panbronchiolitis in a single Japanese worker exposed to tungsten and cobalt compounds (116).

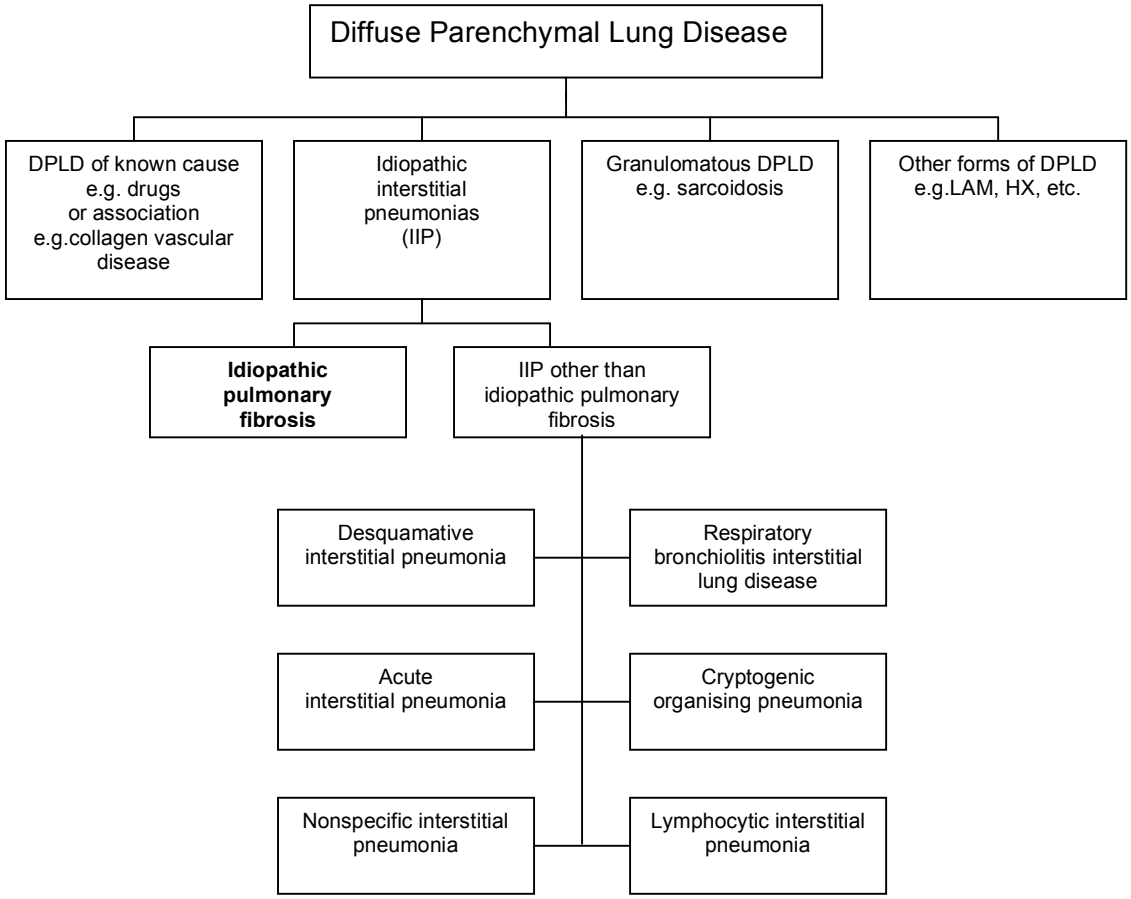
4.6 PULMONARY FIBROSIS/DIFFUSE PARENCHYMAL LUNG DISEASE

The area of fibrotic lung disease is complex, and changing constantly in terms of its classification. This fact makes the task of reviewing the appropriate occupationally relevant literature challenging (117-119). Nevertheless, there are some important recent data relating to pulmonary fibrosis, and its potential relationship to work.

Traditionally, lung fibrosis referred to an irreversible and progressive scarring process of the lungs, and was normally termed either cryptogenic fibrosing alveolitis (CFA) or idiopathic pulmonary fibrosis (IPF).

More recently however, the term diffuse parenchymal lung disease, using a more pathologically based classification, has been proposed and generally accepted by Europe and the USA (117, 118, 120). In this new system, idiopathic pulmonary fibrosis refers to a specific histological pattern of “usual interstitial pneumonia”.

Classification of Diffuse Parenchymal Lung disease ATS/ERS consensus statement 2001. [Ref. (118)]



Additionally, and to add further to the complexity, various other respiratory conditions (some work related and some not so), such as extrinsic allergic alveolitis and sarcoidosis, can progress to pulmonary fibrosis in their own right, and subsequently appear indistinguishable from idiopathic (or unknown cause) forms of this disease.

In this section, recent evidence relating to pulmonary fibrosis in the occupational context will be reviewed, allowing for some inevitable degree of content overlap between this and other sections of this report.

Recently derived UK data from a general practice population estimate that the 12-month period prevalence of IPF is between 15–18/100,000 person-years, and the median survival from diagnosis of the condition is approximately 3 years. These data suggest that there are at least 2000 new cases of IPF each year in England and Wales. General population-based data in the UK (and the USA) suggest a median age of presentation at 70 years, and it is uncommon below the age of 50 (117).

The aetiology of IPF remains largely unknown, although viruses such as Epstein–Barr, cytomegalovirus and influenza have been implicated in the pathogenesis (121). Observational studies have found potential occupational risk factors that include farming, hairdressing, painting, stone cutting, and exposure to metal dust, textile dust and bird, vegetable and animal dust (122-125). A recent Swedish case control study

using a detailed postal questionnaire studied 140 patients with idiopathic pulmonary fibrosis against 757 control subjects. They found after adjusting for age, sex and smoking an increased risk in men for IPF to birch dust (odds ratio, OR 2.7) and hardwood dust (OR 2.7) (126). Exposure to metal dust was significantly associated with an increased risk of IPF (OR = 9.55) in a Japanese study (127).

The National Institute for Occupational Safety and Health (NIOSH) recently reviewed its mortality surveillance system for occupational respiratory diseases, 1999 to 2003 (121). In this period, there were 84,010 deaths from IPF, the majority of whom were in white males aged over 75, correlating with other estimates of demographic. The authors found statistically significant increases in risk estimates for IPF in those who had been potentially exposed to wood and metal dust, in particular those working in three different environments; (i) wood building and mobile homes, (ii) metal mining and (iii) fabricated structural metal products. These findings are consistent with the previously observed elevated risk for those exposed to metal and wood dust (the former noting a linear relationship), from Hubbard *et al* (128, 129).

Recent case reports considered by the ATS proceedings (123) have also identified IPF as being associated with various occupations that involve dust or fume exposure, including diamond polishing, industrial car cleaning, dairy work, welding, gold extraction, and dental work.

Various specific examples of possible IPF occupational risk are now dealt with individually.

An unusual potential emerging occupational cause of pulmonary fibrosis has been identified recently, related to indium tin oxide (ITO) exposure. This material is typically constituted by 90% indium oxide and 10% tin oxide, and used in a variety of electronic applications, most notably in liquid crystal displays (LCD). Hamaguchi *et al* (130) performed a cross-sectional survey at two ITO manufacturing and two ITO recycling plants in Japan. Ninety-three indium-exposed and 93 non-exposed workers were studied, with symptom questionnaires, spirometry, high resolution thoracic CT scanning (HRCT), and serum immunochemistry. Whilst an increase in interstitial lung disease was not identified in the exposed group, a statistically significant increase in two proteins, KL-6 and SP- D was found in those exposed to the ITO. These findings are of interest as KL-6 is a high molecular weight glyco-protein, previously identified to be elevated in idiopathic pulmonary fibrosis (131-133), and SP-D is a surfactant protein, which although not as sensitive or specific as KL-6 has still been shown to be elevated in pulmonary fibrosis (134). The authors concluded that exposure to hardly soluble indium dust represents a risk for interstitial lung damage, and this conclusion is further supported by two recent case reports (135, 136), a cross sectional study, and several animal studies (137).

