MD Thesis

Respiratory disease in workers exposed to metal working fluids

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Abstract

The largest UK outbreak of respiratory disease in metalworking fluid (MWF) exposed workers (Powertrain) led to a heightened awareness of the health hazards associated with MWF. A literature review identified 29 outbreaks of ill health associated with MWF exposure with a peak incidence between 1996 and 2000. Microbial contamination was suspected but no unifying causative agent could be found. Six different case definitions for extrinsic allergic alveolitis (EAA) were indentified, only one of which was validated. The process of developing an evidence based case definition for MWF-EAA required the identification of a group of patients with unequivocal MWF associated EAA. The Powertrain database (created at the time of the outbreak and subsequent follow up appointments) was utilised and an Expert Panel of five occupational lung disease consultants concluded that there was sufficient clinical evidence to diagnose 14 workers as definite cases of EAA. By calculating the positive predictive value of the data points relevant to a diagnosis of EAA combined with knowledge and experience of previous EAA diagnostic criteria, it was possible to develop a new evidence-based EAA diagnostic score (the MWF EAA Score). The MWF EAA Score was applied to the Powertrain data demonstrating agreement with the Expert Panel opinion in over 80% of the cases with a greater number of workers correctly classified than with other published diagnostic criteria[1]. The score was also applied to previously published case series of workers diagnosed with MWF EAA, in order to externally validate the new EAA rating system. The MWF EAA Score appeared to perform well and there was sufficient data provided in almost half of these published cases indicating that the MWF EAA Score would have shown agreement. This scoring system is a simple and reproducible tool and provides an evidence-based case definition suitable for use in future UK outbreaks.

Contents

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Introduction

The History of Occupational disease

Occupational disease is any illness associated with a particular occupation or industry. Such diseases result from a variety of chemical, biological, psychological and physical factors that are present in the work environment or are encountered in the course of employment [2].

The first recorded observation of occupational disease may be that documented in the 4th century BC by Hippocrates. The Greek physician described a case of severe lead colic suffered by a worker who extracted metals. During the middle ages the German mineralogist Georgius Agricola made a detailed study of gold and silver mining operations. He described the primitive methods of ventilation and personal protection in use and the "difficulty in breathing and destruction of the lungs" caused by the harmful effects of dust inhalation. A more comprehensive account of occupational disorders was written by the 'father of occupational medicine', Bernardino Ramazzini. His book entitled 'Diseases of Workers' contains descriptions of the diseases associated with 54 different occupations including mercury poisoning of Venetian mirror makers. Ramazzini believed that a physician must determine the patient's occupation in order to discover the cause of the patient's disorder [2].

The Industrial Revolution of the 18th century had a profound impact on occupational diseases. Industrial growth led to crowded, unsanitary working and living conditions; as well as new machinery and exposure to toxic materials; with a corresponding rise in occupational mortality and morbidity. Charles Turner Thackrah, a Leeds physician, described lung diseases caused by dust that commonly afflicted miners and metal grinders and documented this in his book 'The Effects of the Principal Arts, Trades and Professions . . . on Health and Longevity . .' (*1831*) [2].

In the twentieth century, although some of the original occupational diseases were largely conditions of the past, new diseases continued to be described. In the first half of the 20th century, asbestos-related disease was identified. The incidence of mesothelioma is still increasing with 153 deaths in 1968 to 2347 in 2010. Over 80% of asbestos related deaths in 2010 were among men, due to asbestos exposures mainly in the workplace [3] .

As well as increased mortality and morbidity, occupational respiratory disease is also associated with increased sickness absence rates, in 2011/2012 667 000 working days were lost due to work related breathing or lung problems[4]. Affected workers may also be forced to relocate or leave employment with subsequent loss of income, and benefit requirements, with a third of workers with occupational asthma (OA) being unemployed up to 6 years after diagnosis [5-13]. These factors combine to produce a huge burden on society which has been estimated at an annual cost between 4,600 euros to 9,670 euros per ‘‘average’’ afflicted person (at 2004 prices) [14]. In 2003 there was an estimated 631 new cases of OA and the Health and Safety Executive (HSE) has estimated that the overall costs to society from these new cases of OA ranges from £3.4 to £4.8 million per year over the lifetime of the disease [15].

With the introduction of new materials and changes in manufacturing practices, new occupational diseases are continuing to be discovered. For example, lung disease has been associated with exposure to indium, nylon flock, nanoparticles and the world trade center disaster [16]. It is important that novel causes of occupational disease are identified in order to, where possible, lead to changes in the work place to protect others and by so doing reduce their risk of disease. Diacetyl (used as an artificial butter flavouring) exposure in popcorn manufacturing has been associated with lung disease, including bronchiolitis obliterans, in factory workers [17] and to a lesser extent consumers [18]. This association has been supported by research [19] and has lead to recommendations by government authorities to attempt to reduce the risk of associated lung disease. HSE state fumes should be controlled in accordance with the Control of Substances Hazard to Health (COSHH) regulations [20]. These regulations commence with substitution where possible with a safer chemical. This has been attempted but evidence suggests that using chemically similar agents may lead to the same respiratory problems [21].

Occupational Asthma

Classical asthma is a common respiratory disease in Britain affecting approximately 5 – 10 % of adults [22]. Patients with atopic asthma often present with recurrent episodes of wheezing, shortness of breath, coughing and chest tightness. These symptoms may be precipitated by contact with allergens or irritants and in part relate to changes in airway calibre, and hyper-responsive airways [23]. These changes form the basis of established diagnostic tests for asthma which include demonstrating variable airflow obstruction by examining serial peak flow records, documenting airway reversibility to inhaled bronchodilators, and measuring the level of airway responsiveness to non-specific inhaled irritants such as histamine and methacholine. Chronic inflammation is also present in asthmatic airways, with an associated increase in eosinophils, mast cells, and Th2 lymphocytes [24]. Untreated, this may lead to airway remodelling with goblet cell hyperplasia, reticular basement membrane thickening, vascular proliferation, and smooth muscle hypertrophy [23]. The resulting eosinophilic bronchial inflammation may be demonstrated by higher than normal numbers of eosinophils in the sputum of patients with active asthma [25], and this is used as an alternative objective method of monitoring asthma control in some centres [26].

Recent evidence supports the estimate that occupational factors account for approximately one in six cases of adult asthma. The annual population incidence of occupational or work-related related asthma ranges from an estimated 12 to 300 cases per million workers [27-35]. It is estimated that OA accounts for somewhere in the region of 9-16% of all new adult cases of asthma [36-38], making it the most frequently reported work-related airway disease in Britain [4]. A significant under-identification of OA is thought to persist [35 39]. In the UK this can be demonstrated by the number of OA reported cases each year (321 cases) [40], compared to the suggested annual population incidence of occupational or work-related related asthma ranges from (an estimated 12 to 300 cases per million workers) [41].

OA may be caused by a demonstrated or presumed immunological response to a workplace exposure (sensitiser induced occupational asthma), or can be due to high level irritant exposure, (for which the most clear example is reactive airways dysfunction syndrome, RADS). Work-exacerbated asthma refers to unrelated asthma

(preceding or with concurrent onset with work) which is worsened either on a sporadic or frequent basis by conditions at work [42].

Sensitiser induced OA can often be related directly to a specific antigen exposure. Overall, the most frequently reported agents include isocyanates [27 30 33-35 43-47], flour and grain dust [27 30 33-35 43-45 47], latex [27 28 33 35 45 47], aldehydes [27 30 33-35 47], hairdressing products [27 34], adhesives [35], metals or metal working fluids [28 30 33 34 45], resins and wood dust [27 30 33-35 46], colophony and fluxes [28 30 33 34 44 46 47] and animals [28 30 34 35 43 47].

OA should be suspected in individuals of working age who develop symptoms of asthma; particularly those who report worsening symptoms at work or improving symptoms during holiday periods and those with exposure to a known or presumed sensitiser [48 49]. Workers developing this condition often do so within the first 1-2 years of exposure [42 50], although longer latent periods do occur, particularly in workers exposed to bakery allergens [51]. Typical symptoms of occupational asthma include episodic wheezing, breathlessness, chest tightness and coughing, all of which may occur at or after work. Such work-related symptoms may be associated with allergic eye or nasal symptoms. Specifically, rhino-conjunctivitis may precede or coincide with the onset of OA, the risk of OA development being highest in the year following the onset of rhino-conjunctivitis. If OA remains unrecognised, ongoing allergen exposure is associated with accelerated lung function decline and chronic persistent asthma may develop. This form of chronic respiratory ill health may persist after allergen exposure has ceased, requiring long-term medication and health service utilisation [41 50].

Certain factors have been shown to affect an individual's risk of developing OA. Atopy is the tendency to produce specific immunoglobulin IgE on ordinary exposure to common allergens, demonstrated by immunological testing or a history of allergic disease (asthma, eczema or hay fever). The European Respiratory Society (ERS) Task Report concluded there is no relationship between atopy and the outcome of occupational asthma [14 52]. The British Occupational Health Research Foundation (BOHRF) state that the risk of developing OA to certain high molecular weight agents that induce the production of specific IgE antibodies has been shown to be increased in atopic individuals [53-75]. The ERS Task Force conclude that a longer duration of bronchial hyper responsiveness was seen in those workers with asthma induced by

high molecular weight allergens compared with low molecular weight allergens [14]. Maestrelli et al. in their review of 36 papers agree with the task force that high molecular weight antigens and older age at presentation are negative predictors of outcome [76]. An increased incidence of OA has also been linked to the higher levels of sensitisation seen in exposure to more concentrated levels of antigen [51 54 57 62 64 68 69 74 77-100].

Some groups have identified smoking as a factor that increases the risk of occupational asthma in workers exposed to certain asthmagens, for example: isocyanates [94 101 102], seafood (fish and crustacea) [64 103 104] and platinum salts [13 82]. Although the ERS Task Force Report found that despite smoking cessation being beneficial to the prognosis of asthma in general, smoking at the time of diagnosis does not seem to have a major impact on the prognosis of OA [14]. This is in agreement with Maestrelli et al. who found smoking at diagnosis did not seem to influence the outcome of occupational asthma [76]. Both concluded that older age at presentation was associated with a poorer prognosis [14 76].

Occupational rhinitis and occupational asthma commonly occur together, especially with high molecular weight sensitisers [105 106]. The onset of rhinitis may coincide with or precede the onset of OA, in which case the risk of developing OA is highest in the first year after the onset of occupational rhinitis [57 61 95 106-111].

Investigations of suspected occupational asthma

Investigations in to OA aim to provide evidence to support or reject the hypothesis that a person's asthma is related to their working conditions. They can be categorised in to pulmonary function testing to demonstrate the work associated variation in lung function and allergen testing to identified the causative agent.

Fishwick et al. approved the British Thoracic Society (BTS) Standards of care for occupational asthma [112] and confirmed there is a considerable evidence base for the use of serial peak expiratory flow (PEF) measurements (recorded at least four times a day for at least three continuous weeks) to investigate workers when OA is suspected. High-quality recordings can be obtained for over 70% of patients, on

condition that the appropriate training and explanation is provided [112]. While these tests may be susceptible to errors, they offer the best and easiest first-line approach to assessing physiological response to asthmagens at work. All recordings should be entered onto a computer for analysis using suitable software. A calculated work-effect index allows charts to be graded positive, equivocal or negative for a diagnosis of OA [112]. A positive chart has a quoted sensitivity of approximately 75% and a specificity of 95% for a diagnosis of OA [113-116], although these estimates are quality dependent and pooled estimates suggest 64% sensitivity and a specificity of 77% [117]. It is important to note that PEF charts do not confirm a specific cause nor do they distinguish OA from work-aggravated asthma [118].

Pre-shift to post-shift changes in lung function may support a diagnosis but they are frequently absent in people subsequently confirmed to have OA as they have a high specificity but only low sensitivity. It is recommended that pre-shift and post-shift forced expiratory volume in one second (FEV_1) changes are only used in conjunction with other diagnostic approaches [112 119-121].

Skin prick and serological testing are highly sensitive for detecting specific IgE and hence type I sensitisation and OA caused by most high molecular weight agents. However these tests are not specific for diagnosing asthma or OA. This means that there are some asymptomatic sensitised workers who will never develop occupational asthma [14 69 112 117 122 123].

While assessment of non-specific bronchial responsiveness to inhaled irritants such as histamine and methacholine is a useful diagnostic investigation, single and serial measures have only moderate specificity and sensitivity for the diagnosis of OA [117 124-127]. However a positive specific broncho-provocation test, that is a change in airway calibre associated with increasing levels of exposure to a specific antigen, comes closest to a gold standard test for the diagnosis of OA, provided exposures received are equivalent to those in the workplace [14]. However due to lack of standardisation, the complexity of the test and the inability to always replicate exposures in the workplace, a negative tests does not necessarily exclude OA [14 103 119 120 128-133]. The laborious nature of a specific broncho-provocation test and the availability of more convenient alternatives mean it is generally reserved for the more difficult diagnostic conundrums [112].

Frequent monitoring of FEV_1 or PEF on multiple days of work, during and between periods of exposure to the suspected agents is referred to as a workplace challenge and is sometimes used to aid diagnosis. Workplace challenges are an alternative but are not standardised and lack external validation [134]. One way of approaching this type of challenge is to take data from non-exposed days to calculate a mean and 95% CI of the 'expected' FEV_1 at each time point. These are compared with FEV_1 values measured on exposed days [112].

Newer techniques are available to investigate potential cases of OA. The measurement of sputum eosinophils and exhaled nitric oxide maybe helpful in the diagnosis [129 135-142] but the absence of them does not exclude OA [125 127 136 137 139 141-143].

The use of ENO as a surrogate marker for monitoring airway response to specific inhalation challenges (SIC) was demonstrated by Sastre et al. [144]. 65 workers with suspected OA were evaluated, 45 of whom had positive specific inhalation challenges (SIC). It was found that a baseline FeNO value of 25 ppb predicted a positive SIC with 60% sensitivity and 80% specificity. The increase in % FeNO cut off point providing maximal sensitivity and specificity for predicting a positive SIC was 41% (sensitivity 50%, specificity 95%). It was concluded that asthmatic reactions induced by occupational agents during SICs are associated with a consistent increase in FeNO, however, the predictive diagnostic capacity of FeNO measurements is low [144].

Disease Prevention

Disease prevention can be divided into primary, secondary and tertiary prevention. Primary prevention in occupational disease aims to prevent the onset of the condition. Such measures include limiting exposure to known asthmagens by hygiene methods, such as ventilation or substitution of the asthmagen with a less harmful agent. It is important to education a workforce exposed to asthmagens, regarding symptoms potentially attributable to exposure, how agents in the workplace can affect health and how best to avoid problems. Key to this positive strategy is the development of a workplace culture that encourages workers to report health

complaints and an understanding of the action plan were they to report work-related respiratory symptoms [14 112].

Respiratory protective equipment has a role to play where control at source is not feasible, however, although it reduces the incidence it does not completely prevent occupational asthma [101 145 146].

Health surveillance, as defined by HSE, is a system of on-going health checks to detect ill health effects at an early stage [147]. This is an important part of secondary prevention which aims to identify disease at a pre-symptomatic stage or early stage. Fishwick et al. in a multi-centre hospital study, demonstrated a mean delay of four years between the onset of symptoms and a confirmation of diagnosis in a group of patients that were largely not afforded annual health surveillance [148]. This contrasts with the findings of Mackie et al. who found a mean delay of nine months in those whose symptoms were detected at health surveillance and who attended for subsequent investigations [149]. Although it is difficult to dissociate the effects of health surveillance from the effects of other risk management procedures it is felt that outcome is improved in workers who are included in a health surveillance programme [150].

Respiratory questionnaires, lung function testing and where appropriate identification of specific IgE by skin prick test or serology are commonly used in health surveillance. There is no generally accepted questionnaire for use in surveillance for OA and some studies of the value of questionnaires to detect asthma suggest that they are insensitive and may lead to an underestimate of the prevalence of asthmatic symptoms [151-153]. It has also been suggested that spirometry may lead to no or few additional cases of asthma that are not identified by questionnaire and can identify many false positives if technique is poor [149 154 155]. Skin prick tests and serological tests can detect specific IgE in workers who have become sensitised to specific allergens (mainly but not exclusively high molecular weight allergens). As IgE sensitisation is related to exposure, sensitisation rates can be used as an indirect measure exposure control and an increased risk of occupational rhinitis and/or OA in workers [156 157]. A combination of these investigation and importantly good technique and correct interpretation of their findings should be able to detect a largely

preventable condition, however health surveillance in OA continues to prove challenging [158].

Tertiary prevention aims to alleviate the effects of established disease. The avoidance of further exposure to the causative agent increases the likelihood of improvement or resolution of symptoms and reduces the chance of additional deterioration [99 159-168]. However, unfortunately the symptoms and functional impairment of occupational asthma may persist for many years after avoidance of further exposure to the causative agent [169]. The chance of a positive outcome is improved in those workers who have relatively normal lung function at the time of diagnosis [124 160 165 170-173], who have a shorter duration of symptoms prior to diagnosis [11 160 163-165 172-178] and who have shorter duration of symptoms prior to avoidance of exposure [11 165 172 176-179].