A case report has recently described IPF in an Israeli bus driver, whose driving cabin was insulated with glass-rock wool (vitreous) fibre (138). The roof of the cabin was in a poor state of repair, and the authors postulate that glass-rock wool may be an aetiological agent, as fibres were found in both bronchiolar lavage and trans bronchial biopsy. The authors felt it necessary to publish the report as a previous review of the respiratory health effects of man-made vitreous (mineral) fibres had not found any definitive evidence of harm (139).

Traditionally in Turkey, the most used cooking utensils are made from copper coated in tin oxide by a “tinner”. This process involves treating tin with sulphuric acid and aluminium oxide, before heating the base copper and rubbing it with a tin bar, potentially releasing tin oxide vapours. A study of 24 tinners with HRCT found that 11 had diffuse parenchymal lung disease, of which nine had respiratory bronchiolitis interstitial lung disease. In addition, one had evidence of usual interstitial pneumonia, and one had non-specific interstitial pneumonia (140). The authors concluded that due to the various properties of the substances involved the risk to respiratory health from this process is higher than that seen for work with tin alone (associated with the relatively benign pneumoconiosis, stannosis).

Paraffin fumes have also recently been described as possibly leading to interstitial pulmonary fibrosis, even many years after exposure has ceased (141, 142). These papers also suggest that an acute inflammatory phase following exposure may be important in the pathogenesis.

Animal studies have also suggested an association between high radiation lung dose from plutonium exposure and the subsequent development of fibrosis. A recent retrospective study of nuclear weapons workers found that plutonium exposure may cause lung fibrosis in humans at absorbed lung doses above 10 Sv (143).

Airway-centred interstitial fibrosis is a relatively new and rare disease that has only recently been described in the literature. It is characterized by bronchial fibrosis and localized interstitial pulmonary fibrosis centred on the airway. This condition has been potentially associated with the inhalation of a variety of substances, both environmental and occupational. A recent case report links this disease to the inhalation of cleaning products (144).

Finally, anthracofibrosis is an emerging potentially fibrotic disease, defined as bronchial stenosis with black (anthracotic) pigmentation of the overlying mucosa. This condition has previously been largely attributed to tuberculosis. Three patients were reported in a case series of anthracofibrosis without mycobacterial infection, although they had previous occupational exposure to mixed dusts, including silica, suggesting that mixed mineral dust was the most probable cause (145).

In the same year, seven cases from a UK hospital were described, of whom only one had evidence of TB, but six of whom had worked with a variety of dusts. The authors suggested that anthracofibrosis is an exaggerated endobronchial form of the more common condition, anthracosis, seen in coal miners and other mineral dust exposed workers. These seven patients had presented over a 13 year period, and displayed little disease progression, suggesting that this is a relatively benign condition (146). This remains a rare disease with only 100 reported cases in the literature.

4.7 EXTRINSIC ALLERGIC ALVEOLITIS

Extrinsic allergic alveolitis (EAA, also termed hypersensitivity pneumonitis, HP) is a non-IgE immunologically mediated lung disease caused by the inhalation of and subsequent sensitisation to various antigens. Acute, sub acute and chronic forms of this condition are described. It is assumed (the natural history of this condition is poorly understood) that if exposure continues to the offending antigen once the disease has initiated, alveolitis can progress to permanent pulmonary fibrosis and scarring. The

comments in this section of the report must therefore also be read in conjunction with those relating to lung fibrosis.

The clinical features of this condition depend upon the stage of the disease, but include fever, cough, breathlessness, and weight loss. An associated antibody response to the putative antigen can sometimes be demonstrated in workers with EAA, but such antibodies can also be seen in antigen-exposed individuals without the disease.

A definitive diagnosis of EAA is often difficult, as no one single diagnostic test is conclusive, and hence the process of diagnosis usually relies on clinical, radiological, physiological and immunological investigations.

The mainstay of treatment is removal from the offending antigen once a diagnosis is confirmed, though in some cases systemic corticosteroids are used to quicken resolution of the inflammatory process. Failure to remove affected workers at this time point may lead to progressive disease.

A vast array of potential causes of EAA are described in the historic literature, varying from environmental to occupational in origin, and include bacteria, fungi, animal proteins, plants and chemicals (122, 147).

As EAA is not an emerging or “new” occupational respiratory disease, the recent literature consequently focuses on review series, and new potential causes of this condition, often in the form of case reports. Certain examples are given below relating to recent literature.

Mushroom workers lung – Mushroom workers are already considered a high risk population for developing EAA, and recent data focuses on exotic mushroom varieties that can cause this condition (148). In 2007, a case report from Australia described EAA in two people who had been employed for several years in the spawning shed of a mushroom farm. Their disease resolved on removal from exposure without the need for corticosteroid treatment (149). Furthermore, a Japanese case report described a 72-year-old Shiitake mushroom grower, with over fifty years exposure, who was diagnosed with chronic EAA. The subsequent literature review identified that five patients with chronic EAA caused by Shiitake mushrooms had been reported in Japan (150). Twenty two people working with Bunashimeji mushrooms in Japan have also been diagnosed with EAA (151, 152), as have workers with Enoki mushrooms (153, 154). Recent reports have also suggested complementary health practitioners may be at risk from developing EAA in the handling of exotic mushrooms in the course of their work (155).

Metal working fluid – exposure to contaminated metal working fluid (MWF) has been responsible for workplace outbreaks of EAA in the USA over the last 15 years and more recently also in the UK.

A US based case report describes a machine operator in an automotive factory with a lung biopsy compatible with EAA, and an illness pattern traceable to the work environment. There was clinical improvement on removal from exposure to metalworking fluids, although respiratory symptoms recurred following subsequent re-exposure. A detailed workplace investigation following this sentinel case showed that five of six large reservoirs of metalworking fluids grew *Mycobacterium chelonae* (or *Mycobacterium immunogenum*), an organism previously speculated to cause outbreaks of EAA in car manufacturing plants. This organism has also been shown to

cause EAA like pathological changes in mice (156). The employer, metalworking fluid supplier, workers union, and the National Institute for Occupational Safety and Health were notified of this event and since then, no further cases have been documented in this workplace (157).

In the UK, various recent work has contributed to the evidence base. A single case of EAA likely to be due to metal working fluid exposure led to a workplace investigation using symptom questionnaires, spirometry, serology, and air and MWF sampling. Despite visible 'fungal' contamination of MWF, airborne fungi were detectable in only one sample, whereas the MWF cultured *Eurotium sp., Fusarium sp.* and *Pseudomonas sp*. Precipitating IgG antibodies to *Pseudomonas sp*. were identified in four of the eleven people investigated, and to an extract of the MWF in three, suggesting this as the cause of the outbreak (158).