The European Respiratory Taskforce identified nine studies that compared the effects of persistent exposure to causal agents, with those workers who attained complete avoidance [14 44 99 161 165 170 180-183]. In workers diagnosed with OA, 33.7% of those who avoided further exposure recovered from their asthma whereas symptoms persisted in 93% of patients who remained exposed. The two studies that provided information on worsening of asthma reported that the condition deteriorated in 10 (59%) out of 17 subjects who remained exposed, but in none of those who avoided exposure [181 182].

Unfortunately, although tertiary prevention through redeployment to a non-exposed area may lead to improvement or resolution of symptoms or prevent deterioration in some workers, it is not always effective [104 159 161 164 165 184 185]. In practice the advice to completely avoid exposure maybe rejected for social or financial reasons [186]. In this setting, reduction of exposure may be a useful alternative although once sensitised a worker's symptoms may be precipitated by exposure to extremely low concentrations of the allergen. Respiratory protective equipment is effective only if it is worn, removed, stored and maintained correctly. It has been demonstrated that air fed helmet respirators may improve or prevent symptoms in some but not all workers who continue to be exposed to the causative agent [164 187-191].

The cost of occupational asthma

There is consistent evidence derived from workforce and clinical case series that about one third of workers with OA are unemployed up to six years after diagnosis [5-13 192] and that loss of employment following a diagnosis of OA is associated with loss of income [5 6 9 10 12 162 192-194]. In comparison with other adult asthmatics those with OA may find employment more difficult [8 9] and their financial loss may be greater [194]. Based on prices in 2004, an annual total cost per ‘‘average’’ person diagnosed with OA was estimated at £305–£2,735 [15]. The best case scenario for a worker is that they are relocated to jobs without exposure to the causative agent. It has been shown that these workers are more likely to remain in employment and are unlikely to leave those jobs because of their asthma [195].

Extrinsic allergic alveolitis

Extrinsic allergic alveolitis (EAA), or hypersensitivity pneumonitis (HP) as it is more commonly referred to outside the UK, was first described in the early 20th century in farmers exposed to mouldy hay or straw, hence the term farmer's lung [196 197]. EAA is a group of immune mediated lung diseases resulting from an inappropriate response to the inhalation of an antigen to which the subject has been previously sensitized immunologically. This typically results in shortness of breath, a restrictive lung defect and interstitial infiltrates seen on lung imaging caused by the accumulation of T lymphocytes in the lungs [198-200].

Over time a larger number of antigens have been described from a variety of environmental settings, e.g. farmer's Lung (*Thermophilicactinomyces, Aspergillus* spp, *Candida albicans, Sporobolomyces* spp, *Micropolyspora faeni*) bird fancier's lung (avian proteins), bagassosis (*Thermoactinomyces sacchari*), mushrooom worker's lung (*Thermoactinomyces* sp, *Agarieus hortensis* spores) and hot-tub lung (*Mycobacterium avium intracellulare*) [200 201]. Most EAA causing antigens are organic particles; however some chemical compounds (e.g. isocyanates and zinc) can act as haptens which link the host albumin to create an antigenic particle [202 203].

The pathogenesis of EAA involves repeated antigen exposure, immunological sensitization of the host to the antigen and immune response causing respiratory and systemic symptoms. Only a small percentage of those exposed to an antigen will be susceptible and therefore develop EAA. Interstitial and alveolar inflammation with granuloma formation is the characteristic result of the immune response [201]. This is thought to involve a combination of type III hypersensitivity reactions; supported by the lag in onset of symptoms after initial exposure and high levels of antigen specific IgG in serum and bronchalveolar lavage (BAL) and type IV delayed hypersensitivity reactions to the inhaled antigen; supported by the presence of granulomas [201] and evidenced by anecdotal clinical accounts. Such histories include the confirmation of EAA in a patient with known hypogammaglobulinaemia and therefore an inability to mount a type III hypersensitivity reaction [204] and the development of EAA in a patient with AIDS, when she was successfully treated with anti retrovirals [205].

Studies regarding the incidence or prevalence of farmer's lung over the past two or three decades, have illustrated the difficulties in studying the epidemiology of EAA. Methodological issues including study design and the definition of farmer's lung have made definite conclusions elusive [198] [206-208]. The majority of studies are cross-sectional surveys in order to determine the prevalence of farmer's lung or associated markers such as the presence of precipitating antibodies against offending antigens. Few if any cohort studies have been published on the incidence of the disease [207] [209-211]. Those patients admitted to hospital with such extreme symptoms that they underwent investigations so rigorous to enable the diagnosis of farmer's lung, e.g. chest X-ray (CXR), high resolution CT scan (HRCT), Bronchoalveolar lavage (BAL) and/or lung biopsy, are likely to represent severe manifestations of the disease process. Thus the prevalence of disease estimated using epidemiological reports based on cases admitted to hospital are likely to under estimate the true burden of disease [207].

Prevalence rates vary widely between countries and are influenced by factors such as climate, seasonal and geographical conditions, local customs, smoking habits and differing work practices and processes [198]. In a population based study, the estimated annual incidence of interstitial lung disease was 30 per 100 000. In that study, EAA accounted for less than 2% of the incident cases, however the study was conducted in New Mexico, in a dry environment that is not propitious to the development of many forms of EAA [212].

Clinical presentation of EAA varies and has traditionally been divided in to acute, sub-acute or chronic [203]. The mode of presentation depends on the frequency, intensity and duration of exposure to the aetiological agent and on the host's immunological reaction. Classification of EAA in to acute and chronic forms can be misleading as it may be assumed that there is an inevitable progression from acute to chronic disease if antigen exposure continues. The interaction of antigen exposure and host response in the initiation and progression of the disease is considerably more complex and the clinical course of the disease is unpredictable [198].

Typically both respiratory and systemic symptoms are apparent. Respiratory symptoms such as cough and shortness of breath are usual but not universal. In the acute form systemic symptoms often predominate, presenting with recurrent

episodes of flu like illness consisting of chills, fever, sweating, headaches, nausea, general malaise and lethargy. Symptoms usually begin 2-9 hours after exposure and peak after 6-24 hours, potentially lasting for days. The subacute form may occur gradually over weeks and tends to have more predominant respiratory symptoms. The chronic form has an insidious onset with increasing cough and shortness of breath over months. Fatigue and weight loss may be prominent features [207]. Recent research using the SF-36 questionnaire concluded that compared with patients with idiopathic interstitial pulmonary fibrosis with similar pulmonary function, patients with chronic EAA perceived a significantly lower quality of life [213].

Clinical examination may be normal, particularly between episodes of acute exacerbations, or may demonstrate signs such as bibasal crackles, fever, clubbing and in cases of severe chronic disease, right sided heart failure and cyanosis [198 203 214]. Lacasse et al., during their work evaluating predictors of hypersensitivity pneumonitis, studied 116 patients with HP and found that 87% had inspiratory crackles, 32% were cyanosed and 21% had clubbing [215].

Others have suggested a classification that takes in to account the progression of the disease (acute intermittent, acute progressive, chronic progressive, chronic non-progressive) that can only be assessed retrospectively [206 216]. Lacasse et al. addressed the issue of clinical diagnostic criteria of EAA by completing a prospective multi-centre cohort study in order to develop a clinical prediction rule for the diagnosis of active EAA. This tool was designed to aid physicians by calculating an accurate probability of EAA and so assist in decision making regards further investigations to rule the diagnosis in or out [207 215]. Girard et al. re-analysed the data that had been collected for the development of the Lacasse prediction rule [215], to determine whether the current classification of EAA truly reflected categories (‘clusters’) of patients with maximally differing clinical patterns. A two cluster solution best fitted the data. Cluster one (41 patients) had more recurrent systemic symptoms (chills, body aches) and normal CXR. Cluster two (127 patients) had significantly more clubbing, hypoxaemia, restrictive patterns on pulmonary function testing and fibrosis on HRCT. Nodular opacities on HRCT were seen equally in both clusters [217 207]. There was considerable disagreement between the current classification of EAA and the result of Girard’s analysis.

Investigative results are often variable and there is no gold standard test with which to diagnose EAA. The diagnosing physician may initially suspect EAA on the basis of the presenting history and examination findings. A key element in the history is often exposure to a known causative agent. For example mouldy hay causing farmer's lung and avian droppings or feathers leading to bird fancier's lung. If the allergen is not recognised by the physician or is a novel agent, as is the case with metalworking fluids (MWF), the diagnosis may be missed. Patients are often initially diagnosed with an infective condition [198 203].

Investigation of suspected extrinsic allergic alveolitis

Blood tests may be helpful. In the acute setting peripheral blood neutrophillia and lymphopenia are common. Inflammatory markers may also be raised. If the specific antigen is known it may be possible to demonstrate serum antibodies in a peripheral blood sample. This shows significant exposure but does not prove causation [198]. For example, 10% of people exposed to *Saccharopolyspora rectivirgula*, the main agent in farmer's lung, develop antibodies; but only 0.3% will develop the EAA [218]. Nevertheless, specific antibody analysis can be useful as supportive evidence. In Girard's clinical prediction model, positive serum antibodies were found to be a significant predictor of EAA (odds ratio: 5.3; 95% CI: 2.7-10.4) [207].

Chest X-ray (CXR) is often one of the initial steps in the investigation of suspected EAA. In the acute phase it would be expected to show small, poorly defined nodulation, occasionally symmetrically sparing the apices or bases. A diffuse, soft, patchy infiltrate may also be seen with or without nodulation however in 20% of cases it is normal [219 203]. In the chronic fibrotic phase a linear element, particularly at the periphery, becomes more distinct and there is a loss of lung volume. None of these findings are specific to EAA [203].

More sensitive than CXR and commonly key to the diagnosis of EAA is the high resolution computed tomography scan (HRCT). A study of 21 patients with subacute and chronic bird breeder HP found 7 patients to have normal CXRs but all 21 had abnormal HRCT [220]. However, Lacasse et al. found that 16 of 199 (4%) patients with proven EAA had a normal HRCT [215].

Due to the radiological similarities with pulmonary oedema and the rapid resolution of symptoms, patients with acute EAA rarely undergo HRCT imaging. In subacute disease, the characteristic HRCT pattern is the presence of patchy or diffuse ground-glass opacities (reflecting the presence of diffuse interstitial pneumonitis and to a lesser extent a degree of organising pneumonitis), poorly defined centrilobular nodules (secondary to cellular bronchiolitis), mosaic attenuation on inspiratory images and expiratory air trapping (due to small airway obstruction by cellular bronchiolitis or constrictive bronchiolitis) [221].

No one radiological finding is pathogonomic for EAA, for example ground glass changes can be seen in a variety of other disease, e.g. pneumocystis carini pneumonia, bronchoalveolar carcinoma and alveolar haemorrhage; but a combination of these findings supports the diagnosis of EAA. The combination of increased attenuation (ground glass), decreased attenuation (air trapping) and normal lung attenuation on an inspiratory film, is referred to as 'head cheese' (the different densities seen in a slice of a specific continental sausage) [199].

Chronic HP is characterized on HRCT by the presence of reticulation and traction bronchiectasis and bronchiolectasis due to fibrosis, superimposed on findings of subacute HP. The fibrosis typically spares the lung bases but can be patchy, random, or have a predominantly subpleural and peribronchovascular distribution. The radiological and pathological findings frequently overlap with those of nonspecific interstitial pneumonia and usual interstitial pneumonia. EAA must always be considered as a diagnosis in patients found to have changes consistent with these diagnosis [203] [221].

The role of pulmonary function testing (PFT) is two-fold. It may assist in diagnosis, and also, if abnormal, can guide therapy and monitor response. Pulmonary function testing has no role in discriminating EAA from other interstitial lung disease [215]. The typical pattern would be one of a restrictive defect (with a reduced forced expiratory volume in one second (FEV^1) and a reduced forced vital capacity (FVC) and because of the inflamed or fibrotic alveolar wall membrane, it would be expected that the gas transfer would be reduced [222] [203]. This is however far from consistent and spirometric findings may be normal, obstructive or mixed. In farmer's lung the most frequent defect is obstructive due to emphysema [223]. Girard et al. found that 39 of the 177

patients (22%) in whom the transfer factor of the lung for carbon monoxide (TLCO) had been measured had results in the normal range (defined as TLCO > 80% predicted) at the time of the diagnosis [207].

When comparing HRCT and PFT as means to monitor disease progression in 92 patients with chronic EAA, Walsh et al. found that HRCT patterns, especially the extent of traction bronchiectasis and honey combing, are superior to PFT and are strongly predictive of poor survival [224].

Inhalation challenges involve inhalation of the suspected causative antigen, usually at the workplace or as specific provocation tests in controlled conditions, with monitoring of symptoms and lung function [225]. These are occasionally used but there are no standardised techniques available or criteria defining a positive response. Some experts state that further studies are needed before recommending inhalation challenges in the diagnosis of EAA [207]. Others, however, feel that in some cases inhalation challenges provide useful information in the diagnosis of patients [203].

Bronchoalveolar lavage (BAL) and the measurement of white cell sub-type, is an invasive test that is used in some centres to aid diagnostic evaluation of interstitial lung disease. It is traditionally thought that EAA can be differentiated from other causes of interstitial lung disease based on the proportion of different cell types. A normal lymphocyte count rules out all but residual disease [207] [226]. Although the presence of an alveolar lymphocytosis would support a diagnosis of EAA, it is by no means pathognomic as it can also occur in other respiratory conditions e.g. sarcoidosis [227], silicosis [228], bronchioloitis obliterans with organising pneumonia [229] [230], drug induced pneumonitis [231], non-specific pneumonitis [231].

Lymphocytosis is also seen in asymptomatic exposed people. Cormier et al. studied 24 asymptomatic dairy farmers. Thirteen had serum precipitins to *Micropolyspora faeni* (MF) antigens (Group 1), and 11 were seronegative control subjects (Group 2). Thirteen of 24 subjects (9 in Group 1 and 4 in Group 2) had a high percentage of lymphocytes (greater than or equal to 20%) in their BAL [232]. Cormier et al. also concluded that although an increase in BAL lymphocytes is seen in acute Farmer's Lung Disease it does not correlate with physiological changes [233]. To verify the outcome of this lymphocytosis in asymptomatic farmers, they were restudied 2 or 3

years later. All subjects were still working on the farm and none had had symptoms suggestive of farmer's lung disease. Lymphocytes from BAL were still increased in 9 of 12 subjects, whereas 3 had returned to normal; of the 15 subjects with previous normal values, 3 now had an abnormal lavage lymphocytosis. There was no correlation between lung function variations and the percentage of lymphocytes in the previous or the present BAL. It was concluded that a bronchoalveolar lymphocytosis is a persistent phenomenon in a large number of asymptomatic dairy farmers, and that this finding does not seem to be related to significant disease [226].

Twenty seven of the asymptomatic farmers with or without precipitins or lymphocytosis on BAL were restudied 20 years after the initial study. 16 were subjects were missing, 11 refused follow up, 3 had died and 2 could not be located. Only one of the 27 described shortness of breath and that was thought to be secondary to asthma. It was concluded that serum precipitins and asymptomatic lymphocytic alveolitis in an asymptomatic exposed dairy farmer have no clinically meaningful long-term consequences [234].

Sarcoidosis is typically associated with a predominance in CD4+ T cells and a CD4+/CD8+ ratio of >1 compared to an increase in CD8+ cells and a ratio <1 in EAA [235]. Traditionally this has been used to differentiate the two conditions however it is now known that CD4+/CD8+ ratio in EAA can be increased to levels as high as those seen in sarcoidosis [236-238]. Recent studies suggest that in chronic EAA and asymptomatic exposed people, a low CD4+/CD8+ ratio is typical; however in the acute presentation a predominance of CD4+ cells can be expected [201 239]. Type, dose and duration of inhaled antigen may also play a role in the CD4+/CD8+ ratio [200 201 240].

The histopathology of EAA has been well described. During the active phase of the disease biopsy would typically show an interstitial alveolar infiltrate consisting of plasma cells, lymphocytes and occasional eosinophils, usually accompanying small necrotising granulomata. Interstitial fibrosis is common and bronchiolitis is found in about half of cases. Vasculitis is not a feature [203 214]. In chronic stages, widespread fibrotic reaction is a predominate feature. Emphysema is also a recognised complication of long term EAA [223], however the mechanism for this is not clear [220].

Transbronchial biopsy (TBB) performed at bronchoscopy is thought to be of limited usefulness in the diagnosis of EAA, as documented in farmer's lung by Lacasse et al. Analysis of 105 TBBs (55 cases of farmer's lung matched with 50 control samples with other parenchymal disease) was performed by two independent pathologists. The assessors were asked to assign each TBB in to one of four diagnostic categories: (1) probable farmer's lung, (2) possible farmer's lung, (3) nonspecific and (4) alternative diagnosis. 48.6% of the TBBs were considered to be nonspecific. It was concluded that TBB should be reserved for patients with intermediate pretest probability of farmer's lung [241]. A retrospective study in China, including 96 patients with HP also concluded that TBB was of limited value, giving a positive result in only 8.2% of cases [242].

Open lung biopsy is more likely to provide a useful tissue sample enabling recognition of a characteristic combination of interstitial pneumonia, bronchiolitis, and granulomatous inflammation [243]. This needs to be weighed against the invasive nature and associated risk of the test as well as the potential change in clinical management depending on the findings of the biopsy. Several retrospective studies have addressed these issues, with mixed results. The diagnostic yield, i.e. the proportion of specific diagnosis obtained from the procedure, ranged from 34% to 100%; therapy was altered in 46% to 76% of cases. The selection of patients for lung biopsy, the timing of the procedure along the course of the disease and the expertise of the pathologist are all factors that contribute to the variation in results [207]. It has been recommended to only perform surgical biopsy on those patients with unusual clinical presentation or when the clinical course or response to therapy is not as expected [244].

Lung biopsy can have a key role in recognising patients with chronic hypersensitivity pneumonia and hinges on recognition of a characteristic combination of interstitial pneumonia, bronchiolitis and granulomatous inflammation. Late-stage disease is associated with fibrosis that may mimic other forms of fibrotic lung disease, including importantly UIP. The available evidence suggests that fibrosis predicts a worse prognosis, although this has not been prospectively validated [221 245].

Diagnositc Criteria

The lack of one specific test to diagnose EAA has led to the formation of many diagnostic criteria in an attempt to standardise the diagnosis [203] [210] [244] [246]. These criteria generally consist of a combination of signs, symptoms and investigative results, none of which have been validated (table 1and 2).

Table 1: Summary of diagnostic criteria for EAA for clinical purposes [207]

Author	Minor Criteria	Major Criteria
Terho [210]	1.Exposure to offending antigens (revealed by history aerobiological or microbiologic investigations of the environment, or measurements of antigen specific IgG antibodies 2.Symptoms compatible with HP present and appearing or worsening some hours after antigen exposure 3.Lung infiltrations compatible with HP visible on chest x-ray	1.Basal crackles 2.Impairment if the diffusion capacity 3.Oxygen tension (or saturation) of the arterial blood either decreased at rest, or normal normal at rest but decreased during exercise 4.Restrictive ventilation defect in the spirometry 5.Histological changes compatible with HP 6.Positive provocation test either by work exposure or by controlled inhalation challenge
Richerson et al [203]	1.The history and physical findings and pulmonary function testing indicate an interstitial lung disease 2.The X-ray film is consistent 3.There is exposure to a recognised cause 4.There is antibody to that antigen	
Cormier et al [248]	1.Appropriate exposure 2.Inspiratory crackles 3.Lymphocytic alveolitis (if BAL is done) 4.Dysponea 5.Infiltrates on chest radiograph or HRCT	1.Recurrent febrile episodes 2.Decreased DLCO 3.Precipitating antibodies to HP antigens 4.Granulomas on lung biopsy (usually not required) 5.Improvment with contact avoidance or appropriate treatment
Schuyler [246]	1.Symptoms compatible with HP 2.Evidence of exposure to appropriate antigen by history or detection in serum and/or BAL fluid antibody 3.Findings compatible with HP on chest radiograph or HRCT 4.BAL fluid lymphocytosis 5.Pulmonary histological changes compatible with HP 6.Positive ‘natural challenge’	1.Bibasilar rales 2.Decreased DLCO 3.Arterial hypoxaemia either at rest or during exercise

Table 2: Probability (%) of having hypersensitivity pneumonitis* [207 217]

				Crackles			
				+		-	
Exposure to a known offending antigen	Recurrent Episodes of symptoms	Symptoms 4-8 h after exposure	Weight loss	Serum precipitins		Serum precipitins	
				+	-	+	-
+	+	+	+	98	92	93	72
+	+	+	-	97	85	87	56
+	+	-	+	90	62	66	27
+	+	-	-	81	45	49	15
+	-	+	+	95	78	81	44
+	-	+	-	90	64	68	28
+	-	-	+	73	33	37	10
+	-	-	-	57	20	22	5
-	+	+	+	62	23	26	6
-	+	+	-	45	13	15	3
-	+	-	+	18	4	5	1
-	+	-	-	10	2	2	0
-	-	+	+	33	8	10	2
-	-	+	-	20	4	5	1
-	-	-	+	6	1	1	0
-	-	-	-	3	1	1	0

-Absent + present *All the predictors are dichotomous variables.

Treatment

The ideal treatment for EAA is removal of the patient from the offending antigen or in circumstances where this is not possible, to substantially reduce the exposure. The achievability of this is variable for example, farmers are often reluctant to change profession. There are means of significantly reducing the amount of antigen exposure in the farming industry, e.g. ensuring adequate drying of fodder, using silage instead of hay and avoiding the barns when animals are eating [207]. Similarly pigeon fanciers unwilling to stop their pastime are encouraged to reduce the time spent with their pigeons, avoid excess handling of the birds and activities that involve high levels of exposure and increase loft ventilation [201]. Antigen exposure can be further reduced by the application of appropriate respiratory protection.

A study reviewing 142 patients with EAA found that 75 (53%) did not have a demonstrable causative antigen. After adjusting for mean age, presence of fibrosis, mean % forced vital capacity (FVC), diffusing capacity of the lung for carbon monoxide (DLCO) and history of smoking, survival was longer for patients with an identified causative agent (median, 8.75 years vs 4.88 years; P = .047) [247].

Pharmacological treatment for EAA is limited in its value. 36 patients in the acute phase of farmer's lung were randomised in to two groups, one group was treated with corticosteroids and the other was given a placebo**.** Following one month of treatment there was a significant difference (p = 0.03) in DLCO between the treatment groups. However, after a follow-up of 5 yr no statistically significant differences were found between the treatment groups in FVC, FEV_1, or DLCO [248].

These findings compare to those previously reported by Mönkäre in 1983, when in a prospective study of farmer's lung disease, 93 patients were subjected to a follow-up period of an average of 18.6 months. Lung function, examination and CXR findings were recorded at intervals of one, three, six and 12 months and every six months after that. The patients were treated with either a zero, four or twelve week course of corticosteroids. Lung function or the prognosis of working capacity did not seem to be related in any way to the amount of corticosteroids received. However, corticosteroids were found to improve the appearance of CXR changes. It was

concluded that corticosteroids should be given to severely ill patients to improve symptoms, but no apparent benefit is derived from long-term treatment [249].

Treatment with less traditional immunosuppressants such as rituximab, a B lymphocyte depleting monoclonal antibody, have also been used in patients with severe progressive interstitial lung disease resistant to corticosteroids, including EAA, with some success. However more research needs to be completed in order to validate these findings and assess safety outcomes [250].

Unfortunately on some occasions, even with apparent discontinued exposure, the disease process will progress. The reason for this is not clear. In bird fancier's lung (BFL), despite intensive environmental control measures, bird antigen can be found in patients' homes for up to 18 months after the removal of the bird. This may account for the persistence of symptoms in some cases. In severe cases of BFL, the preferred option maybe to temporarily relocate the patient away from the room in which the bird was housed [251].

When patients are in the chronic phase of the disease, the disease pattern is one of irreversible fibrotic changes and little can be done to improve the clinical picture other supportive treatments such as pulmonary rehabilitation [252] and supplementary oxygen and in some cases lung transplantation [198]. However, when compared directly to patients with idiopathic interstitial pulmonary fibrosis causing the same amount of fibrosis, the prognosis of patients with chronic EAA was favourable [253].

Metal working fluids

History

Metal working operations such as drilling, grinding and boring, create significant heat as well as other waste products such as metal debris and swarf (metal turnings). Metal working fluids (MWFs) are used as coolants and lubricants to facilitate manufacture of metal components. The fluids carry away metal chips and protect the surfaces of the metal being processed [254].

As early as 31 BC, Vitruvius who's ten books, the only work of its kind to survive from the Roman world, describes a water pump with bronze pistons and cylinders that were machined on a lathe with 'oleo substracti', indicating the use of olive oil to precision turn the castings [255]. In China, Sung Ying Hsing (1637) wrote about the advantage of oil in cart axles. Hooke (1685) advised on the need for sufficient lubrication for carriage bearings, and Amontons (1699) explained laws of friction in machines through experimentation. In the same year (1699), De la Hire described the practice of using lard oil in machinery. Desaugliers (1734) suggested that the role of lubricant was to fill up the imperfections on the surfaces and act as tiny rollers, and Leupold (1735) recommended that rough surfaces should be lubricated with tallow (animal based fat) or vegetable oil [256].

One of those most important factors in the development of lubricants was the discovery of huge amounts of petroleum in the USA in 1859. Petroleum at that time was largely refined for the production of kerosene for illumination and fuel. Oil was considered a by product and as such was discarded. The refiners, forced to find a solution to what was becoming an environmental problem, induced industry to use oil for lubricant applications. As a result petroleum oil began to replace some of the popular animal and vegetable oil-based lubricants [256].

In 1938 in Germany, Schallbroch, Schaumann and Wallichs provided empirical evidence through experimentation, to support the relationship between tool life and cutting tool temperature. In the US, during the same time period, Ernst, Merchant and Shaw studied the mechanics of the cutting process. Merchant found that the right type of cutting fluid could greatly reduce the frictional resistance in both metal deformation and in chip formation, as well as reduce the heat produced in

overcoming friction. This heralded many more experiments by several researchers. Compiling the findings, Ernst, Merchant and Shaw theorised that if they could combine those chemicals that had been proved to be effective friction reducers, with water, in the form of a stable chemical emulsion, a new cutting fluid having both friction reducing and cooling attributes could be created. In 1945, as a result of this research, their company compounded a new type of 'synthetic' cutting fluid. Two years later the same company introduced the first 'semi synthetic' MWF. It was a preformed emulsion very similar to a soluble oil but with better rust control and chip washing action [256].

Modern day

Transformation in the workplace lagged behind the science with a gradual change from neat mineral oil use to the more modern emulsions. The composition of clean MWFs is variable between companies and is continually reviewed in the light of improving science. Formulations typically contain a 5-7% content of oil (either mineral oil, semi synthetic or synthetic oil) in a water emulsion, with other chemical constituents to enhance the performance of the product, e.g. emulsifiers, anti-weld agents, corrosion inhibitors, extreme pressure additives, buffers (alkaline reserve) and biocides [256].

In use, the fluid complexity is compounded by contamination with substances from the manufacturing process (such as tramp oils which refer to hydraulic oil or grease leaking from the machinery) and particulate matter from grinding and machining operations. Furthermore, water-based metalworking fluids support microbial growth, which introduces biological contaminants such as bacterial and fungal cells or cell components and their related biological by products such as endotoxins, exotoxins, and mycotoxins [257].

MWFs are used in vast quantities worldwide. In 2007, the United States used approximately 420 000 metric tons of MWF, 305 000 metric tonnes were used in Western Europe, and 815 000 metric tonnes in the Asia/Pacific region [258]. Annually in the USA, 1.2 million workers in machine finishing, machine tooling, and other metalworking and metal-forming operations are potentially exposed [257]. The Health

and Safety Executive (HSE) estimates that in the UK there are 100 000 to 200 000 people that are exposed to MWFs. Workers can be exposed to the fluids by breathing aerosols generated in the machining process, or through skin contact when they handle parts and equipment covered with the fluids [259].

MWF is typically sprayed on to the moving parts of machinery, drains away and is collected in a reservoir, referred to as a sump, from where it is re-circulated. Some metal working machines employ stand alone small volume sumps, where as in large plants, many machines can be fed from a single shared sump (e.g. containing more than 200,000 litres of MWF) [260]. Given the cost of MWFs, the larger reservoirs of MWF are typically kept for long periods (months to years) and changes to their composition are therefore more likely. The high water content of modern MWFs makes them highly susceptible to colonisation both by bacteria and fungi because of the combination of the correct requirements for microbial growth, including nutrient sources (from the MWF, from water used as a diluent and from dust, swarf and debris accumulating in sumps); environmental conditions conducive to microbial growth (temperature and aeration; ability to form biofilm on surfaces) and source of microbial inoculums (water, dust, swarf and debris). This is exacerbated by the length of time MWF is in use but modified by controls to reduce microbial colonisation, including MWF management and the addition of biocides where appropriate. Consequently, any MWF system in use potentially may have a dynamic population of microbial contamination. Typically MWFs are formulated at high pH (pH~9.0) but excessive growth of microorganisms can lead to increased acidity. Due to evaporative loss, the concentration of emulsion based MWFs can also change which impacts on their performance. The accumulation of metal fines and other chemical contaminants may lead to deterioration in the performance of a MWF, which therefore may need regular monitoring and adjustment [259 261].

Health and Safety

HSE provides guidelines on mist and fluid control, cleaning and management of sumps and bacterial control. Well maintained fluid contains less than 2% tramp oil, metal fines below 100 mg per litre of fluid, and less than 10^3 CFU/ml (1 000 colony-

forming units per millilitre of fluid) [262]. In the early 1990s in the UK, the occupational exposure standards (OESs) for highly refined mineral oil mists were derived from the work of the American Conference of Govermental Industrial Hygienists and were set at 5 mg/m^3 for an 8h time weighted average and 10 mg/m^3 for short exposures. These measurements refer only to the quantity of oil suspended in an air sample. However, as modern MWFs are more complex mixtures containing mainly water with multiple additives, it was concluded by the Health and Safety Advisory Committee on Toxic Substances that the previous OESs should not apply to modern MWFs including mineral oil derived MWFs. The committee concluded that due to the lack of evidence of an inhalation level that would not cause ill health, it was not possible to derive a new safety standard. In the absence of OESs, HSE developed a package of guidance regarding the assessment and control of personal mist exposure, good fluid management and correct training, in order to try and effectively manage health risks associated with exposure to MWFs [259 263].

In the USA, in 1998, The National Institute of work Safety and Health (NIOSH) recommended that exposures to MWF aerosols be limited to 0.4 milligrams per cubic meter of air (thoracic particulate mass – particles that can penetrate the upper airways and enter the lungs) or 0.5 milligrams per cubic meter of air (total particulate mass), as a time-weighted average concentration up to 10 hours per day during a 40-hour working week. The recommended exposure limit (REL) is intended to prevent or greatly reduce respiratory disorders associated with MWF exposure. It is acknowledged that some workers have developed adverse respiratory effects when exposed to MWFs at lower concentrations [257].

In 2002 a survey lead by HSE, of 24 sites using MWF in the UK found that fluid management was found to be of a poor standard with high levels of bacteria, endotoxins and metal fines in sumps. Control of other factors such as water-mix fluid concentration was also poor. However, in general, occupational exposure to mineral oil MWF mist was controlled to <3 mg/m^3 (8h time weighted average) and water mixed MWF mist to <1 mg/m^3. Although these values did not necessarily represent best or safe practice, they were thought to be representative of the industry as a whole and were instituted as the new guidance values [259 263].

Disease associated with MWFs

Until the middle of the 20th century, the primary route of personal exposure to MWFs was through the skin. Consequently, historically, the use of neat mineral oil as a MWF was associated with skin disease such as folliculitis (inflammation of the hair follicles), dermatitis, and skin cancer [260]. These problems were found mainly on exposed areas, for example the neck, hands, arms and thighs. The association between exposure to mineral oils and squamous cell cancer of the skin, particularly the scrotum, has been well documented since the 1800s [264-266]. The International Agency for Research on Cancer has concluded that hydrocarbon mineral oils used in metal machining are carcinogenic [267]. At this time respiratory problems were not commonly reported and largely restricted to a rare lung condition called lipoid pneumonia, due to oil retention within the lung [268 269]

With the introduction of high speed machinery, significant exposures to MWFs can potentially occur via inhalation of the mist. This change in technology and the resultant change in the possible route of entry have turned public health attention toward potential effects on the digestive and respiratory systems. A number of papers have discussed the potential increased risk of cancer associated with exposure to MWF, especially to straight oils [270]. Significant associations have been made between straight oil exposure and an increase risk of bladder, oesophageal, laryngeal, colon, rectal cancer and malignant melanoma [271-275 276]

Other researchers have noted association between soluble MWF and cancer of the larynx, oesophagus, skin, and brain, and noted a relationship between synthetic MWF and cancer of the oesophagus, liver, and prostate [274 276]. The carcinogenicity of MWFs is beyond the remit of this thesis.

Despite a move away from mineral oil based MWFs, dermatological problems remain prevalent, from both irritant and allergic contact dermatitis [277]. Soluble metal working fluids are strong alkaline solutions (pH of approximately 9) and contain numerous additives and solvents. These solutions may cause irritant dermatitis by removing the natural protective oils from the skin, and directly damaging skin proteins. Allergic dermatitis is less common than irritant dermatitis, but allergic skin responses may

occur due to additives in MWFs and dissolved metal impurities such as chrome, and nickel [260].

Over recent decades, the changing composition of MWFs has been accompanied with a change in the associated occupational disease profile. In addition to skin disease, the use of water-based MWFs has led to an increase in respiratory diseases, It has become evident that as well as dermatological conditions, outbreaks of respiratory disease have been reported particularly OA and EAA, but also bronchitis and humidifier fever. For those physicians specialising in occupational lung disease, the presence of individuals suffering from these conditions has illustrated the emerging problem.

In 1983, Hendy et al. described one of the first reported cases of OA secondary to MWF in the UK [278]. Subsequently in 1998, Robertson et al. wrote a case series of twenty five patients occupationally exposed to MWFs and who had been referred to an occupational respiratory clinic with work-related asthmatic symptoms [261]. MWF as a potential cause of EAA amongst machinists was first identified by Bernstein et al. in 1995. They reported a case series of six workers from an automobile manufacturing site, exposed to a synthetic MWF [279]. In 1997, due an increasing awareness of outbreaks of respiratory ill health associated with MWF exposure, a workshop was set up to discuss eight clusters of EAA. They concluded that a risk exists for this granulomatous lung disease where water-based fluids are used and unusual microbial contaminants predominate. The workshop participants identified knowledge gaps regarding risk factors, exposure-response relationships, intervention efficacy and natural history, as well as surveillance needs to define the extent of the problem in this industry [280]. The thesis will cover the association between MWFs and allergic respiratory disease in detail.