EAA due to MWF has recently been studied in the US, where it is estimated over 1.2 million workers are involved in machine finishing, machine tooling, and other metalworking operations. Cases of EAA caused by MWF were identified through the Occupational Disease surveillance system in Michigan, and from referrals to the Division of Occupational and Environmental Medicine at Michigan State University. Each subject received a clinical examination, an occupational history, lung function testing, radiography, and in some cases lung biopsy. Seven cases of suspected EAA were identified in 2003-2004 from three factories making car parts in Michigan which were then subject to environmental sampling with air monitoring and microbial sampling results. Each plant used semi-synthetic MWFs. As a result of the investigation the plants conducted a MWF management program including biocide additions. Two of these factories had recently changed their MWF before the cases arose, and Mycobacteria were found in fluid from these two sites. The authors concluded that EAA due to MWF is under-recognized by health professionals, and that current surveillance systems are inadequate to provide a true estimate of the incidence. Additionally, EAA was found in environments with exposures well below the Occupational Safety and Health Administration (OSHA) permissible exposure limit for MWF, and in one case associated with exposures well below the National Institute of Occupational Safety and Health (NIOSH) recommended exposure limit (159). However, despite the findings of atypical *Mycobacterium* in contaminated MWF, a causative link is not proven and more recently doubt has been cast over this association as a potential cause (164).

Outbreaks of contaminated MWFs have also occurred in Europe, the largest of which affected workers in a Midlands car engine-manufacturing plant. These workers were exposed to MWF that cooled, lubricated and cleaned machines used to craft car parts. Subsequent analysis of the fluid revealed *Acinetobacter* and *Ochrobactrum*, and precipitins to *Acinetobacter* were detected in serum of seven of 11 workers tested, with precipitins to *Ochrobactrum* detected in three (160).

Attempts have been made in recent years to improve the composition of MWFs to reduce these outbreaks, but cases and outbreaks are ongoing (161).

In addition to EAA, contaminated MWF exposure has also been associated with the development of occupational asthma (OA), in addition to rarer occupational respiratory disorders. For example, whilst EAA and OA were described relatively commonly during a recent UK outbreak of respiratory ill health in a car manufacturing plant, lipoid pneumonia, chronic bronchitis, bronchopulmonary aspergillosis and UIP variant

pulmonary fibrosis were seen, some of which have been described in previous outbreaks (162, 163).

This is an area of current interest for respiratory research in many countries, as despite recent work the exact cause remains unclear, but limited challenge data and precipitin studies suggest it relates to used rather than pristine MWF. This is also the subject of an independent piece of work being carried out by HSL for HSE (164).

Farmer's lung – Data from 50,000 farmers and spouses from the Agricultural Health Study found that approximately 2% of farmers and 0.2% of spouses reported physician-diagnosed farmer's lung during their lifetime. Assessment of current and lifetime exposure histories identified that handling silage, high pesticide exposure events and ever use of organochlorine and carbamate pesticides were associated with farmer's lung in mutually-adjusted models. In particular, the insecticides DDT, lindane, and aldicarb were positively associated with farmer's lung among farmers. Current animal exposures were also positively associated with farmer's lung, particularly for poultry houses and dairy cattle (165).

Examination of the 1988-1998 National Center for Health Statistics (NCHS) "Multiple Cause of Death Data" and the 1988-1994 Third National Health and Nutrition Examination Survey data (NHANES III) also adds to the evidence base relating to EAA. Proportionate mortality ratios (PMRs) were determined for 11 respiratory conditions among 6 agricultural groups: crop farm workers, livestock farm workers, farm managers, landscape and horticultural workers, forestry workers, and fishery workers. Crop farm workers and livestock farm workers had mortality for EAA between 10 and 50 times higher than would be expected (166).

Similarly, the National Institute for Occupational Safety and Health (NIOSH) and the National Center for Health Statistics reviewed multiple cause-of-death data for the period 1980-2002. Among industries, mortality rates for EAA were significantly higher for agricultural production, livestock production and crops. Among occupations, mortality rates for EAA were significantly elevated for farmers (except horticulture), suggesting that the agricultural industry is closely associated with EAA mortality (167).

Other related diseases have recently either been reported, or further case reports have been published. These are discussed below, although the exact origin of these cases (and whether they purely reflect EAA alone) is less well understood.

Yacht-makers lung – A case report has recently described a 46-year-old female worker at a yacht manufacturing company, reporting progressive dyspnoea, chest tightness, and cough, related to work where she was exposed to a variety of chemicals. There was improvement in symptoms following treatment with oral corticosteroids and avoidance of work environment, and subsequent normalisation of spirometry. The most likely causative agents were postulated to be dimethyl phthalate and styrene (168).

Fluorocarbons are widely used in industry, and have been reported to cause polymer fume fever, reactive airways dysfunction, and bronchospasm (or narrowing of the airways). The term “horse rug lung” has been suggested after inhalation of industrial fluorocarbon used as a waterproofing spray for horse rugs has been reported to cause both an acute and chronic alveolitis (169).

Further suggested causes of EAA are isocyanates in an automobile painter (170), dry

sausage mould in French salami makers (171), zinc fumes in welder (172), exposure to 1,1,1,2-tetrafluoroethane (HFC134a) as a coolant in a diode–laser in an individual who worked in removal of body hair (173), and a case has been reported in a female non-smoking onion and potato sorter who was exposed to mould at work (with IgG antibodies to *Penicillium* species and *Fusarium solani*) (174).

An outbreak of EAA has been reported at a hardwood floor plant. Three out of 13 workers had confirmed cases of EAA and the remaining 10 workers had positive specific IgG antibodies to *Paecilomyces* mould. The drying process employed at the plant was suspected of being responsible for the massive *Paecilomyces* contamination at the factory (175).

Glass dusts mixed in resin, generally known as glass fibre-reinforced plastic (GRP) have been shown to cause non-specific respiratory disorders in animals and humans. To evaluate this substance further, 29 men employed in different GRP processing operations and exposed to production dusts, were studied with a clinical review, basic tests, and bronchoalveolar lavage. It was found that the inhalation of GRP, independent of environmental concentration, caused alterations of the pulmonary interstitium that microscopically were identified as an acute alveolitis (176).

Chicory worker's lung; handling chicory leaves has been reported to cause EAA, based on symptoms of broncho-alveolitis with pyrexia, positive precipitins to moulds present on chicory (especially Fusarium) and the disappearance of the clinical and radiological manifestations following cessation of exposure to chicory (177).

4.8 BRONCHIOLITIS OBLITERANS

Bronchiolitis obliterans (also known as obliterative bronchiolitis, OB) is a condition characterised by inflammation and injury to the airways distal to the bronchi, resulting in scarring and subsequent chronic airway obstruction or obliteration (178, 179). Symptoms of this condition are non-specific, but generally include progressive exertional shortness of breath and cough. The condition is usually progressive and largely irreversible, often necessitating lung transplantation.

Previous reports have potentially implicated various inhaled agents as causative, and include; ammonia (180), chlorine (181), nitrogen dioxide (182), sulphur dioxide (183, 184), acetic acid (185, 186), nitric acid (185) and cooking oil fumes (187). These occurrences are, however, rare and are usually associated with an acute massive exposure to a particular agent. More recently, a new cause has emerged in the food flavouring industry, with potential to cause a more chronic problem.

Diacetyl (2,3-butanedione) is a yellow liquid used in the food manufacturing industry to add a buttery flavour to dairy products, bakery goods, and other foodstuffs. The US Food and Drug Agency has designated diacetyl the status “generally recognized as safe” (GRAS) as a direct ingredient of food under the Federal Food, Drug and Cosmetic Act, and consumption of low levels of diacetyl present in food has not been shown to present a human health risk (188) despite widespread ingestion. For example, an occupational hygiene investigation (189) estimated that in excess of 100, 000 kg was used in the US in 2005.

The first cases of OB related to diacetyl came to light in May 2000, describing problems

at a microwave popcorn factory in Missouri, USA (190-192). Initially eight workers were reported, although a further case had come to light by the time a detailed case review was performed on these sentinel cases in 2004 (193). The workers developed symptoms between five months and nine years after working at the plant. Their median age was 41 (range 27-51), and the majority were never smokers or ex-smokers with a less than ten pack year history. Eight of the nine underwent HRCT, all of which were compatible with OB. Three underwent thoracoscopic lung biopsy, of which two were consistent with OB. Some of the cases continued to deteriorate once exposure at work had ceased, although after two years had passed all remained stable. Five of the nine were placed on a lung transplant waiting list.

Initially the cause of this outbreak of OB was unclear. Kreiss *et al* (192) performed a clinical evaluation and exposure assessment on the plant workers. There was an increase in respiratory symptoms and obstructive spirometry in those workers who worked in the part of the plant where the microwave popcorn was produced, leading to the conclusion that "they probably had occupational bronchiolitis obliterans caused by the inhalation of volatile butter-flavouring ingredients". Other exposures did potentially occur in the environment, as sampling for volatile organic compounds in the air of popcorn manufacturing plants has detected over 100 different types, and while the contribution of diacetyl seems not to be currently questioned, the possible contributions of other compounds in these workers is still unresolved (194).

Additionally, there is evidence for the biological plausibility of diacetyl vapours causing lung damage. A study in rats (195) investigated the toxicity of inhaled diacetyl at concentrations up to 365 ppm, in either a continuous exposure for six hours or as four short but intense exposures over six hours. A separate group inhaled a single pulse of approximately 1800 ppm of diacetyl. The rats were autopsied between 18 and 20 hours after exposure and it was found that the inhalation of diacetyl caused epithelial necrosis and inflammation in the nose, larynx, trachea, and bronchi. The bronchi were affected at diacetyl concentrations of 294.6 ppm or greater; the trachea and larynx were affected at diacetyl concentrations of 224 ppm or greater. Both pulsed and continuous exposure patterns caused epithelial injury.

Morgan *et al* (188) also evaluated the effects of diacetyl exposure in mice and noted injury in the terminal bronchioles, dependent on the route and duration of exposure. The results were interpreted as showing "clinically relevant diacetyl exposures result in a pattern of injury that replicates features of human OB". These findings were, however, questioned by Finley *et al* (196), who felt the level of exposure in the animal experiments were higher than for human workers.

A study in 2007 of the mutagenicity of diacetyl in mouse lymphoma cells found a dose related increase in the number of mutant colonies, indicating the need for further *in vivo* testing to allow comparisons to be made to human occupational exposures. Also, a study of induced sputum in workers exposed to diacetyl has shown evidence of increased neutrophilic inflammation (197).

Further case reports continue to appear (198) suggesting that the problem is ongoing, and a potential case of the disease has also occurred in an individual who had consumed two bags of microwave popcorn per day (199).

It is not just popcorn workers who are potentially at risk from this condition. A UK based case report in 2008 (178) proposed the term "food-flavourers lung", after a 36 year old

non smoker developed a clinical syndrome compatible with OB, whilst working in a crisp factory exposed to diacetyl on an intermittent basis. This episode potentially followed an unusually high exposure to diacetyl, which was sufficient to cause conjunctival irritation. On removal from the exposure, the individual remained stable but limited, both clinically and on lung function testing.

A Dutch study (200) reviewed workers at a diacetyl manufacturing plant. The plant had recently closed, so workers had ceased exposure. Using questionnaires and spirometry, an exposure history and symptom assessment was carried out. Those with abnormal spirometry were referred for further investigation including full lung function testing and radiology. Four cases of OB were found in 206 identified workers who had worked at the plant between 1960 and 2003.

A report from the CDC (201) documents seven non-smoking flavouring workers in California, who developed severe obstructive lung disease over a variable length of time (1 month – 5 years) after starting work in the flavouring industry. The article points out that despite the link between diacetyl and lung disease being well documented in 2002, and NIOSH issuing guidance in 2004, by 2006 many manufacturers had still not taken adequate steps in terms of exposure control and medical surveillance. The occupational hygiene investigation mentioned above (189) tested 16 different facilities, and found diacetyl at a level similar (although duration and frequency of worker exposure may have differed) to that found by NIOSH in the factories that had potentially caused the original problems.

OB can have a particularly rapid speed of onset, potentially occurring within a few months of exposure. This clearly has implications for health surveillance and early detection. NIOSH has issued guidance in this area on its website (202) effectively stating that performing health testing at least annually would be advisable, since existing information makes it difficult to specify the interval between testing. They also note that the relatively rapid onset of severe airways obstruction in some affected workers suggests that more frequent intervals (perhaps every three months) may be appropriate in some situations. Conducting more frequent testing if abnormalities related to flavouring exposure are detected is also recommended in a particular workforce, and also that workers should not wait for regularly scheduled testing to report symptoms. This approach has been shown to be effective, in one factory a 1 litre drop in FEV_1 over the space of 4 ½ months was picked up in one worker allowing early intervention and removal from exposure (203).

Other respiratory diseases have been described as potentially related to diacetyl exposure, and include; asthma, lung fibrosis, tracheo- and bronchio-malacia, granulomatous pneumonitis and bronchioltis obliterans with organizing pneumonia (204, 205).

Flock-workers lung – Over the last 10 years, several cases of a particular occupational interstitial lung disease, termed ‘‘flock worker’s lung’’, have been reported among workers exposed to nylon flock in North America and Europe (206). There is a particular histological pattern seen (lymphocytic bronchiolitis and peri-bronchiolitis with lymphoid aggregates), (207). Flock is made up of synthetic or natural fibres cut from a loose rope of thin continuous strands, and applied to an adhesive-coated substrate. Synthetic materials that produce flock include nylon, rayon, polyester and polypropylene. Flock is used for the manufacture of many plastic items including fabrics, upholstery, carpets, fishing nets, and bags. A recent study in a Turkish factory

(206) found that exposure to polypropylene flock was associated with a restrictive defect on pulmonary function testing and a reduced diffusing capacity. There were also increased serum interleukin-8 and tumour necrosis factor-α levels, indicative of an ongoing inflammatory process.

4.9 PNEUMOCONIOSIS

Pneumoconiosis, a dust related lung disease, may be classified as either fibrotic or non-fibrotic, and many different causes are reported in the literature.

Silicosis, coal workers pneumoconiosis, asbestosis, berylliosis, and talcosis are examples of fibrotic pneumoconiosis, whereas siderosis (iron oxide), stannosis (tin oxide), and baritosis (barium sulphate) are non-fibrotic forms of pneumoconiosis (208, 209).

Coal working has long been recognised as a cause of pneumoconiosis, as well as a cause of increased mortality (210, 211). More recently, COPD was also linked to coal dust exposure in the UK, established in law by a High Court case in 1998 (212-213). In the UK, the coal industry has declined rapidly over the last 25 years, but there are still active deep and surface mines operating.

Surveys from the US show that cases of coal workers pneumoconiosis are still being diagnosed, and in certain cases rapidly progressive pneumoconiosis, suggesting that even in the modern era of mining preventative measures are not always adequate to prevent disease (214, 215). It has been suggested that by assessing bioavailable iron content within coal, its toxicity and pneumoconiotic potential can be predicted, specifically before large-scale mining is undertaken (216).

Recent reports on other forms of pneumoconiosis are limited, but do include some longitudinal data from 726 slate workers in North Wales followed up from 1975 to 1998. This analysis revealed an excess death rate against matched controls, following adjustment for age and smoking status. The excess deaths were mainly due to respiratory disease and pneumoconiosis, and felt to be mainly due to the slate work. The authors discussed that the accuracy of pneumoconiosis as a cause of death was debatable, due to the general paucity of appropriate radiology close to death (217).

In the late 1990's, three serecite workers in Brazil were diagnosed with pneumoconiosis. Serecite is a form of mica that ordinarily contains silica. However, the subsequent lung biopsies showed lesions compatible with mixed dust fibrosis with no silicotic nodules, leading the authors to conclude that exposure to fine sericite particles was associated with the development a pneumoconiosis, but distinct histologically from silicosis (218).