Aims of this research

1. To better understand MWF-related health problems by firstly reviewing the findings from previous outbreaks.

2. To analyse data from a large UK outbreak in order to develop guidance for use in future health investigations.

Chapter 1: Review of outbreak investigations of ill health associated with the use of Metalworking Fluids

Introduction

Although cases of OA and EAA due to MWF exposure had previously been described, the first major UK outbreak was investigated by HSE in June 2005. This was at the Longbridge Powertrain plant, where engines were constructed for the car industry [260] [281]. An investigation was triggered following the diagnosis of twelve individual cases of EAA in workers from this site. Extensive clinical, microbiological, immunological and hygiene studies were completed. Attention was focused on the use of water based MWFs and wash fluids (used to clean machined engine components). Out of a total workforce of 836, 87 workers (10.4%) met case definitions for occupational lung disease, comprising 19 cases of EAA, 74 cases of occupational asthma, and 7 cases of humidifier fever. Despite a very detailed outbreak investigation, the cause of the outbreak was never fully established. Results of air monitoring between May 2002 and October 2003 showed that concentrations of MWF in the air were generally below the HSE guidance value of 1mg/m^3 [259] [263]. In October 2003 the levels of mineral oil mist in air were between 1 and 4 mg/m^3 with an average concentration of just above 1mg/m^3. Although microbial contamination/endotoxin levels were low in the main shared MWF reservoirs, individual MWF sumps and component wash machine fluids were very heavily colonised. Bacterial contamination was therefore implicated in the outbreak and the majority of the cases of EAA showed immune precipitin responses to these bacteria [260]. The occurrence of this large outbreak demonstrated that adherence to the Occupational Exposure Standard (5 mg/m^3 for a 8-hour time-weighted average reference based on the measurement of oil mist) applicable in the UK at that time, did not prevent cases of respiratory disease [259] [263].

The results of the Powertrain investigation served to highlight the difficult area of ill health and occupational exposure to MWF, which led to the subject being formally discussed by the government Working Group on Actions to Control Chemicals (WATCH). Members of WATCH commented that previously published literature suggested a possible difference in the geographical distribution of cases of respiratory disease versus reported skin disease, attributable to MWFs [282]. For

example, it was noted that Nordic countries had reported very little respiratory disease and more commonly reported skin disease (i.e. dermatitis). The UK and USA were the countries that had experienced large outbreaks of respiratory disease amongst staff working with water based MWF. It was asked whether this difference was attributable to the way that MWFs were managed or was a consequence of the way that occupational illness is investigated and reported in these countries. At a subsequent WATCH meeting (June 2007), recommendations were made to review published studies, papers and reports from around the world referring to outbreaks of disease amongst MWF workers [283].

To enable a full assessment of the international scale and distribution of outbreaks it was important to review international published and non-published studies of ill health outbreaks attributable to work with water based MWFs. Data about the potential 'triggers' for these investigations of ill health, the methodology employed and the outcome of each investigation was summarised (see appendix 1). The objective was to seek explanations for the apparent differences in the reported prevalence of respiratory and skin disease between these countries.

Methodology

To better understand the demographics of disease associated with MWFs a two phased approached was utilised. In the first stage a detailed literature search was carried out, to identify and review all previously published 'outbreak' investigations related to ill health associated with use of water mix MWFs. For the second stage, in an attempt to gain further information, contacts were made with European occupational ill health reporting networks.

Literature review of published outbreaks

Before commencing the literature searches an experienced team (consisting of two occupational lung disease specialists, two microbiologists and an immunologist) identified appropriate search terms in consultation with the HSE library information search team. These terms were divided into two groups (Table 3).

Searches were carried out combining each term in list one with each term in list two. The searches were based upon proximity of these terms i.e. appearing in any order within the document abstract but no more than five words apart. The HSE library services then independently completed the search on OSHROM (HSELINE, NIOSHTIC, CISDOC, RILOSH and OSHLINE) databases, Embase, Medline, Healthsafe and Web of Science (Table 4), between 1990 (prior to the large scale introduction of water based MWF) and October 2008.

A total of 1346 references were located and the titles and abstracts of these reviewed by relevant specialists within the team. Relevant references were identified and allocated to topic groups based on content and relevance to the review. Following this sift a total of 331 'relevant' studies were short listed and entered into Endnote reference database (Table 5).

The selected publications were further sifted by the team to select studies that reported the outcome of investigation of ill health associated with MWFs (this included reviews of ill health related to use of MWFs). The inclusion and exclusion criteria used for this sift are summarised in Table 6.

The second sift resulted in a total of 40 studies that met the inclusion criteria and which documented incident investigations of respiratory and skin disease attributed to water based MWF. Each publication was read in detail and the background, methodology and results summarised. On closer inspection articles that no longer met the criteria laid down in Table 6 were excluded. Some of the discarded articles, although not referring directly to an outbreak of ill health associated with MWF, were reviews of outbreak investigations, which summarised useful information.

The final sift of the papers resulted in thirty-five relevant articles, twenty-nine concerning outbreaks of ill health attributed to MWF. Seventeen publications concerned outbreaks of respiratory disease only, four outbreaks of skin disease only and eight outbreaks of skin and respiratory disease. Review articles were also examined and those that referred to outbreaks of disease were used as supporting evidence. These details are summarised in Table 7.

Table 3: Summary of search terms

List 1	List 2
Asthma	MWF
Bronchitis	Metalworking (near) fluid
Breathing difficulties	Metal (near) working (near) fluid
Irritant (near) respiratory	Cutting fluid
Hypersensitivity (near) pneumonitis	Sud (near) machine (near) metal
Impaired (near) lung (near) function	Coolant/s (near) machine (near) metal
Extrinsic (near) allergic (near) alveolitis	Slurry (near) machine (near) metal
Respiratory (near) disease	Soap (near) machine (near) metal
Respiratory (near) problem	Metal removal fluid/s
Humidifier (near) fever	Lubricant/s/lubrication
Health	Oil mist
Outbreaks	Machining (near) fluid
Skin	
Dermatitis	
Reversible airway obstruction	
Investigation	
Epidemiological	

Table 4: Summary of publication databases searched

Search engine	No references found
OSHROM (HSELINE, NIOSHTIC, CISDOC, RILOSH & OSHLINE)	566
Embase and Medline,	388
Web of science	306
Healthsafe	86
Total	1346

Table 5: Summary of number of papers for each topic related to MWF

Topic of reference	No abstracts
Immunology	35
Microbiology	82
Exposure studies	96
Clinical investigations of lung disease	37
Clinical investigations of skin disease	48
Outbreak investigations of lung disease	57
Outbreak investigations of dermatitis	21
Review articles about MWF and ill health	60
Review articles about specific respiratory conditions and MWF	10
Review articles about specific dermatological conditions and MWF	10
Review articles about 'general health' problems and MWF	16

Table 6: Summary of criteria used to select incident investigations

Criteria used to identify incident investigations of ill health associated with MWF
<u>Inclusion criteria</u> Outbreaks had to involve more than one worker at a particular site Evidence that the workers suffering ill health had been exposed to MWFs Clinical studies that were precipitated by evidence of an outbreak
<u>Exclusion criteria</u> Outbreaks of ill health associated with use of neat MWF oils were excluded

Table 7: Summary of the incident investigation studies

Category	No articles	Not related to topic
Outbreaks of lung disease	31	25
Outbreaks of skin disease	12	12
Simultaneous outbreaks of lung and skin disease	8	8
All outbreaks	35	29
<u>Other relevant publications</u>		
Reviews about general ill health due to MWF	3	
Reviews about lung disease outbreaks due to MWF	3	
Reviews about dermatological disease due to MWF	2	

Data from national reporting schemes and other experts

To identify further useful information about the relative incidence of respiratory and dermatological ill health associated with use of MWFs, government bodies, national reporting schemes, and experts were contacted.

The American National Institute for Occupational Safety and Health (NIOSH) investigates symptoms or cases of disease thought to be occupational in origin. Their investigations are all published on their website and had been identified on the previous library based literature search [284].

The PEROSH (Partnership for European Research in Occupational Safety and Health) website (with links to fifteen European institutes of Occupational Safety and Health in fourteen countries) was examined for content related to cases of ill health associated with MWF [285]. Direct contact with PEROSH staff was made, resulting in additional data from National reporting schemes in the UK (THOR), France (French national occupational disease surveillance and prevention network), the Netherlands (Nederland's Centrum voor Beroepsziekten), Czech Republic (the Czech Registry of Occupational Diseases), and Finland (from the Surveillance of Working Conditions and Health at the Finnish Institute of Occupational Health).

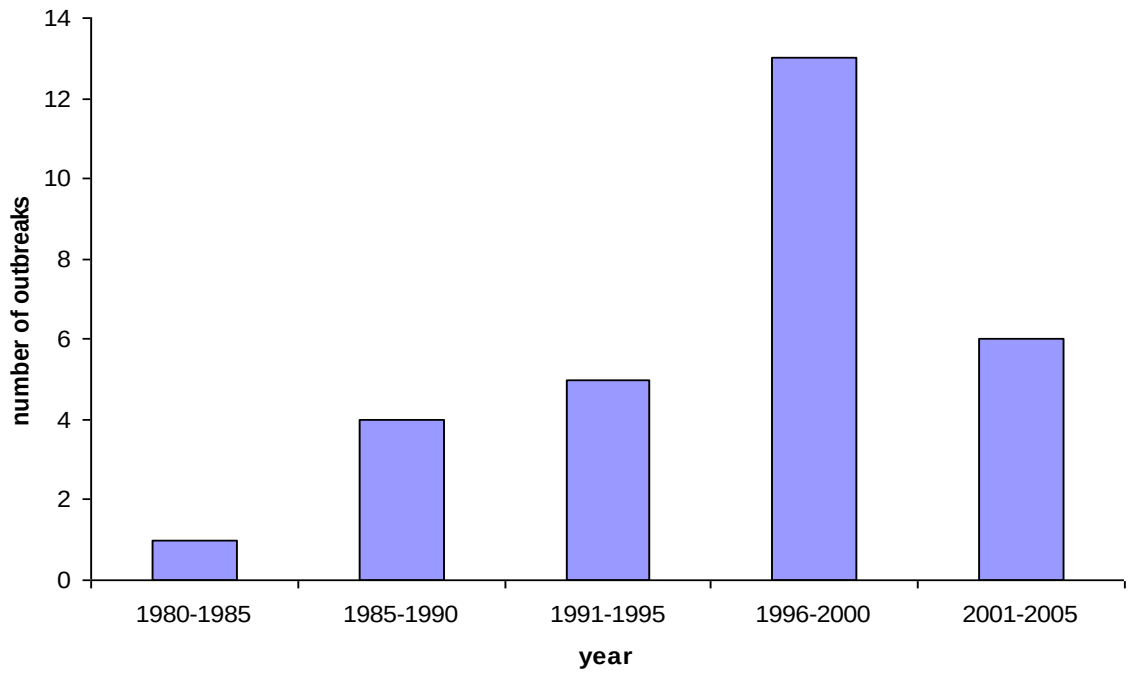
The European Agency for Safety and Health at Work website was also examined for information on outbreak investigations or reported data on ill health associated with MWF [286].

Results

General summary of the incident investigations of respiratory and skin disease at plants using metal working fluids

The outbreaks showed a peak incidence between 1996-2000 (Figure 1). The date allocated is, where it could be identified, the date of diagnosis of the sentinel case, and where this was not available, the date on which the outbreak was recognised. In some cases there was a lag time (sometimes a few years) between initial case diagnosis and the investigation of the outbreak, and between the investigation of the outbreak and subsequent publication of investigation.

Figure 1: Year of onset of outbreak of respiratory and skin disease



Twenty-nine outbreak investigations met the full criteria for inclusion in the review i.e. involved ill health in one or more workers from any particular site, with evidence of exposure to water based MWFs. Summary details for these are provided in the following figures. Most of the outbreaks reported respiratory disease, either in isolation, or in association with skin disease (Figure 2a). The majority of these originated in the United States (Figure 2b), most commonly in the car manufacturing or aerospace industry (Figure 3a), and predominantly in large workplaces (Figures 3b

and 3c). Seventeen publications concerned outbreaks of respiratory disease only, four outbreaks of skin disease only and eight outbreaks of skin and respiratory disease (Table 8)

Table 8: Summary of the published incident investigation outbreaks

Disease(s) investigated	Number of published papers	Locations of investigations
Respiratory disease only	17	14 (USA) & 3 (UK)
Skin disease only	4	4 (USA)
Respiratory & skin disease	8	7 (USA) & 1 (Croatia)
Total	29	

Figure 2a and 2b: a) Proportion of outbreaks by type of ill health investigated; b) country of outbreak where ill related to use of MWF investigated

Fig 2a

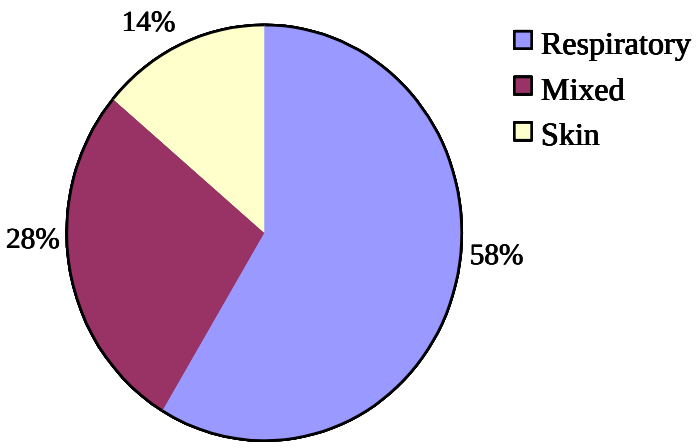


Fig 2b

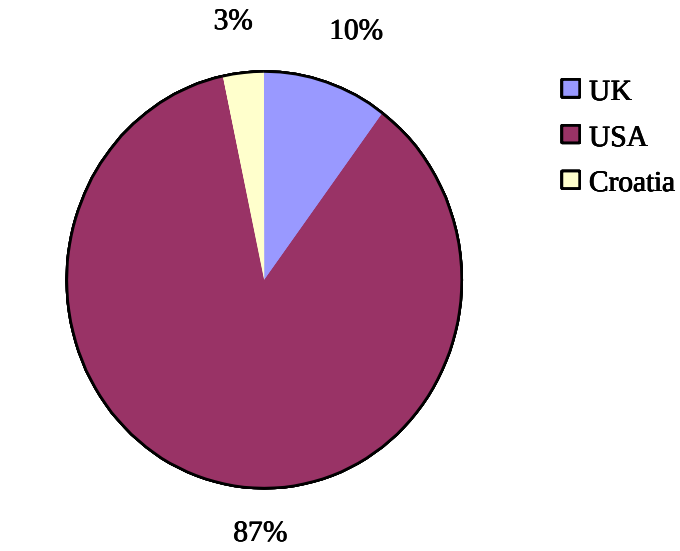


Figure 3a, 3b & 3c: a) Outbreak of ill health by type of industry using MWFs; b) outbreaks by numbers of exposed workers; c) outbreaks by total number of employees at plant

Fig 3a:

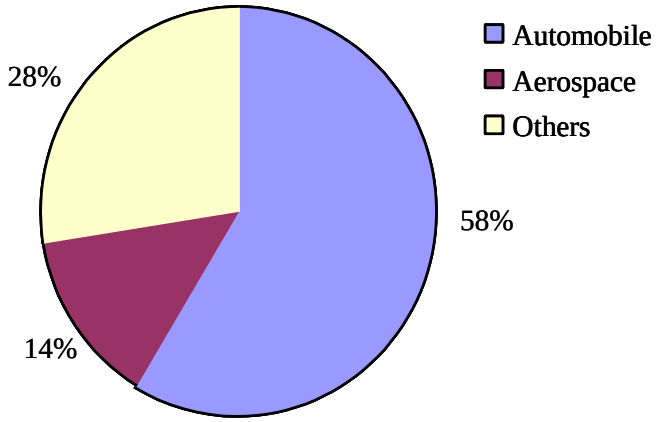


Fig 3b

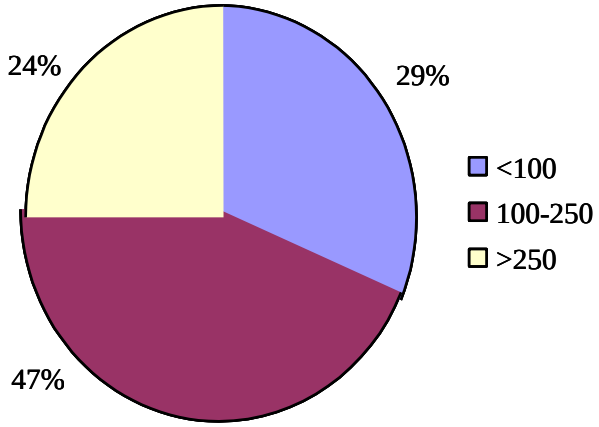


Fig 3c

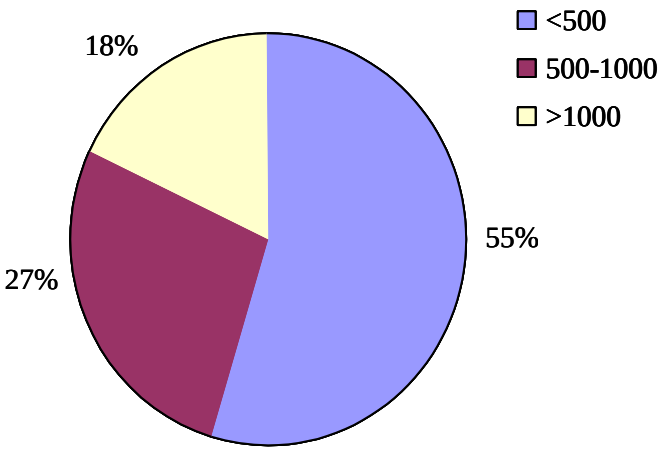
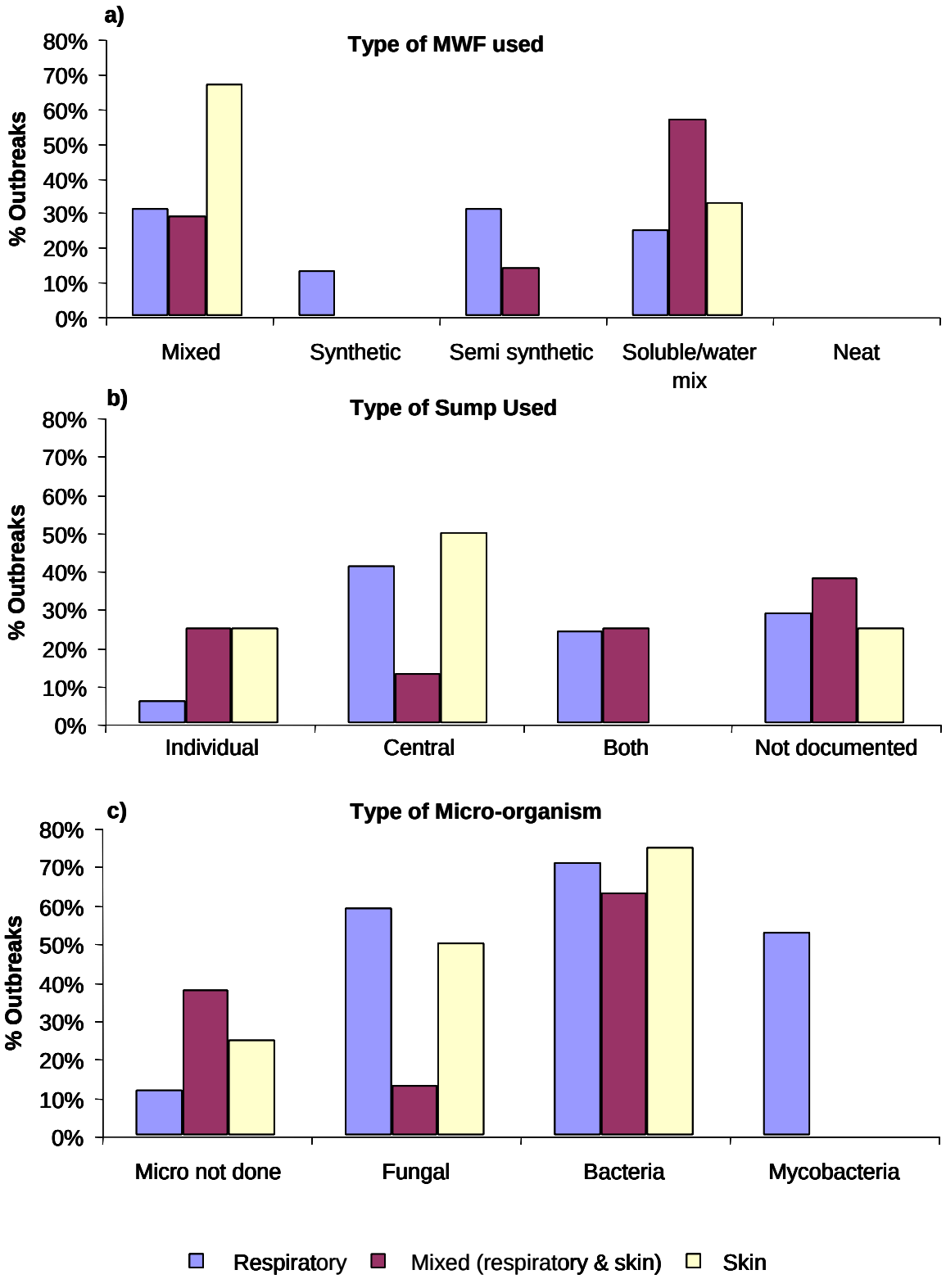


Figure 4a, 4b & 4c: a) Type of MWFs used by companies where outbreaks of illness occurred; b) Use of MWF sumps at companies where outbreaks of illness occurred c) Types of micro-organism identified at outbreaks of ill health



Outbreaks of ill health have been described with exposure to all types of water based MWFs (Figure 4a), and more commonly linked to machines with shared central sumps, rather than individual sumps (Figure 4b). Microbial contamination of MWFs was commonly found during outbreak investigations (Figures 4c). Most commonly isolated were Gram-negative bacteria in different taxonomic groups (80% of all identified isolates). Although mycobacteria (irregular non sporing Gram positive rods) were reported as being isolated in 59% of outbreak investigations, they comprised only 3% of the identified isolates (Figure 5).

Figure 5: Types of bacteria identified at outbreaks of ill health

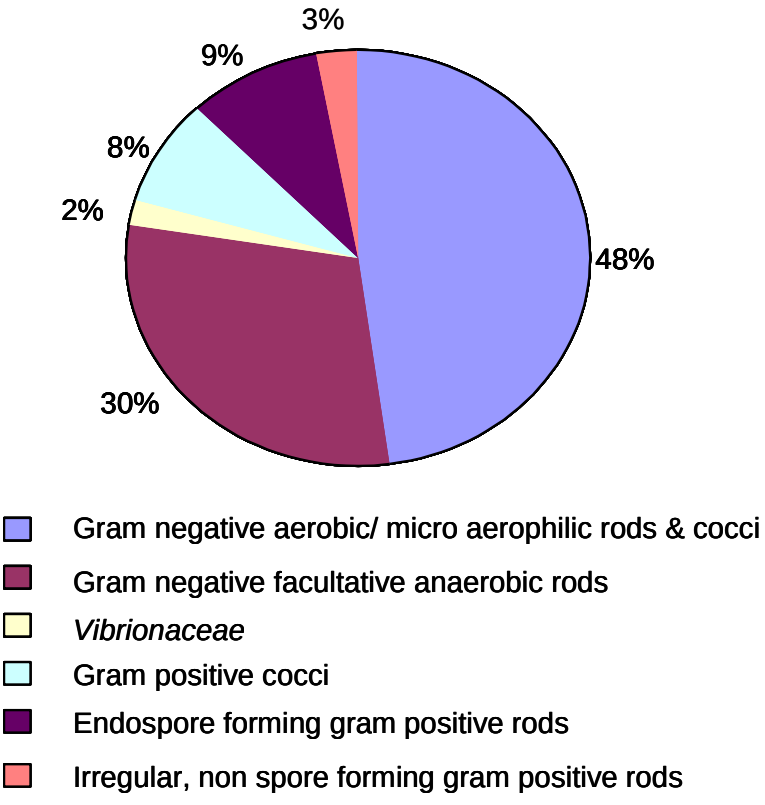


Table 9: Summary of incident investigations of respiratory ill health

Year of initial case	Country	Industry	Workforce	Exposed workers	MWF aerosol levels	Type of MWF used	Ref
1983	UK	Aeronautical	NA	NA	Oil mist 0.66 mg/m^3	Soluble/water mixed, neat	261 278
1992	USA	Automobile	NA	16	NT	Synthetic	279
1994	USA	Automobile (3 sites)	NA	NA	NT	Soluble	287
1995	USA	Automobile	1,592		Oil mist mean 0.8 mg/m^3, total particulate mean 1.0 mg/m^3 (<REL)	Synthetic	1
1995	USA	Automobile	1600	800	Oil mist < REL	Synthetic, soluble/water mixed	288
1996	USA	Automobile	NA	265	3 PBZ > REL 0.08-1.17 mg/m^3	Soluble/water mixed, semi synthetic	289
1997	USA	Aeronautical	1600	80	20/21< REL	Soluble/water mixed	290
1997	USA	Firearms	1100	450	39 samples for oil mist. Mean 0.66 mg/m^3	Semi synthetic	291
1997	USA	Aeronautical	120	105	All < REL 0.09-0.38 mg/m^3	Neat oil, soluble/water mixed, semi synthetic, synthetic	292-294
1997	USA	Automobile	1000	338	5 out of 9 >REL 0.33-1.29 mg/m^3	Soluble/water mixed, semi synthetic neat oil,	295
1999	USA	Automobile (3 sites)	700	NA	NT	NT	296
1999	USA	Automobile	462	250	4 out of 70 μ REL	Semi synthetic	297
2000	USA	Automobile	400	150	0.059-3.5 mg/m^3	Semi synthetic	298-300
2000	USA	Automobile	2000	NA	All but 1 < REL	Semi synthetic	301 302
2003	USA	Automobile (3 sites)	942(mean)	NA	All < REL	Semi synthetic	303
2003	UK	Automobile	836	NA	Generally < HSE guidance	Soluble/water mixed	260 281
2005	UK	Small component manufacture	<50	21	NT	Soluble/water mixed	304

Note*: REL* = recommended exposure limit set by NIOSH.
*NIOSH recommends a REL MWF aerosol of 0.4 mg/m^3 thoracic particulate (the proportion of the aerosol that penetrates below the larynx in the respiratory system) as a time weighted average (TWA) concentration for up to 10 hours per day during a 40 hour week. Measurement of total particulate is an acceptable substitute for measuring thoracic particulate and the NIOSH REL is 0.5mg/ m^3 [257].
HSE guidance for MWF concentration in air: 1mg/m^3 and for mineral oil mist in air: 3mg/m^3 [259 263].

Table 10: Summary of respiratory conditions and immunology test in incident investigations of respiratory ill health

Year of initial case	Respiratory symptoms/diagnosis other than EAA and OA	Cases of EAA	Cases of OA	Immunological tests	Ref
1983			**13** (+7 equivocal **OA**)	*NT*	261 278
1992		**6** (diagnostic criteria not documented)		All 6 $^{+}$ve IP test to *Pseudomonas sps*	279
1994		**6** (**D**) confirmed by biopsy **14** (**P**) cases		2 workers tested, -ve IP to standard commercial antigen panel (bac, fungi, avian)	287
1995	**12(OB), 6 (B), 3 (COPD), 10 (other)** Out of 71 who self reported symptoms and were then assessed by a physician	**20** cases 10 (**D**), 5 (**P**), 4 (**Po**) (+ 2 that were diagnosed by a physician but did not the meet diagnostic criteria)	**3**	-ve IP to unused MWF, biocide or lysed *M. Chelonae*. +ve IP to used MWF.	1
1995	**6** (**OB**)	**7** (physician diagnosed)	**12**	All EAA cases $^{+}$ IP test to used MWF, strongest +IP to Acineobacter. All EAA cases $^{-}$ve IP test to *M. chelonae*, biocides and *Xanthomas maltophilia*	288
1996		**14** (physician diagnosis)		$^{+}$ve IP test against *M.chelonae*	289
1997	Of 84 (79% of exposed workers) who completed questionnaire: **S:** 57% of EX 'v' 43% of UEX; **TC**: 29% of EX vs 13% of UEX; GA: 40% of EX vs 23% of UEX; **SB:** 30% EX vs 19% of UEX; **C:** 39% EX vs 26% of UEX.			*NT*	290
1997	Of 515 Ex workers and 435 Uex Symptoms > *EX* than *UeX* **SB:** 11% of *EX*: v 5% of *UeX* **C:** 26% of *EX* v 11% of *UeX*			*NT*	291

1997	**B:** 2 cases	**38** cases, **16** of which are biopsy proven. (does not differentiate P/Po/D)			292-294
1997	35 of 131 EX questionnaire respondents had **WR** 'v' 4 of 131 UNEX.	1		*NT*	295
1999		**8** (physician diagnosed) (over 3 work sites)		↑ IgG to Mycobacterium + other organisms	296
1999	229 of 462 workers over 3 sites, one of which (dept 8700) was the source of complaints of ill health, responded to a questionnaire. 41 of 66 respondents from Dept 8700 had **C** 'v' 46 of 163 respondents from other departments.		**2** (+ 8 workers with an asthma like condition not diagnosed as **OA**)	*NT*	297
2000	**3** (**OB**), **2** (**RS**), **1 (SB**)	**30** (18 physician diagnosed and 12 with criteria)	**14**	*NT*	298-300
2000		**7** 3 (**D**), 2 (**P**), 2 (**Po**)		IL-8 levels ↑ in exposed. $^{+}$ve IP (to *M.chelonae* + *fusarium*) >EAA than non-EAA	301 302
2003		**7** (physician diagnosed)		*NT*	303
2003	**15** (**OB**), **7 (HF**)	**19**(at least **Po**)	**74**	10/12 cases of EAA had +ve IP test to μ 1 microbe	260 281
2005	**6/8** (**WR**) **2/8** (**SS***)*	**1** (physician diagnosed)		+ve IP in 4/11 cases to *Pseudomonas sps*	304

Tests: **ND** not detected; **NT** not-tested
Symptoms: **C** cough; **GA** generalised aches; **SB** shortness of breath; **W** wheeze; **WR** work related respiratory symptoms; **RS** respiratory symptoms; **SS** 'flu like' systemic symptoms, **S** Sinus symptoms; **TC** tightness of chest
Respiratory diagnosis: ***B*** bronchitis not necessarily occupational; **HF** humidifier fever; ***OB*** occupational bronchitis; **RS** rhinosinusitis; **UIP** usual interstitial pneumonitis,
Description of cases: **D** definite cases; **P** probable cases; **Po** possible cases;
Exposure: **W** entire workforce; **EX** exposed; **UEX** unexposed

Table 11: Microbiological investigations in incident investigations of respiratory ill health

Year of initial case	Presence of micro-organisms	Viability CFU/ml of MWF	Viability in air CFU/m^3	Ref
1983	*Klebsiella, Proteus, Bacillus*, no fungi, *Myc* not mentioned	NT	NT	261 278
1992	*Pseudo, Aspergillus, Staph, Rhodococcus, Bacillus*. *Myc* in sputum.	<10 *CFU/ml* (fungi) $1.1X10^6$-$1.3x10^6$/*ml* (bacteria)	NT	279
1994	NT	NT	NT	287
1995	>100 different isolates incl. bacteria, fungi + *Myc*	NT	NT	1
1995	Several diff isolates incl. *Bacillus, Pseudo* + fungi + *Myc*	ND	525 – 4200 CFU/m^3	288
1996	*Myc* was predominant microbe, also *Pseudo* + fungi	$1.4x10^3$ – $1.0 x10^7$ CFU/ml	26-363 microbes/ft^3	289
1997	ND	ND	ND	290
1997	Several different isolates incl. fungi + *Myc*	$<10^1$ to $>3 x 10^7$ CFU/ml	NT	291
1997	Several different isolates incl. *Moraxella*, fungi + *Myc* in 1 sump only	Mean 10^7 CFU/ml	Mean 388 CFU/m^3	292-294
1997	Several different isolates incl. *Pseudo* + fungi + *Myc*	ND	NT	295
1999	*Myc, Pseudo, Bacillus*, fungi, yeasts	Up to 10^7 CFU/ml	some > 9 424 CFU/m^3	296
1999	Gram –ve + fungi	$6.3x10^5$ – $2.5x10^8$ CFU/ml	NT	297
2000	Several other isolates incl. *Myc* + fungi	Up to 10^7 CFU/ml	NT	298-300
2000	*Myc* + fungi	NT	NT	301 302
2003	*Myc*	ND	ND	303
2003	*Acinebacter, Ochrobacter*	None in main sump	NT	260 281
2005	*Fusarium, Pseudo*, fungi	50% samples < 100 *CFU/ml*, others $1.4 x 10^5$ – $8.2 x 10^6$ *CFU/ml*	$1.2x10^4$ – $2.1x10^7$ CFU/m^3	304

Tests: **Myc** *Mycobacterium chelonae*; **Pseudo** *Pseudomonas*; **CFU** viable colony counts; **ND** not detected; **NT** not-tested; **ml** millilitre; **m^3** cubic metre of air

Table 12: Summary of incident investigations of respiratory and skin disease

Year of initial case	Country	Industry	Exposed/total workers	MWF type	Aerosol MWF	Ref
1988	USA	Automobile	152/NA*	Soluble/water mixed	Oil mist 7 PBZ 0.14mg/m^3 – 1.08 mg/m^3	305
1990	USA	Aluminium ingots	150//NA	ND	NT	306
1990	USA	Roof bolts	55/66	Soluble/water mixed	PBZ 0.16 – 1.06 mg/m^3	307
1998	USA	Automobile	NA/850	Straight + Semi synthetic	2/7 PBZ > REL	308
1998	Croatia	Automobile	NA/ /NA	Soluble/water mixed		309
1999	USA	Aerospace	204/345	Soluble/water mixed + Synthetic	1/55 > REL	310
2003	USA	Steel bars and coils	50/NA	Straight + Soluble/water mixed	All 4 PBZ > REL 0.57 – 2.6 mg/m^3	311
2005	USA	Bicycle	30-40/520	Soluble/water mixed		312