Aluminium pneumoconiosis has also recently been reported in a 26-year-old man who was a lifelong non-smoker, with a history of welding aluminium parts. VATS lung biopsy revealed evidence of airway and parenchymal inflammation consistent with aluminium pneumoconiosis (219). Furthermore, a granulomatous disorder resembling sarcoidosis has also been attributed to aluminium (220).

Pneumoconiosis has also been reported in a 62-year-old man who had worked as a welder for 35 years (arc welder's lung). Chest CT scan showed progressive massive

fibrosis, and transbronchial lung biopsy revealed abundant iron particles in the alveoli, with positive staining for Fe (Berlin blue stain). This case was relatively atypical, as arc welder's lung rarely presents as PMF, more often behaving like EAA (221), with an HRCT pattern of diffuse ill-defined micronodules.

Dental technician's pneumoconiosis is a recent term proposed for the interstitial disease potentially caused by the exposure to complex substances used by dental technicians. Case reports relating to this problem are ongoing, and the pathogenesis likely relates to the complex exposure mix, including metal dusts, silica, plaster, wax and resins, chemical liquids and methyl methacrylate used in the dental industry (222), (223).

Finally, recent data suggest a potential individual genetic susceptibility for the development of various pneumoconioses (224).

4.10 CHRONIC BERYLLIUM DISEASE

Beryllium (Be) is a silvery-grey metal, strong but light and has excellent electrical and thermal conductivity. It is often alloyed with other metals, and is widely used in a variety of industries. Appendix 4 lists the main industrial uses.

Estimates of exposure to beryllium vary from country to country, although an evaluation by Kauppinen (225) in the European Union suggested about 67,000 people were exposed through work in the early 1990's. An estimate in 2004 (226) suggested between 24,400 and 134,000 people currently working in government and private industry in the USA were potentially exposed to beryllium at a level greater than 0.1µg/m^3. In the UK, estimates are lower, with between 500 and 1000 people currently being exposed through work (227).

Beryllium has two main effects on the lungs; acute and chronic beryllium disease. Acute beryllium disease, presumed to be a chemical pneumonitis (or alveolitis) was first described in Europe in 1933 (228) and the USA in 1943 (229). This tends to present during (or soon after) exposure with shortness of breath, fever and radiological infiltrates seen on the chest X-ray. Usually, acute beryllium disease resolves following removal from exposure, although can lead on to chronic lung fibrosis (230, 231).

The second effect, chronic beryllium disease (CBD) was first described by Hardy and Tabershaw in 1946 (232), in fluorescent light bulb workers. It is a chronic granulomatous disorder affecting the lungs or skin, caused by a cell-mediated sensitisation to beryllium. Clinically, CBD causes a dry cough, wheezing, shortness of breath, fatigue, and weight loss (231, 233).

Additionally, a subclinical type of CBD is identified, characterized microscopically by the presence of non-caseating granulomas. This condition is differentiated from clinical CBD purely by the absence of symptoms, chest X-ray abnormalities or lung function changes (234).

Traditionally, beryllium disease was classified by the Beryllium Disease Case Registry criteria, which addressed two areas; (i) establishment of significant beryllium exposure and (ii) objective evidence of lower respiratory tract disease. Therefore, CBD was generally only diagnosed in those with clinical symptoms. Beginning with approximately

300 known cases in 1951, the Registry increased rapidly to include 606 cases by 1958, 760 cases by 1966, and 898 by 1983 (235, 236). Following exposure reduction in the 1950s, and the decrease in cases reported to the registry, it had been thought that CBD was becoming less relevant. However, it is now clear that this was not the case as further cases began to emerge in the 1980s, at lower exposures, often identified using newer immunological testing techniques (233).

With the advent of these new tests, the term beryllium sensitization (BeS) was defined. Individuals have a hypersensitivity reaction to beryllium, but no evidence of respiratory disease (237). A proportion of people exposed to beryllium (and its compounds) can therefore become sensitized, with the prevalence of beryllium sensitization in exposed worker populations ranging between 0.8% and 12% in various studies (238).

The prevalence of CBD in workers is generally lower than the sensitization prevalence, and has been reported to range between 0.4% and 8% (238). Additionally, CBD has been shown to occur many years after first exposure (233, 239, 240), even if exposure has ceased, and can occur even after fairly minimal exposure levels (so-called "by-stander exposure"), (233). The relationship between BeS and CBD is not well understood, and the prevalence of those with BeS who have CBD at the time of initial assessment varies in different studies from 14% to 100% (239).

CBD can also occur with rapid onset, within three months of exposure (241), although a dose response relationship has also been suggested (242, 243), as has a relationship specifically to the characteristics of the workplace (244).

In recent years, as exposure to beryllium has been reduced, a new type of classification of beryllium health effects has been suggested (237). This is summarised below in Table 1.

Table 1; Diagnostic criteria for beryllium health effects Ref. (237)

1. Beryllium sensitization

    a. Evidence of a beryllium-specific immune response as indicated by
        - abnormal blood Be Lymphocye Proliferation Test (BeLPT) or
        - positive beryllium skin patch test
    b. No evidence of granuloma on lung biopsy

2. Subclinical CBD

    a. Evidence of a beryllium-specific immune response (see 1a above)
    b. Histopathological changes on lung biopsy consistent with CBD such as
        - non-caseating granulomas
        - mononuclear cell infiltrate
    c. No respiratory symptoms or physiological abnormalities

3. Clinically evident CBD

    a. 2a and b above for CBD *and*
    b. Clinical signs and symptoms, including
        - respiratory symptoms such as cough or shortness of breath
        - physical examination findings such as crackles on chest examination

- chest x-ray abnormalities revealing a reticulonodular infiltrate
- physiological impairment with abnormal pulmonary function testing, exercise testing, or gas exchange

CBD was first postulated to be an immune-mediated disease in 1951 (245), and beryllium sensitization was initially defined by the beryllium skin patch test. However this test is not currently in widespread use in the surveillance of beryllium workers because of concerns that the test itself might induce sensitization or worsen existing CBD (234, 237).

It is important to stress that beryllium sensitization can occur through skin contact as well as due to inhaled particles, and this needs to be considered when assessing exposed workers (238). Additionally, there is also evidence to support a background rate of beryllium sensitization in certain individuals not occupationally exposed to beryllium, further causing difficulty in interpretation of workplaces. This has been confirmed in several studies, both in the US and Japan, (with skin patch testing as well the BeLPT) with estimates ranging from 1–5% (234). This “natural” rate of sensitisation may be expected, because Be is widespread in nature, is present in some common materials such as tobacco or coal, and is used in certain dental work.

In an attempt to try and establish the natural history of BeS, a longitudinal study by Newman *et al* (239) monitored a cohort of beryllium-sensitized individuals at two yearly intervals, using bronchoalveolar lavage and repeated transbronchial lung biopsies to determine progression to chronic beryllium disease. In total, 55 people were followed up and 17 (31%) developed CBD within an average follow-up period of 3.8 years. Thirty-eight of the 55 (69%) remained sensitized, but without disease, after an average follow-up time of 4.8 years, and certain workers with BeS remained disease free up to 12 years later.

In those who progressed, there was no difference in those who were still exposed to Be and those who were no longer exposed. No personal exposure monitoring data was available, but using work history information it appeared that workers with possibly higher or more consistent exposures (i.e. machinists) were more likely to progress to CBD. A follow up study is ongoing.