Table 13: Summary of incident investigations of respiratory and skin disease

Year of initial case	Respiratory symptoms	OA	Skin symptoms	Microorganisms & *M. chelonae*	Microorganisms in MWF	Ref
1988	NA (**C + SB**)	NT	10/13 (**R)**	NT	NT	305
1990	6/78 (**acute WR**)	NT	70% eye irritation 44% skin irritation	Predominantly gram +ve	NA	306
1990	8/37 (**B)**	NT	14/37 (**R**)	Mainly *Pseudo sps*	$2.5x10^6$ – 2.5×10^8 CFU/ml	307
1998	5/13 (**SB + Wh**)	NT	5/13 (*R*)	NT	NT	308
1998	18 of **W** (**B/Pn**)	NT	NA/20 (**SI**)	Several diff isolates incl. *pseudo* + yeast	Average = $3x\ 10^5$ CFU/ml	309
1999	64/188 EX (SB) 10/92 UEX (**SB**)	1 (+ 8 A)	63/188 EX(**R**) 9/92 UEX (**R**)	*Bacillus sps* + *Pseudo sps*	1/55 PBZ > REL	310
2003	12/35 interviewed (**RS**)	NT	11/31 interviewed (**R**)	Several diff isolates No fungi or *Myc*	Up to 4.2×10^5 EU/ml	311
2005	2/12 (**RS**)	NT	12/34 (**R**)	NT	NT	312

Tests: ***ND*** not detected; ***NT*** not-tested; NA not available
Respiratory Symptoms: ***C*** cough; ***SB*** shortness of breath; ***Wh*** wheeze; ***WR*** work related respiratory symptoms; ***RS*** respiratory symptoms; ***SS*** 'flu like' systemic symptoms
Respiratory diagnosis: ***B*** bronchitis not necessarily occupational; ***HF*** humidifier fever; ***OB*** occupational bronchitis; **A** asthma, not proven to be work related; ***RS*** rhinosinusitis; ***UIP*** usual interstitial pneumonitis
Skin symptoms: ***R*** rash
Skin diagnosis: ***ID*** irritant dermatitis; ***AD*** allergic dermatitis**;** ***SI*** skin infection;
Description of cases: ***D*** definite cases; ***P*** probable cases; ***Po*** possible cases;
Exposure: ***W*** entire workforce, ***EX*** exposed; ***UEX*** unexposed
Other symptoms: ***WR*** work related respiratory symptoms; ***RS*** respiratory symptoms; ***SS*** (flu like' systemic symptoms; ***OI*** ocular irritation
Tests: ***CFU*** viable colony counts; ***ND*** not detected; ***NT*** not-tested, ***ml*** millilitre; $\boldsymbol{m^3}$ cubic metre of air

Note: No case of EAA reported in these studies and no immunological tests described.

Table 14: Summary of incident outbreaks of skin disease only in date order

Year of initial case	Country	Industry	Exposed/total	MWF type	Aerosol MWF	Ref
1986	USA	Hydraulic pumps	140/NA	*NA*	*NT*	[313]
1995	USA	Automobile	NA/NA	Soluble/water mixed	Oil mist: 0.27-0.47 mg/m^3	[314]
2000	USA	Air compressors	NA /350	Neat oil +Soluble/water mixed + semi synthetic +Synthetic oil	50% > *REL*	[315]
2003	USA	Automobile	NA/NA	Soluble/water mixed Semi-synthetic oil Synthetic oil	*NT*	[316]

Table 15: Summary of clinical investigations of incident involving skin disease only in date order

Year of initial case	Skin	Microorganisms & *M. chelonae*	Ref
1986	30/55 interviewed and examined (D)	*NT*	[313]
1995	8/8 interviewed (R)	Several gram –ve, no fungi	[314]
2000	5/12 interviewed (R)	Pseudomonas sps + Citrobacter sps	[315]
2003	57% exposed (R) 0% unexposed	Several isolates of bacteria and a yeast	[316]

Exposure: **REL** recommended exposure limit set by NIOSH at 0.4/mg m^3 in 1999 for an 8hr TWA
Specific skin symptoms: **D** (dermatitis); **ID** (irritant dermatitis); **AD** (allergic dermatitis**); SI** (skin infection); **R** (rash)
Other symptoms: **WR** (work related respiratory symptoms); **RS** (respiratory symptoms); **SS** ('flu like' systemic symptoms); **OI** (ocular irritation)
Tests: **NA** (not available); **ND** (not detected); **NT** (not-tested)

Additional evidence provided by reporting schemes and experts

The second phase of the review involved collecting information through the Health and Safety Laboratory's (HSL's) European and American network of contacts and by examining websites for national reporting data. Details from a range of countries were made available, including information, of varying detail from France, the Netherlands, Switzerland, Austria, Germany, Czech Republic, Italy, Spain, Finland and Canada. Through HSL contacts, unpublished data also was obtained for the UK from The Health and Occupation Reporting Network (THOR), and from other European occupational reporting networks. Data was received from the Czech Republic, the Netherlands, and Finland. The websites of Partners in the European Research into Occupational Safety and Health (PEROSH) [285] and the European Agency for Safety and Health at Work [286] were searched for information on outbreaks of ill health associated with MWF.

USA

No national reporting data could be identified from the USA. NIOSH have completed forty-one Health Hazard Evaluation (HHE) reports because of complaints of ill health associated with MWF. Between 1998 and 2006, NIOSH received a total of twenty-three HHE requests concerning exposure to MWFs. The results of the twenty three NIOSH evaluations indicated that thirteen of the fifteen facilities where air samples were collected, had air concentrations of MWF mist above either the US REL of 0.5 mg/m^3 for total MWF particulates or 0.4 mg/m^3 for the thoracic particulate mass (as a time-weighted average concentration for up to 10 hours per day during a 40-hour work week). Spirometry and medical record reviews revealed respiratory symptoms in thirteen of the facilities, skin symptoms in twelve, occupational asthma in three, and hypersensitivity pneumonitis in three. This collection of investigations showed almost an equal split between skin and respiratory disease.

When comparing the NIOSH investigations, there was great variability in the extent to which these investigations were carried out. This concern was recognised by NIOSH and currently is under review. Some of these investigations were very extensive and

involved screening of the entire workforce, with detailed clinical investigations alongside exposure monitoring and microbiological and immunological tests. Some of the outbreaks originally investigated by NIOSH were also followed as a longitudinal studies with detailed mapping of MWF aerosol emissions and the application of diagnostic criteria for EAA [293 298]. Other investigations involved small-scale sampling of the work force, with a limited clinical and hygiene investigation. These samples either consisted of workers randomly assigned for investigation or ill workers selected by the union and management. After questioning, those that stated they had symptoms were not always offered further evaluation.

UK

Within the UK, some cases of occupational disease are reported to The Health and Occupation Reporting Network (THOR). This is a research and information dissemination programme reporting on the incidence of occupational disease and work-related ill health. The programme consists of a group of closely linked national occupational health surveillance schemes dating back to 1989. Data is collected from a research network of over 2000 specialist physicians and specially trained General Practitioners throughout the UK. The data is collated, stored, analysed, reported and disseminated by the Occupational and Environmental Health Research Group at the University of Manchester. Chest physicians report cases of work-related respiratory disease to the Surveillance of Work-Related Respiratory Disease scheme (SWORD). Approximately 490 respiratory physicians throughout the UK participate in reporting occupational respiratory disease. Twenty one of these are 'core' reporters who report every month; the remainder are sample reporters who are sampled at random and report for one month only each year. Consultant dermatologists report work-related skin diseases to the Occupational Skin Surveillance scheme (EPIDERM). A reporting scheme for occupational physicians (OPRA 1996) also records occupational ill health [317].

THOR data shows, overall, much greater numbers of reported skin disease compared to respiratory disease caused by MWF exposure. Between 1993 and 2007 there were six hundred and sixty six cases of contact dermatitis reported to

EPIDERM (Figure 6a and 6b) compared to two hundred and sixty three estimated cases of respiratory disease reported to SWORD (Figure 7a and 7b). It is recognised that due to the design of the scheme, these are likely to be underestimates of the total number of cases, although the relative proportion of skin and respiratory disease may be more accurate. This data suggests that skin disease attributed to exposure to MWF has a higher incidence than respiratory disease in the UK however because of the Powertrain outbreak, in 2004 the incidence of respiratory disease overtook that of dermatitis[318]. The impact of respiratory disease compared to skin disease is potentially more significant on a personal level and this information is not reflected by comparing incidence.

Between 1996 and 2007 occupational physicians reported five actual (twenty seven estimated) cases of work-related respiratory disease attributed to metal working fluids to OPRA. Of these cases, 60% were diagnosed as occupational asthma, 20% inhalation accidents and 20% other respiratory disease (a diagnosis of chrome rhinitis). Occupational physicians reported ninety-two actual (598 estimated) cases of work-related contact dermatitis attributed to MWF. The most frequently reported industry sector for work-related contact dermatitis cases attributed to metal working fluids was manufacture of metal components, motor vehicles, and trailers [318].

HSE runs a separate reporting scheme. The Reporting of Injuries, Diseases and Dangerous Occurrences Regulations 1995 (RIDDOR) places a legal duty on: employers, self-employed and people in control of premises; to report work-related deaths, major injuries or over-three-day injuries, work related diseases and dangerous occurrences (near miss accidents). The RIDDOR came into effect on 1 April 1996. The Regulations only apply to England, Scotland and Wales (Northern Ireland will develop similar proposals at a later date). Reports are submitted to the health and safety enforcing authorities and the information used to target action to improve ill health prevention and control [319].

HSE provides a list of reportable diseases and a corresponding list of causative agents. Only if an employee develops a disease linked to a corresponding activity is it reportable through RIDDOR. At the time of this research, occupational dermatitis caused by MWFs was a reportable condition and therefore employers were legally

obliged to report it through RIDDOR; this is not the case for EAA caused by MWF exposure [319].

Figure 6a & b: a) Work related dermatitis recorded in EPIDERM (1993-2007) attributable to MWFs b) Work related dermatitis recorded in OPRA (1996-2007) as attributable to MWFs

Fig 6a:

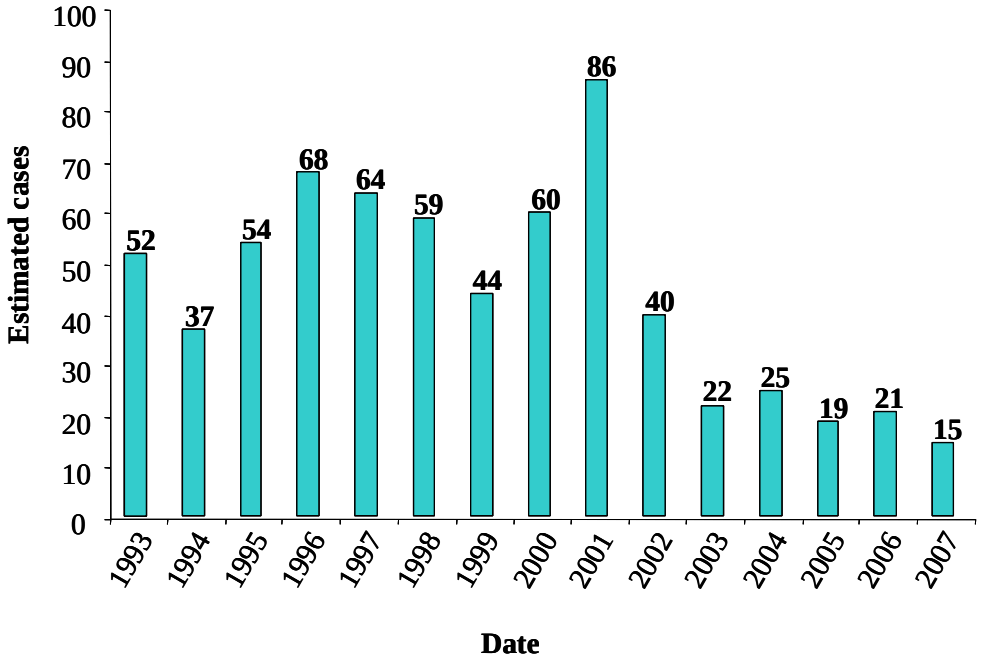


Fig 6b:

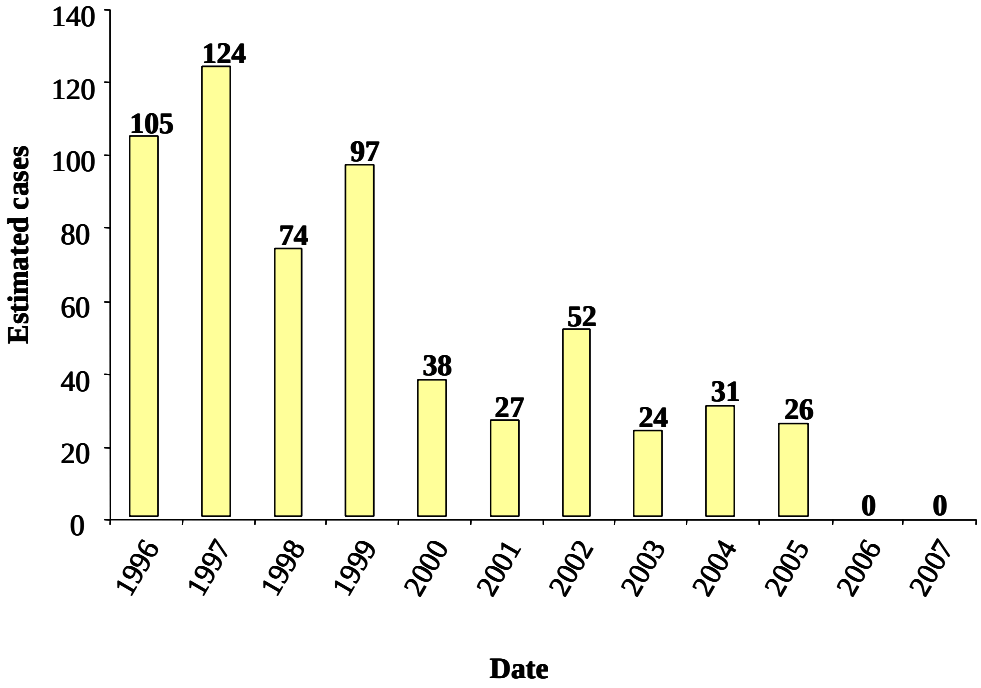


Figure 7a & b: a) Cases of work related respiratory disease recorded in SWORD (1989-2007) as attributable to MWFs b) types of work related respiratory disease recorded in SWORD (1989-2007) as attributable to MWFs

Fig 7a

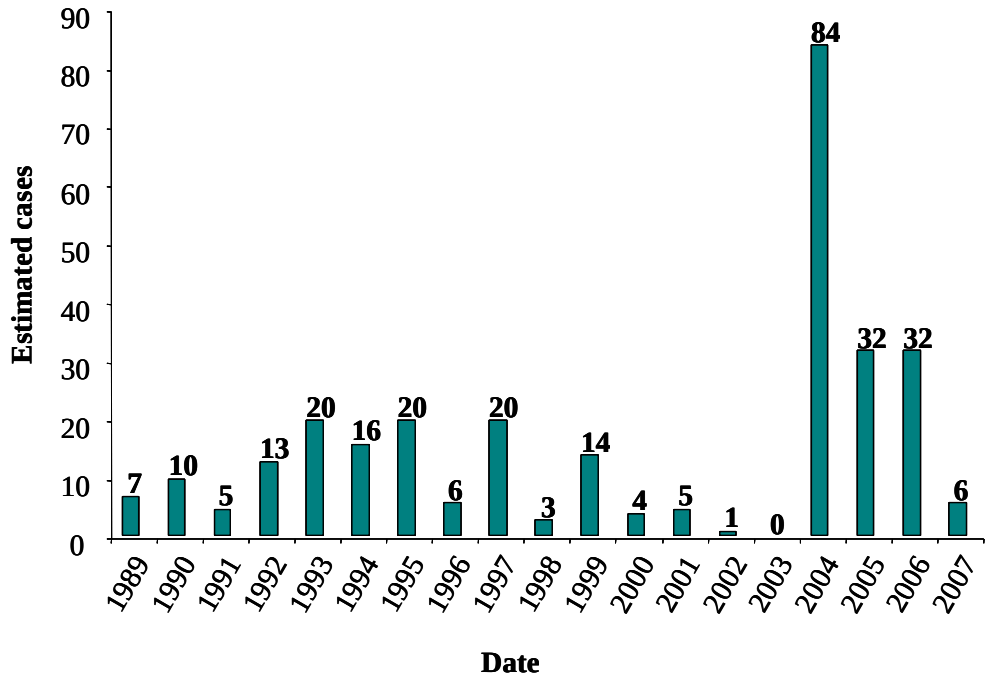
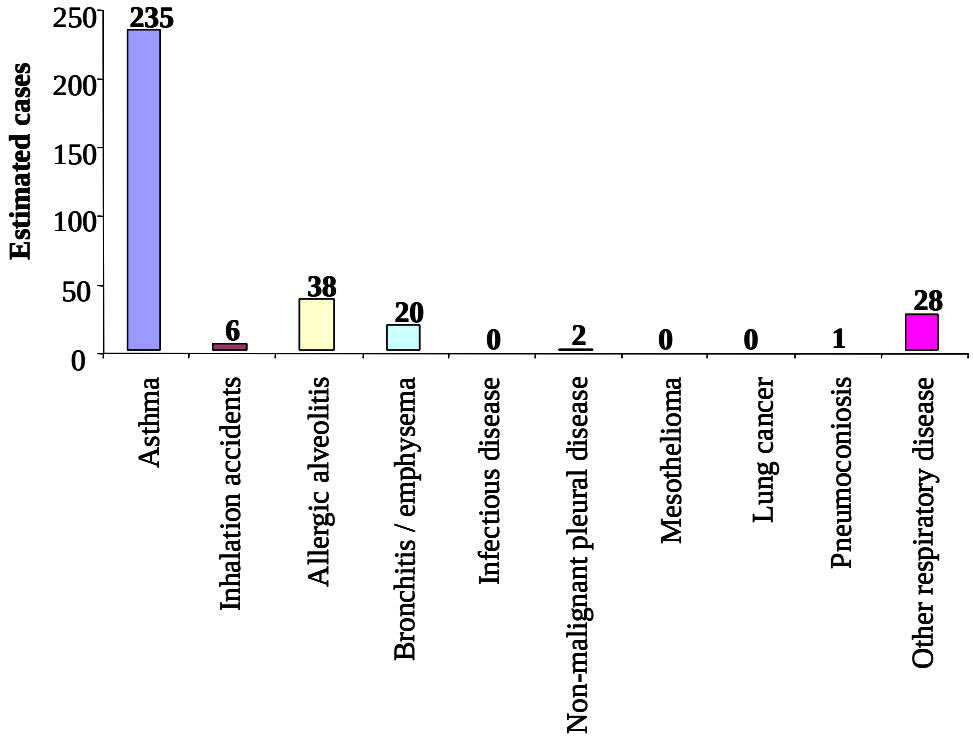


Fig 7b



France

Observatoire National des Asthmes professional (ONAP) involves a network of occupational and chest physicians who are asked voluntarily to report cases of occupational asthma. Between 1996 and 1999 they identified 2178 cases of OA. Papers reviewing their findings detail the most common causes of OA as flour, isocyanates and latex. MWF are not specified, however 343 cases of OA are under the causative category of “other” and 198 under “undetermined” [27].

Documents from the National Research and Safety Institute for occupational accidents prevention in France (INRS) show that there have been eight reported cases of OA thought to be secondary to MWF between 1991 and 1999. It is recognised that this does not reflect the true number of affected workers. An estimate of the incidence in the entire exposed population is less than 10 cases per year but the validity of this estimate is poor. Dermatological disease in France is officially recorded at under 100 cases per year, although it is recognised that the true incidence of disease is likely to be 50-100 times that officially reported [320].

Vincent Bonterre from the French national occupational disease surveillance and prevention network (RNV3P) responded to a request for information regarding reported MWF ill health. RNV3P collect data from thirty occupational disease consultation centres in university hospitals, where patients are referred for a potentially work-related disease. A generous data set was supplied concerning patients that were exposed to MWF and whose physician (GP or specialists) ask the occupational disease centres for advice to explore the work-relatedness. Bonterre noted that health surveillance in France is based on a statutory declaration system and encounters the same problem of underreporting seen in schemes involving insurance companies [321 322].

Considering RNV3P 2001-2007 data relating to any disease, any “attributable cause” (Figure 8), and any type of MWF (without taking into account co-morbidities) there were 1014 reports concerning workers that have been exposed to MWF. These reports came for thirty occupational disease centres and included 924 men (mean age 43, SD=15) and ninety women (mean age 44, SD=12). There were 579 reports concerning skin disease and 151 reports concerning respiratory disease [321 322].

When analysing the subset of the data where MWF has been identified as the main exposure rather than just a co-exposure, there were 536 reports of either respiratory or skin disease. These were reported from twenty-four occupational centres and concerned 480 men (mean age 38, SD=12) and fifty-six women (mean age 42, SD=11). Ninety-six cases of respiratory diseases were documented, most frequently diagnosed as asthma (n=40), COPD (n=12) and hypersensitivity pneumonitis (n=5).

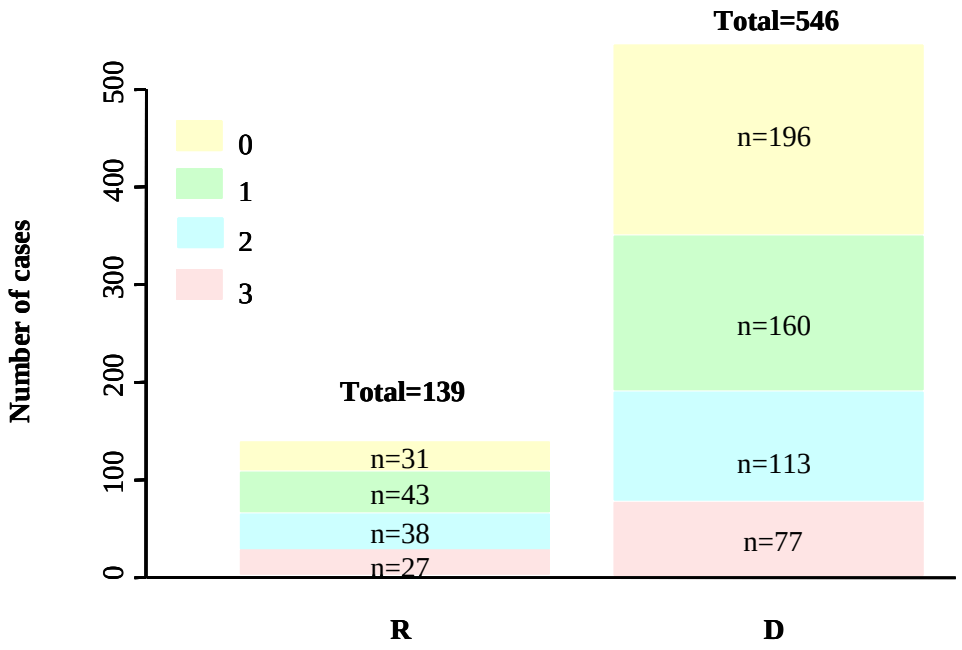
Four hundred and forty cases of skin disease were noted, most frequently allergic contact dermatitis and irritant contact dermatitis. In seventy-three cases of contact dermatitis the underlying mechanism was unknown, and there were also four cases of urticaria. Seventy one percent of the patients (n=350) came from manufacturing industries (including metal working), sixteen percent (n=78) came from automobile repair and domestic product repair sectors [321 322].

Finland

Finland has a compulsory reporting scheme, where physicians are required to report every case of occupational disease to the Finnish Register of Occupational Diseases (FROD). In a recent study based on the FROD data, the incidence of skin disease in machinists (1.62 per 1000 person years) was about three-fold that of the total working population [323]. Based on statistics collected by FROD and the patient register of the Finnish Institute of Occupational Health (FIOH) during 1992-2001, skin diseases were found to be the second most common occupational disease of machinists, after musculoskeletal injuries, accounting for twenty seven percent of all occupational diseases. A cross sectional study was completed to investigate the frequency of skin and respiratory symptoms using telephone interviews to question 757 machinists and eighty four controls in sixty four- sites using MWF. Suuronen et al. 2007, found that one in five of the interviewed machinists had symptoms of recurring or prolonged hand or forearm dermatitis in the previous year. This was an increase of five-fold compared to the office-based controls [323].

Figure 8: Numbers of respiratory (R) and skin disease (D) cases associated with exposure to MWFs between 2001-2007 in France

Fig 8:



Key:
0: no link between exposure and disease
1: link between MWF exposure and the disease is weak or doubtful
2: possible or direct but not essential link between MWF exposure and disease
3: direct and essential link between MWF exposure and disease

Government statistics reported that between 1992 and 2001 there were thirty reported cases of allergic respiratory disease (mainly asthma) in machinists. This translates to an incidence of 0.2 cases per 1000 persons per year, which is approximately the same as in the total working population [324] [325]. This was not reflected in a nationwide follow up study on asthma incidence by occupation however, where an elevated risk of adult onset asthma in machinists and related workers compared to administrative staff was demonstrated [326]. In telephone interviews by Jaakkola *et al*. 2009, thirty one percent of machinists reported suffering from a recurring or prolonged respiratory symptom within the past year. Compared to the office workers, the machinists had a 2.5-fold risk of respiratory symptoms and a 5-fold increase risk in upper respiratory symptoms. It was noted that machinists

working in areas where the aerosol level was above the mean level of 0.17 mg/m^3 were at increased risk (OR μ 2) of nasal and throat symptoms, cough, wheezing, shortness of breath, chronic bronchitis and current asthma. Workers with a history of at least fifteen years exposure to MWF experienced increased throat symptoms, cough and chronic bronchitis. The workplace assessment identified considerable variation in exposure control measures. One third of the machinery was equipped with functional local ventilation and enclosure. Gloves for dermal protection were not always used, and many were not of material optimal for protection against MWF [324 325].

Detailed exposure assessments were conducted in ten machine shops measuring air concentrations of ingredients and contaminations of MWF and inhalable dusts. The mean concentration of oil mist was 0.14 (range <0.010-0.60) mg/m^3 compared to the recommend limit of below 5 mg/m^3. The concentration of microorganisms was low. All measured aerosol levels, including aldehydes, were below the Finnish occupational exposure limits. The authors concluded that improvements in occupational hygiene to maintain the air contamination well below the recommended limits and protect workers from exposure were needed [324 327].

Czech Republic

Urban, P. from the Czech Registry of Occupational Diseases provided information on the reported occupational diseases caused by MWF in the Czech Republic between 2003 and 2008 (Figure 9a). The design of their reporting scheme was not clear, but over the four-year period there were twelve reported cases of allergic rhinitis, seventeen of allergic asthma, one hundred and twenty three cases of allergic contact dermatitis, one hundred and seventeen cases of irritant contact dermatitis and two cases of acne reported. The incidence of disease was relatively constant across the time period suggesting that major outbreaks of ill health had either not occurred or not been reported [328].

Figure 9a & b: a) Occupational disease attributable to MWFs reported (2003-2008) in the Czech Republic; b) Occupational disease attributable to MWFs reported (2000-2008) in Holland

Fig 9a:

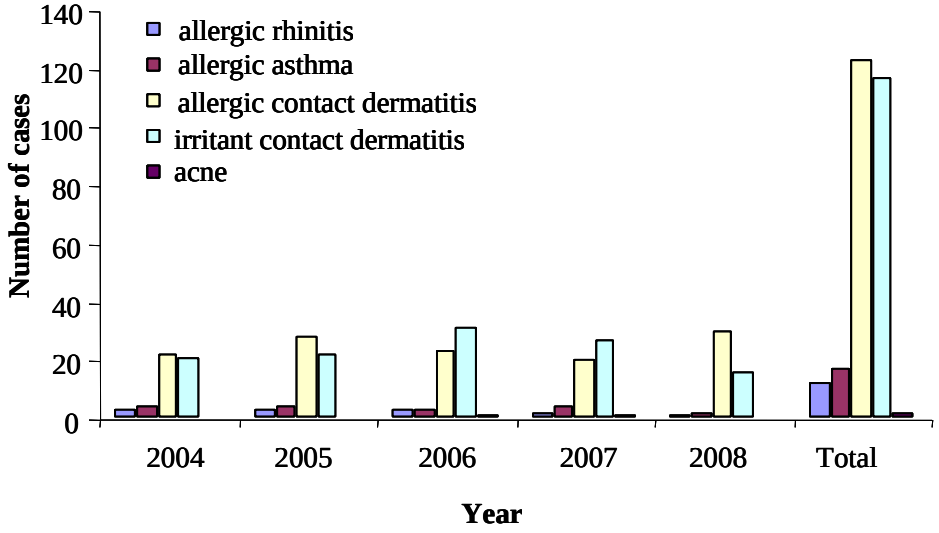
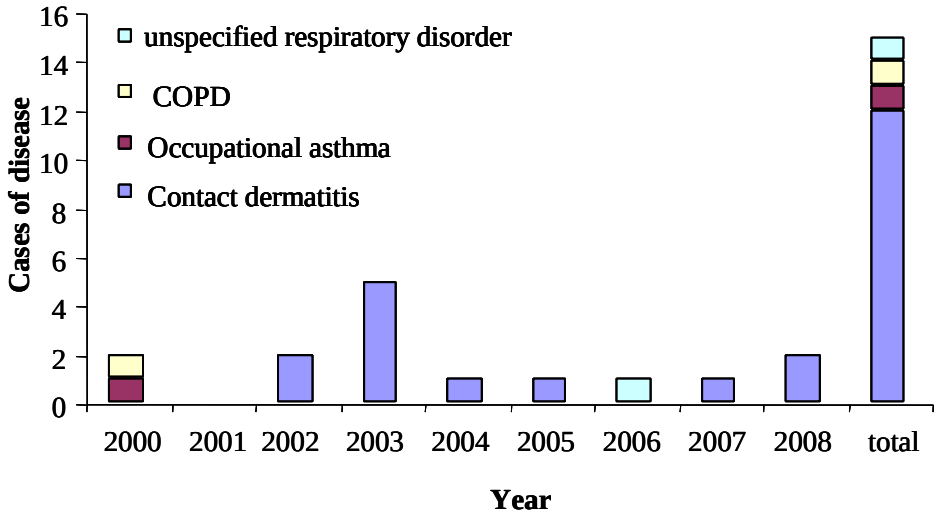


Fig 9b:



Netherlands

In the Netherlands, a small number of cases of ill health attributed to MWFs were reported. Between 2000 and 2008 ((Figure 9b) twelve cases of contact dermatitis were reported, two cases of COPD or asthma, and one of unspecified respiratory disease. Again, the exact nature and purpose of the reporting scheme is not clear [329].

Switzerland

In Switzerland, the metal working industry is reported to be the main cause of work-related skin disease. According to data from the Swiss National Insurance Organisation (SUVA), about seventeen cases of skin disease due to exposure to MWFs are reported per year. Over the past ten years, this has constituted approximately eighteen percent of all cases of work-related skin disease. SUVA data identified four cases of respiratory disease associated with exposure to MWF each year. Approximately half of these were cases of OA, a quarter were disease of the upper respiratory tract, and a quarter due to bronchitis [330].

Austria

There are an estimated 270,000 people involved in the Austrian metal working industry, and approximately 95,000 are reported to come regularly into contact with MWF. Data from the Austrian Social Insurance for Occupational Risks (AUVA) recognized about ten cases of skin disease per year from the industry class 'Metal production and machining'. Identifying the substances responsible for these conditions is not possible based on the data provided in the AUVA statistics. Approximately five cases of respiratory disease are also recognized each year in the same industry class with 80% of this accounted by upper respiratory tract disease and 20% as OA [330].

Germany

Between 1887 and 2007 the Hauptverband der Gewerblichen Berfusgenossenschaften (HBVG) institution(s) were the leading association representing the interests of the 25 trade institutions. The commercial trade associations are the carries of statutory accident insurance for companies in the German private sector and their employees. Reporting of occupational disease is through HVBG, although the exact methods and requirements, and the proportion of the working population that HVBG cover is unclear [331].

In 2005 there were 53,576 notifications of occupational disease to HVBG . Data from HVBG suggests that the number of confirmed cases of skin disease caused by MWF was on average four hundred and twenty three per year. The number of cases of disease of the respiratory tract, linked with exposure to MWF, was twelve per year [330].

A study was also identified of skin disease in a large metal working concern, employing 10,000 employees producing mainly roller bearings. MWF exposure was predominantly due to water miscible MWFs, and occupational related skin disease was common. In the exposed workers who had regular health monitoring, 48% suffered from irritant dermatitis and 6.9% had allergic dermatitis [332].

Italy

No national reporting data from Italy was identified. A study of skin disease in MWF workers by Papa *et al.* in 2000, which included one hundred and fifty metal workers occupationally exposed to metals and metalworking fluids (MWFs). This demonstrated an excess of minor skin disorders in exposed workers (18.6%), when compared to a control group (2%). The prevalence of major skin disorders was similar between the two groups (6.6% versus 5.4%) [333].