A further recent study (246) followed a cohort of 136 beryllium oxide ceramic workers over an 11 year period up to 2003, including those who had since left employment. They were evaluated for beryllium sensitization and chronic beryllium disease. In 1992, the point prevalence of 6% sensitized and 4% CBD was documented. Follow-up was maintained on 83% of the 128 not sensitized in the original testing. Corrected period prevalence for sensitization and CBD were 20% and 14%, suggesting a more than three fold increase in the observation period. However whilst useful, the numbers in these studies are relatively small.

Finally, there is also concern that beryllium exposure can cause lung cancer, and the Agency for Toxic Substances and Disease Registry (ATSDR) and the International Agency for Research on Cancer (IARC) have classified beryllium as a known human carcinogen, whilst the Environmental Protection Agency (EPA) classifies beryllium as a probable human carcinogen.

Exposure limits were introduced in the USA in 1949 by the Atomic Energy Commission, with a daily weighted standard of 2 $\mu g/m^3$. The Occupational Safety and Health

Administration (OSHA) later adopted this as a legally permissible limit but changed the time period to an eight hour average (236, 242, 247). Currently in the UK, the Control of Substances Hazardous to Health (COSHH) Regulations 2002 are set at this same level (21). Whilst it seems that these exposure limits have greatly reduced or even prevented the severe cases of CBD seen previously, they are clearly not protective against beryllium sensitization or subclinical CBD (236, 248). This has led the American Conference of Government Industrial Hygienists to suggest new Threshold Limit Values of between 0.02 and 0.2 $\mu g/m^3$ (242, 249), the lower limit being based on a study by Kelleher (250, 251).

In a study pertaining to exposure limits, Madl found that all workers with BeS and CBD had at least a 5% probability of experiencing beryllium exposures exceeding the 0.2 $\mu g/m^3$ level, and so concluded that maintaining exposures below 0.2 $\mu g/m^3$ 95% of the time may prevent BeS and CBD in the workplace (251). There is also evidence that better respiratory and skin protection in the workplace can reduce sensitization rates in the absence of any change in the airborne exposure levels (252).

In the 1970's *in vitro* immunological testing that resembled the skin patch test began to be developed (253, 254), but it was 1989 when the beryllium lymphocyte proliferation test (BeLPT) was first really suggested as a screening blood test to identify subclinical beryllium disease (255). Prior to this, the test had been discounted as a potential screening tool because the positive cases had normal radiology or lung function testing or due to poor reproducibility of the test. However, with more advanced techniques, and in particular the advent of the transbronchial biopsy, positive tests could now be compared to a tissue diagnosis of subclinical beryllium disease (255).

The main current debate is whether or not to use the BeLPT as part of worker surveillance and monitoring. Clearly the test may identify "subclinical" disease by documenting sensitisation, but there is uncertainty as to the sensitivity and specificity of the test, and concerns about inter- and intra-laboratory variability (233, 241, 254, 256-258).

The BeLPT has been in use since 1987 and began to be used in worker screening or surveillance programmes in the 1990s (234). A review article by Kreiss in 2007 indicated that it has been used in over 15 separate studies, addressing the issues of screening for sensitization and the effectiveness of workplace interventions to reduce this (233). Despite this, although used in some areas, its use is not universal. For example, the US Department of Energy has initiated a comprehensive surveillance program to identify and prevent beryllium disease at its facilities, and Brush Wellman, one of the largest beryllium miners, manufacturers and processors instituted the BeLPT in 1992 (234). On the other hand, the US Department of Defense policy statements have discouraged the use of the BeLPT for surveillance of exposed workers (257).

What is clear is that current opinion over whether or not the BeLPT should be used for screening is divided. Whilst no-one seems to disagree that the test is currently the best available and is very useful at detecting subclinical CBD, there are too many other unknown variables to allow recommendation for routine testing.

There is now good evidence that susceptibility to chronic beryllium disease has a genetic component. Human Leukocyte Antigen (HLA) with a single amino acid variation at position 69 on the HLA-DPß1 gene confers a higher risk of chronic beryllium disease and sensitization (259-261). Approximately 80% of patients with CBD have this

genotype compared to about 40% of the general population. However, at present, due to the relatively high prevalence of this genotype in the population combined with the relatively low prevalence of chronic beryllium disease it cannot be used as a reliable screening tool (233, 238, 259). There are also ethical considerations to take into account, concerning protection of worker confidentiality, and potential employment issues, so genetic testing of beryllium workers is felt to be inappropriate at present (262-265).

Sarcoidosis and berylliosis have many clinical and pathological similarities, and can be difficult to distinguish (266-270). The diagnosis of berylliosis is reliant on a careful clinical history to confirm exposure, exclusion of other causes and confirmation of beryllium sensitization by BeLPT, or alternatively showing beryllium in lung tissue from open biopsy or autopsy.

There are several reports in the literature of berylliosis initially being labelled as sarcoidosis (271), and a study in Israel in 2003 suggested 6% of patients given the diagnosis of sarcoidosis actually had CBD (272). In a prospective case study that evaluated 84 patients with sarcoidosis for potential beryllium exposure, this was recognised and the diagnosis changed to CBD in 34 out of 84 patients (273).

Attempts have been made recently to revise and improve the diagnostic criteria for the BeLPT, including the use of statistical control methods (258), and in 2006, the Agency for Toxic Substances and Disease Registry convened a panel of experts to consider the diagnostic criteria for the BeLPT (257). Developments are ongoing with new techniques and new reagents for this test such as flow cytometry (274-277), and further advances in genetic testing may also play a role in the future. Longitudinal studies of the BeLPT are ongoing. Also, recent technological advances now mean beryllium can be accurately measured in the urine by several centres (including HSL). Exactly how detectable urinary beryllium relates to the development of chronic beryllium disease is currently unknown but it does imply a level of exposure.

4.11 HIGH PARTICULATE LOAD (THE WORLD TRADE CENTRE DISASTER)

The collapse of the World Trade Centre (WTC) on September 11th 2001 offered an unfortunate opportunity to identify the human health effects associated not only with disaster, but also specifically the pulmonary response to high particulate load. The findings of these studies may help understand the more general pulmonary response seen to inhaled particles and irritants.

The fire and subsequent collapse of the two buildings released a cloud of dust and pollutants that persisted for days. Approximately 40,000 rescue and recovery workers were exposed and included fire-fighters and police, as well as a variety of construction, utility, and public sector workers.

These workers have been followed up with exposure assessment questionnaires, physical examinations, spirometry, and chest X- rays. Significant declines in lung function have been noted (278, 279), both initially and on subsequent follow up (280) with respiratory symptoms and spirometry abnormalities being significantly associated with early arrival at the site. Initial research outputs from the study of exposed emergency workers described a persistent cough (281, 282) and reactive airway

dysfunction syndrome (283), More recent follow up has also noted an increased incidence of sarcoidosis or "sarcoid-like" granulomatous pulmonary disease (284).

4.12 ASBESTOS/REFRACTORY CERAMIC FIBRES

Asbestos is now well known to cause respiratory harm, including pleural plaques, pleural thickening, benign pleural effusions, mesothelioma, lung cancer and pulmonary fibrosis (asbestosis).

In general, exposure is now limited by legislation, although due to the long latent period previously exposed workers are still presenting with asbestos related disease, and will continue to do so for some years to come. People with previous asbestos exposure (high-risk groups include; construction and demolition workers, boilermen, shipyard workers, plumbers, electricians, carpenters and joiners) should also be specifically encouraged to stop smoking, because of the potential increased risk of lung cancer (285, 286).

Whilst the effects of asbestos are well known, the long-term effects of manmade vitreous fibres such as refractory ceramic fibres (RCFs) are less well studied. Whilst it is not within the remit of this article to elaborate in detail in relation to this area of research, recent evidence does exist, and is worthy of mention.

RCFs are aluminosilicate glass wools, often used for similar purposes to asbestos, due to their heat resistant properties. These agents have been studied now since the late 1980s, most specifically in relation to both lung function and pleural abnormalities.

Data on long-term lung function decline related to RCF exposure is conflicting in varying studies, so there is no clear evidence of an adverse effect in this area as yet.

In addition, there has also been no increased risk identified for pulmonary fibrosis, lung cancer or mesothelioma death in humans, although of concern is that pleural changes have been seen in some workers (287), and particularly as early animal experiments have indicated an elevated risk of mesothelioma, lung fibrosis and lung cancers related to RCF exposure.

This has led to regulation in their use, and RCFs are currently classified as a Category 2/Group 2B carcinogen by the European Union and the International Agency for Research on Cancer (IARC). A recent review of the literature has suggested that some of these earlier animal experiments used excessive dosages of RCFs and may therefore have overestimated the associated risk of their usage (287).

None the less, given the harm caused by other agents such as asbestos, it seems sensible for now to continue with exposure control until further evidence to the contrary becomes available.

4.13 NANOTECHNOLOGY

Nanotechnology research output has risen exponentially over the last few years, and the remit of this report does not allow a full appraisal of the (even recent) evidence. Nevertheless, it would be inappropriate not to briefly comment on the potential health effects that may be seen as a consequence of nanomaterial exposure.

Paradoxically, nanomaterials produced by the rapidly expanding nanoindustry have the promise of improved health for many, due to the diversity of their potential applications in medicine, but also carry a perceived risk of adverse health effect.

A recent review article produced by NIOSH debates the pros and cons of likely health effects associated with nanoparticle exposure (288). This report concludes that whilst the benefits of nanotechnology dominate current thought, the potential for undesirable human health effects should not be overlooked. Indeed, the report highlights consistently large numbers of studies relating to ultra fine particle exposure and human morbidity, and consequently there is reason to suspect that nanoparticles are likely to cause human disease, "some with long latency".

For example, several rodent studies have shown that carbon nanotubes are capable of producing inflammation, granulomas, fibrosis, and biochemical/toxicological changes in the lungs and mesothelial lining (289-291). As the NIOSH report concludes, further longer term research is needed in this area, but for now both NIOSH and HSE have issued guidance suggesting these agents be treated with caution (292). As an example of the further research in this area, HSL runs a Centre for Interdisciplinary NanoResearch (CiNR), which has ongoing research into for example, exposure assessment, health effects and the effectiveness of protective equipment (310).

4.14 MISCELLANEOUS OCCUPATIONS/DISEASES

Fire-eater's lung – Whilst the exposures are presumably accidental, there have been several case-reports over the last four years of fire-eater's lung or fire-eater's pneumonia. This disease is an acute pneumonitis or lipoid pneumonia induced by hydrocarbon inhalation, often paraffin. There is an acute and chronic form depending on the type and duration of exposure, and treatment is generally based on supportive care (293-301).

Infections – Whilst this is a very wide-ranging topic (generally involving health care workers that have not been included in this review) there are other reported causes of occupational acquired infections. In recent years these include anthrax from working with animal hides to make drums (302), fatal pneumonia from metal workers due to inhalation of *Bacillus cereus* containing *Bacillus anthracis* toxin (303) and ornithosis amongst workers at a poultry abattoir and farm (304).

5 CONCLUSIONS

There is a substantial recent evidence base in relation to occupational lung disease, suggesting that this area remains an important aspect of overall worker health. Indeed, not only has this review identified various emerging issues related to established, or perhaps more traditional occupational lung diseases, but has also highlighted potentially new occupational respiratory diseases.

In addition to issues related to specific diseases, the review of the literature has also identified various cross cutting or general themes relating to respiratory ill health in the workplace. These will also be briefly concluded here.

5.1 SPECIFIC ISSUES

Silica; exposure to crystalline silica in the workplace is still commonplace, and these exposures are potentially able to cause a range of respiratory (and other) diseases. It is important to focus not just on the risk of exposure causing chronic silicosis, but to be aware that acute and accelerated silicosis still occurs.

Recent guidance has been produced relating to health surveillance for silica exposed workers. For example, ACOEM have formulated such guidance designed to assist in the development of appropriate surveillance programmes.

Similarly, recent modelling data published from the Netherlands suggests an approach to health surveillance for silica-exposed workers that may allow a careful and evidence based judgement to be made concerning the need for chest X-ray examination.

Endotoxin/Organic dusts; it is evident that endotoxin and organic dust exposure continue to be associated with respiratory ill health. The highest exposures to endotoxin are generally seen with animal breeding, handling and during cleaning activities. The levels are variable with the type of work undertaken, although there are only a few working facilities with continuous exposures likely to exceed 50 EU/m^3.

However, the health effects associated with endotoxin exposure are often non-specific in nature, and may be associated with reduced FEV_1. Again, these effects are often difficult to interpret, as endotoxin levels in the workplace are variable according to work task.

Whilst a “safe” or recommended level of workplace endotoxin exposure may be adopted in the future, in the interim vigilance appears sensible from all those responsible for the health of exposed workers.

Metal fume fever/Pneumonia; whilst there does seem to be an accepted increase in susceptibility to pneumonia in welders, the mechanism behind this remains unclear, and the size of this potential problem is not accurately known. Further research would seem appropriate to identify the strength of this association and its potential mechanism.

Pulmonary fibrosis; the potential contribution of workplace exposures to the development of pulmonary fibrosis continues to attract research attention. Potential identified causes for this type of host response are varied, and include hard metal lung disease (cobalt and tungsten carbide in particular) and wood dusts.

Often, cases of pulmonary fibrosis present to health care professionals many years after potential occupational exposures have occured. The long latency nature of these conditions makes it more difficult for practicing respiratory health care workers to identify cases where occupation may be relevant, let alone confirm this in an individual case. Interestingly, recent data from Fireman et al (305) have shown that scanning electron microscopy applied to induced sputum (or lung biopsy) can potentially assist in differentiating cause in this condition.

EAA; extrinsic allergic alveolitis is a traditional, established occupational lung disease, although new issues are emerging in the UK. A series of outbreaks of EAA has occurred in workers exposed to contaminated metal working fluids, and although recent literature addresses certain relevant issues, the evidence base requires further development in order to improve understanding of the natural history and prevention of this illness.

Other novel lung diseases characterised as EAA are recently reported, ranging from mushroom workers related EAA (with potential health effects also identified for complementary therapy workers) to lung diseases associated with both glass fibre-reinforced plastic (GRP) and chicory.

Bronchiolitis obliterans (OB); whilst ordinarily regarded as an uncommon disease, occupational causes of OB are identified. The most recent publication data relate to food flavouring inhalation and in particular the link between diacetyl exposure and the subsequent development of OB. The relationship between exposure levels and OB development is not fully understood, and at present there are no known safe exposure limits for diacetyl. Until this issue is resolved, it seems sensible that workplaces using diacetyl adopt a cautious approach. For example, it has been recently suggested that workplaces should institute mandatory respiratory protection for all exposed workers (306).

The likely impact of this condition in the UK is not known, as the current extent of diacetyl usage is not known, although a survey and site visits by HSL/HSE are ongoing to address this specific issue. The results of this exercise may benchmark the size of the at risk worker population, and identify further research needs.

Pneumoconioses; other than the typical established pneumoconioses, dental workers have recently been highlighted as a potential risk group, as new materials are constantly being introduced into this type of work practice. Recent work is also suggests a potential genetic susceptibility to the development of various pneumoconioses.

Chronic Beryllium disease; the development of lymphocyte proliferation testing to identify subclinical beryllium disease has recently revolutionised this field. However, it is evident from this review (and a more detailed review of health surveillance needs for beryllium exposed workers recently carried out at HSL) (307) that there remain uncertainties about the best use of this test. Evidence is continually being produced in

this area, and in particular in relation to the best application and clinical interpretation of the BeLPT test.

High particulate load; both health and organisational related issues have emerged from the evidence published in the aftermath of the collapse of the twin towers of the World Trade Centre. In terms of health issues, affected workers (mostly emergency workers) suffered from a combination of rhino sinusitis, persistent cough, airways dysfunction syndrome (or acute irritant-induced asthma), COPD, pulmonary fibrosis, bronchiolitis obliterans, and cancers of the lung and pleura (308). In addition, a sarcoid like illness has been described.

It was also suggested that the lessons learned from such response to disaster should guide future similar responses, particularly in regard to environmental controls and effective respiratory protection for emergency workers during the first days of harmful exposure (309).

Other; other important emerging areas identified within the review related to the health risks associated with refractory ceramic fibres, and the rapidly expanding area of nanotechnology.

5.2 GENERAL THEMES

General themes emerged from the review of recent respiratory literature relating to occupational lung diseases, and these are summarised below;

(i) *Early recognition of occupational respiratory disease*; in particular, the need for good quality health surveillance advice for each of the main respiratory diseases was highlighted (e.g. beryllium related disease), with the ability to detect at an early and practical point workers who are developing rapid decline in lung function.

(ii) *Diagnostic accuracy of occupational lung disease*; in particular being able to access clinical, imaging an laboratory skills for the proper assessment of workers with potential occupational lung disease, within an MDT environment (for example differentiating sarcoidosis from berylliosis, idiopathic pulmonary fibrosis from hard metal disease or chronic extrinsic allergic alveolitis).

(iii) *Newer technologies*; in particular, addressing the current lack of ability to discern possible harmful respiratory effects from non work related problems in workers exposed to newer hazards, for example nanoparticles (or as yet unidentified hazards).

6 APPENDICES

<table>
<tr><th colspan="2">Appendix 1 - MATRIX – KEYWORDS/DISEASES</th></tr>
<tr><td>occupation*
job*
work*
environment*

combined together with “OR” = JOB TERM</td><td>outbreak* /disease outbreaks
surveillance
clusters
epidemiology
case reports
workplace investigations

combined with “OR” and used when initial search found too many abstracts.</td></tr>
<tr><td colspan="2">respiratory
respiration
lung
chest
pulmo*
pneumo*
thora*
pleura*
alveol*

combined together with “OR” = LUNG TERM.
JOB and LUNG combined with “AND” and then combined with each section below</td></tr>
<tr><td colspan="2">bronchiolitis.mp. /bronchiolitis obliterans/ bronchiolitis obliterans organizing pneumonia
diacetyl
popcorn
flavoring agents/ flavor*.mp./flavour*.mp</td></tr>
<tr><td colspan="2">beryllium
berylliosis
sarcoid*
granulom*</td></tr>
<tr><td colspan="2">metal
fever/welding/inhalation exposure/zinc oxide</td></tr>
<tr><td colspan="2">extrinsic allergic alveolitis
alveolitis
hypersensitivity pneumonitis
pneumomia</td></tr>
<tr><td colspan="2">endotoxin
organic dust toxic syndrome
dust
DTS/OTDS
Fever</td></tr>
<tr><td colspan="2">acute lung injury
pulmonary oedema
ARDS</td></tr>
<tr><td colspan="2">fibrosis/fibrotic</td></tr>
</table>

asbestos pneumoconiosis silic*
rare-earth radioactive radiation idiopathic
attributable adj fraction attributable adj risk

Appendix 2 - Other Databases Searched by HSE infocentre

1. British Nursing Index
2. Embase
3. British Library's Inside Conferences and Conference Papers Index
4. SIGLE
5. CINAHL
6. Cochrane Library
7. Healsafe
8. Oshrom (5 OHS databases: HSELINE, NIOSHTIC, CISDOC, RILOSH, OSHLINE)

Appendix 3; Occupational sources of exposure to respirable crystalline silica [from Rees *et al*]

Sources of exposure	Comment
General work	
Moving, drilling, working, processing, crushing or mining sand, stones or rocks	Free silica content in respirable fraction of dust determines risk
Mining and related activities	
Mining and milling	Country rock* an important determinant of risk. Gold, coal, tin,copper, mica, uranium, crocidolite, iron, important in some regions
Small-scale mining	Under-researched, but exposure may be high
Mining related	Quarrying, tunnelling, excavating, digging wells and boreholes. Country rock and mineral determines risk. Quarrying granite, sandstone, flint, quartzite, shale and slate may produce high levels of quartz. Potency of silica may be reduced in some clays
Major industrial sources	
Foundry	
Ceramics	Pottery, tiles, brick and refractory articles
Glass manufacture	
Furnace masonry	Cutting, grinding, refractory articles
Construction	Cutting, grinding, etc., concrete, tiles or bricks, Digging foundations
Stoneworking and monumental masonry	Making, cutting, abrasive polishing, etc., of tombstones, billiard tables, slate pencils, cladding and surfaces, including granite counter tops
Abrasive blasting with sand (sandblasting) or siliceous material	Very high exposures common. Usually cleaning or preparation for coating of metal pieces, but also unusual applications e.g. sandblasting jeans
Minor industrial sources	
Fillers and scourers	Fine silica may be used for fillers in paints, coatings, plastics, rubber, explosives, dental supplies, etc., or in scouring materials (such as cleaning agents and those used for polishing flour) or grinding materials
Jewellery	Cutting, buffing, etc., semi-precious gems
Diatomaceous earth	Calcined material contains cristobalite
Craft work	Stone carvers, sculpture, pottery. Cases unusual unless frequent exposure, e.g., most working days

*Country rock - rock hosting the mineral or being mined. Silica content varies from location to location, even within a mine.

Appendix 4; Uses and application of Beryllium (Ref. 232, 233)

Technology	Application
Aerospace	Engines and rockets Brakes and landing gear Satellites and gyroscopes Precision tools Altimeters Mirrors
Energy and Electrical	Heat exchanger tubes Microelectronics Microwave devices Nuclear reactor components Oil field drilling devices Relays and Switches
Telecommunications	Undersea repeater housings Cell phones Personal computers Transistor mountings Electrical connectors Switches and springs Electromagnetic shielding
Biomedical	X-ray tube windows Scanning electron microscopes Dental prostheses Medical lasers
Defence	Tank mirrors Springs on submarine hatches Mast mounted sights Missile guidance Nuclear triggers
Fire prevention	Non-sparking tools Sprinkler systems
Automotive	Air-bag triggers Anti-lock braking systems Steering wheel connectors
Miscellaneous	Plastic moulds Bellows Jewellery – aquamarine and emerald Golf clubs Bicycle frames Camera shutters Fishing rods Pen clips Scrap metal recovery and recycling Ceramics

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Other respiratory diseases review

Occupation has been recognised as a cause of respiratory disease for many centuries, and this link is a constantly evolving field as workplaces and exposures change, and new manufacturing processes and materials are introduced. With enhanced communication and reporting schemes, it has become easier to identify new causes and outbreaks of disease. Whilst asthma and COPD remain common in both the general population and the workplace, it is essential to ensure that developments in the less common diseases are not overlooked. This is especially so as whilst these rarer diseases are featured in the literature, they do not occur often in reporting schemes, suggesting that they may be under-recognised clinically. The aim of this report is to review the current evidence base in relation to the less well known occupational lung disorders, specifically to identify any new or emerging causes of occupational respiratory disease.

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