Spain

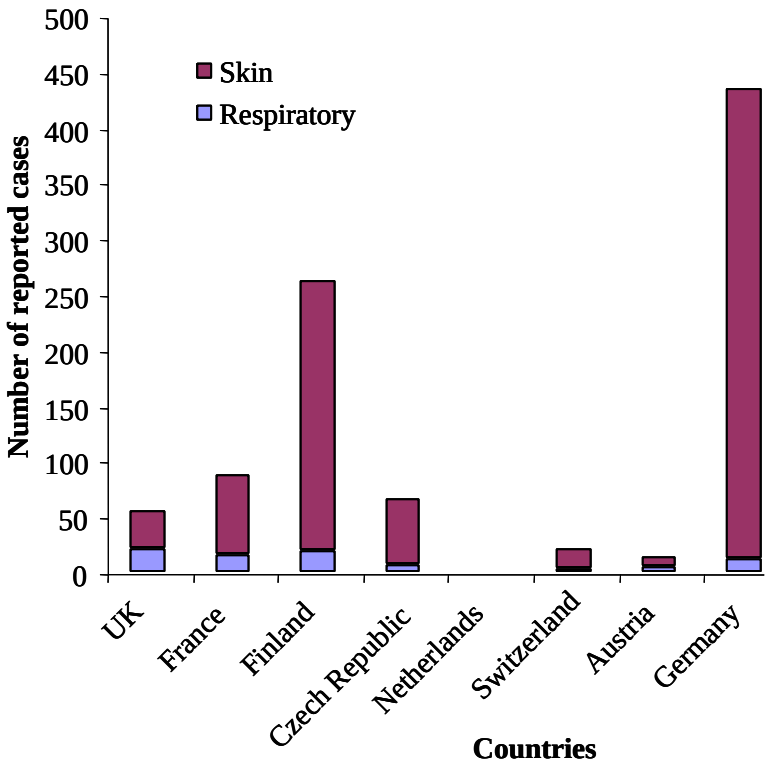
Orrilos *et al. 2006,* based in Catalonia (Spain), implemented a voluntary surveillance system whereby selected physicians, including occupational and respiratory specialists and general practitioners were asked to report cases of occupational respiratory disease. The results of this survey were compared to those of the official compulsory reporting of insurance companies. It was found that the voluntary surveillance had a much higher detection rate of disease and that the official system seriously under reported in Catalonia. The voluntary scheme identified 174 cases of OA in a twelve-month period. None of these were identified in the report as being caused by MWF but twenty four percent were caused by undefined chemicals/agents [35].

European overview

The overall numbers of reported cases of respiratory and skin disease that have been attributed to work with MWFs is summarised in Figure 10.

Figure 10: Relative proportion of respiratory and skin disease attributable to MWF reported by different countries

Fig 10



Discussion

Principal findings

This review identified twenty-nine previously published ill health outbreaks, with a peak incidence between 1996 and 2000. Outbreaks were most commonly of respiratory cases, with or without cases of skin disease, often in large American automobile plants. No clear aetiology for respiratory disease has been established, although microbial contamination of MWF, most often from bacteria, was commonly demonstrated during outbreaks.

Due to the lack of published 'outbreak investigation' studies from Europe, a second phase of the review included data from European reporting schemes where information on ill health related to MWF was available. This was successful in providing some data from the UK, France, Germany, Austria, Switzerland, Holland, Czechoslovakia, and Finland. Each country had a different reporting scheme, some voluntary, for example France and some compulsory, for example Finland. It was suggested that all methods employed were at risk of under reporting and due to the inequality in the information acquired from each country it is difficult to draw direct comparisons. What can be noted is that dermatological disease is generally more commonly reported than respiratory disease.

General limitations

Given the comprehensive nature of the outbreak literature review, it seems unlikely that published outbreaks will have been missed. The conclusions which can be drawn from the published outbreak investigations, are generally limited due to the cross-sectional nature of the studies and may be biased towards a 'surviving population'. This may lead to an under-estimate of cases, not including those workers who previously left employment due to work-related illness. Some of the outbreak investigations have attempted to minimise this by collecting longitudinal data, and by reviewing previous sickness absence records. Environmental investigations during outbreaks may also be limited in usefulness if improvements have been instigated in the workplace prior to sample collection. Again, some investigations had attempted to

allow for this by studying historical records of oil mist levels, sump contamination, and biocide usage when available.

The geographical comparisons that could be made in this study were severely limited by the paucity of published European outbreaks and the lack of a United States national reporting scheme for occupational ill health. Any comparisons made therefore, require examination of data from different sources, limiting their validity. Although we were able to gain valuable reporting data from a range of European countries, their reporting schemes were variable in design making comparisons difficult. We were not able to find national reporting data for certain European countries.

Geographical comparisons of outbreaks

The majority of outbreaks of MWF-related ill health have been reported from America, most commonly in large automobile manufacturing industry. It is not possible to tell from the literature review whether the high number of outbreaks from the United States is representative of a wider problem in that country, or relates to other factors such as reporting bias. One possible explanation to consider for such geographical differences in the incidence of reported MWF outbreaks is differences in socio-economics – that is countries consuming the most MWFs may simply have more disease. This seems unlikely to be the full explanation as the number of reported outbreaks per country is not proportional to the country's consumption of MWFs. In 2007 the United States used approximately 420 000 metric tons of MWF compared with 305 000 metric tonnes in Western Europe and 815 000 metric tonnes in the Asia/Pacific region [334].

Given the industrial sector most commonly implicated in outbreaks, comparison of global car production can also provide some insight to this. Data from 2002 listed the top five car manufacturers as Japan (8.6 million), followed by Germany (5.1 million), the United States (5.0 million), France (3.3 million) and South Korea (2.7 million) . For comparison, the UK produced 1.6 million cars in 2002 which was seventh overall in the world [335]. The lack of published outbreaks from the other four highest car

manufacturers, particularly Japan and Germany, suggests that the relationship between usage and outbreaks is not simply the answer.

Comparisons of MWF exposure for workers in different countries is hampered by a lack of standardised methodology for measuring MWFs, but recommended exposure limits do vary. In the US, NIOSH recommended exposure limits (RELs) for MWFs are 0.5 mg/m^3 for total MWF particulates as a time-weighted average (average exposure over a specified period of time) concentration for up to 10 hours per day during a 40-hour working week [257]. Exposure monitoring in US outbreaks have shown variable results, with cases of respiratory ill health occurring above and below these exposure limits. At the time of the large UK (Powertrain) outbreak, average personal exposures to mineral oil mist were 1.3 mg/m^3, well below the (now withdrawn) UK occupational exposure standard (OES) of 5 mg m^3 for a 8-hour time-weighted average [260]. More recent surveys from Finland and Sweden have found much lower average exposure levels of MWFs, in the region of 0.2-0.4 mg/m^3, and it has been suggested that this may be a possible explanation for the lower incidence of respiratory disease in these countries [325] [327] [336]. This level of exposure is in keeping with the American Conference of Governmental Industrial Hygienists recommended threshold limit value for mineral oils of 0.2 mg/m^3 [337].

Another possible factor to explain the high number of reported outbreaks from the US is the ease by which investigations may be initiated, the resources available for these investigations and the routine publication of their findings. This is likely to vary between different countries and is certainly not the case in the UK. The author is aware of other UK MWF outbreaks that occurred, but which have not been formally investigated in detail and therefore are not reported in the literature [338]. The National Institute for Occupational Safety and Health (NIOSH) carried out 76% of the US investigations and is part of the Centres for Disease Control and Prevention (CDC) a department of Health and Human Services. NIOSH is a non-regulatory investigative body that responds to requests to investigate workplace hazards. NIOSH is not an enforcement agency and has a distinct role from the Occupational Safety and Health Administration (OSHA) whose main mission is setting and enforcing standards [284]. NIOSH is well resourced and has a policy of making all health investigation reports publicly available. Such Health Hazard Evaluations (HHE) are relatively easy to

trigger, only requiring three staff members to formally express concern regarding health in the workplace. The exact nature of the evaluation is dependent on the nature of the complaint and type of workplace. For US MWF outbreaks this has varied from simply reviewing occupational health records, to 'in depth' workplace studies collecting detailed medical, microbiological, immunological and hygiene data. Differences in diagnostic approach may be necessary depending on the type of outbreak investigation and may relate to a countries healthcare system, with variability in the availability of invasive biopsies, or complex radiological tests such as gallium scans. This lack of a standardized approach makes comparisons of outbreaks within the US and between the US and Europe difficult.

Risk factors for disease during outbreaks

A number of respiratory outbreak investigations have examined demographic data for affected and non-affected workers, but no consistent risk factors for MWF-related ill health have been established. Fox et al. compared thirty-four demographic risk factors between cases of EAA and controls, but found no significant differences for age, gender, race, past smoking, family history, or a range of occupational factors [1]. Similarly in the Powertrain outbreak, no differences in smoking history, demographic characteristics, or the length of employment was observed between cases and controls [260]. However, in contrast to this, Hodgson et al. found that workers with EAA were older and more frequently non-smokers when compared to the rest of the workforce [294]. Current cigarette smokers are known to be less likely to develop EAA from any cause, which may affect the incidence of EAA in different workforces with variable smoking prevalence [339].

Personal mist exposures may vary markedly between workers due to a wide range of factors. These include differences in work task, usage of enclosed systems, availability of exhaust ventilation and usage of compressed air [336]. The relationship between exposure and respiratory disease is certainly not straightforward and findings have again been conflicting. Trout et al. were able to demonstrate a dose-response relationship between oil mist exposure and the development of EAA, for low, medium and high exposure category jobs [298-300]. In contrast to this, Hodgson et

al. found no clear association between qualitative exposure measurements and case definitions using logistic regression models [294]. Fox et al. found no significant difference in oil mist exposure levels between EAA cases and controls [1] and Park et al. [175] did not find that cross-shift peak flow decrements were related to exposure category .

Another factor to consider in outbreaks is the type of water-based MWF used in the workplace. A previous study of Canadian apprentices identified exposure to synthetic MWFs to be a significant risk factor in the development of airway responsiveness (a feature of asthma), where as this was not the case for soluble MWFs [340]. Amongst cases of EAA, Fox et al. also found increased odds ratios for exposure to certain MWFs, two of which were synthetic [1]. Our results however, identified respiratory outbreaks associated with all types of modern MWFs, being relatively evenly split between water mix mineral, semi-synthetic, synthetic fluids, or a combination of fluid types. Respiratory outbreaks were more commonly associated with MWF systems with common rather than individual sumps, but it is difficult to interpret the relevance of this without knowing whether this simply reflects the normal pattern of usage of MWF by large industry.

In MWF associated respiratory disease, exposures are complex and the specific agent causing disease is yet to be identified. In specific cases, bronchial challenge testing has confirmed that particular MWF ingredients, for example, alkanolamines, pine oil reoderant and colophony are asthmagens [261 278 341 342]. Exposure to microbial contaminants is however suspected to be the most likely cause of EAA, which would be in keeping with the aetiology of many other types of EAA. This is also supported by immunological responses found during outbreak investigations and limited challenge studies, where responses have been associated with used but not unused MWF [1 260]. The review of the microbiological findings from the outbreaks clearly demonstrated that microbial contamination of MWF was common, most frequently with bacteria. More than 80 different bacterial species were cultured from samples taken during the outbreaks, the largest group being Gram-negative aerobic rods, i.e. *Pseudomonas* and related genera. Other taxonomic groups of Gram-negative bacteria have also been reported, as well as Gram-positive rods and cocci. The bacteria isolated largely reflect the environmental niche generally occupied by these

microorganisms, i.e. soil and water-borne bacteria, highly adaptable and with unexacting nutritional requirements. These bacteria are rarely pathogenic in immunocompetent individuals, but contain material in their cell walls (such as lipopolysaccharide) capable of stimulating the human immune system and enhancing the body's response to allergens [343].

Hot tub lung is a recognized granulomatous condition, which is thought to be a form of EAA caused by exposure to aerosolized *Mycobacterium avium* complex organisms contaminating hot tub water [344]. Opportunistic mycobacteria have also been found as a contaminant in a number of MWF outbreaks [289] and have therefore been suggested to be the aetiological agent responsible for MWF EAA. More recently, French researchers have demonstrated a significantly higher number of precipitin arcs to *Mycobacterium immunogenum* (as measured by electrosyneresis) in 13 workers with MWF EAA, as compared to 12 exposed asymptomatic controls (8/13 having positive arcs). The authors have suggested that this is evidence of causation and that a cut off of five arcs has 77% sensitivity and 92% specificity for diagnosing MWF EAA. This study however further highlights the difficulties of establishing immunological causation in EAA, as 8/13 of the cases also had positive arcs to a bacterium in the MWF and 4/13 had positive arcs to a fungus. In addition, one of the asymptomatic exposed controls had 12 arcs to *Mycobacterium immunogenum*, which was as strong a response as seen in the EAA cases [345]. It is clear that large outbreaks of EAA have occurred in workplaces with minimal [294] or absent mycobacterial contamination [260]. Strong further evidence that *Mycobacterium immunogenum* is not the causative agent in all MWF EAA outbreaks, was seen in the UK Powertrain outbreak, where no mycobacterial DNA was found, none of the workers showed positive precipitin responses to *Mycobacterium immunogenum* and two positive specific challenges were demonstrated to used MWF that did not contain these organisms [260].

Fungal contamination has frequently also been found during MWF respiratory outbreaks, only slightly less commonly than bacteria. Few studies have specifically investigated immune responses to fungal contaminants, although this was not felt to be relevant in the aetiology of the Powertrain outbreak.

Comparison of different types of health outbreak

In terms of comparing types of outbreaks, the majority of these have been of respiratory ill health, either alone or in combination with skin disease. The small number of reported skin outbreaks limits the conclusions that can be made and this may reflect the different clinical consequences of developing skin or respiratory disease. It seems likely that an outbreak investigation is more likely to be instituted following concerns over less common or more serious health problems (such as inability to tolerate the workplace from breathlessness in asthma or alveolitis), than from concerns relating to skin rashes and eczema. For NIOSH studies it should be noted that the focus of an investigation in terms of which disease is looked for, may simply reflect the type of complaint that originally prompted it, e.g. worker concerns of breathlessness may lead to an investigation designed to record asthma and alveolitis, without routinely also recording dermatitis. Outbreaks that have reported both types of illness, however, have generally found skin disease to be more prevalent.

Comparisons are also limited by differences in the type of investigation carried out for different types of health outbreak. For the mixed disease outbreaks, the investigations have generally relied on recording symptoms, where as those for respiratory outbreaks have tended to be much more involved, requiring detailed diagnostic tests. However, some differences can be noted for example respiratory disease outbreaks (70%) more commonly occurred in automobile plants than was the case for mixed outbreaks of respiratory and skin disease (50%). The exposed population was typically higher in the respiratory outbreaks (247 workers), versus that in the mixed outbreaks (140 workers).

Respiratory outbreaks were associated with all types of modern water containing MWFs used in isolation as well as in combination. This pattern was not the same for skin outbreaks, where only one of the three outbreaks in which the MWF type was documented, was associated with a single type of MWF. It is of note that of those outbreaks involving skin disease (+/- respiratory disease) associated with a mixed MWF exposure, each of the 4 types of MWF (including neat oil) are used in at least 50% of the outbreaks.

No clear differences were seen between the types of outbreak in terms of MWF system, with all outbreaks being more commonly associated with the use of shared rather than individual sumps. Bacterial contamination of MWF was consistent in approximately three-quarters of all types of outbreak, where as fungal contamination was found approximately four times as frequently in respiratory outbreaks as the other types. A marked difference in the presence of opportunistic mycobacteria was also found between the types of outbreak, being present in over half of the respiratory outbreaks, but none of the skin or mixed outbreaks. In some cases this reflected its absence, where as in others this simply reflected the level of investigation completed.

Data from European reporting schemes

Data from European reporting schemes was gathered through personal contacts and review of online sources. Although it was possible to obtain useful data from a limited number of European countries with reporting schemes, this may not be representative of the wider European picture. It should also be noted that the data from different reporting schemes is not easily comparable due to a lack of standardisation between countries. The reporting of work-related ill health to such schemes may be a legal requirement (e.g. as in Finland), or voluntary (e.g. THOR reporting in the UK and ONAP in France). The diagnostic certainty required for reporting an illness may also vary, with some requiring it to be more likely than not work-related (e.g. UK), where as other schemes require a much more certain diagnosis, particularly where linked to compensation schemes (e.g. Finland, Austria and Germany). This may be a particular issue for diagnosing respiratory disease related to MWF exposure, where no single aetiological agent has been identified and asthma and alveolitis may both occur in the same workplace. Accurate case reporting may also be difficult in outbreaks where case definitions have been used and have identified some individuals with both occupational asthma and alveolitis [260]. Patients ultimately diagnosed with EAA in outbreaks have often been previously treated for recurrent chest infections, due to the non-specific clinical features of this illness. It is likely therefore that this condition is particularly under-reported. Details on

occupational disease in Spain and Canada were taken from temporary voluntary physician reporting schemes.

Accepting the above limitations it is clear that MWF respiratory and dermatology ill health are reported in the United States, UK and mainland Europe. For the small number of European countries with reporting schemes, it can be seen that dermatological disease is generally more commonly reported than respiratory disease. This may not be surprising, given that the significant respiratory diseases (OA and EAA) are allergic in nature, where as skin responses may be either allergic or irritant in aetiology. Data from France, Switzerland, Austria and Holland show that although total numbers may vary, skin disease is reported approximately 2-4 times more often than respiratory disease. In the UK, reporting of occupational ill health can be via the RIDDOR scheme, which is largely the legal responsibility of employers, or through THOR, which is a voluntary UK sampling scheme aimed to gather data on occupational disease from the physician. The THOR data from over the past 10-15 years shows that prior to the Powertrain outbreak [260], dermatologists reported approximately 5 times as much MWF skin disease each year than respiratory physicians reported respiratory disease [317]. More recently however, there has been a downward trend in reporting of skin disease amongst dermatologists and a large peak of reporting of respiratory disease following the UK outbreaks. It is difficult to compare reporting from the different specialist groups and to know whether these trends reflect a change in disease, a change in reporting practice, or increasing awareness of disease [317].

Data from compulsory reporting to the Finnish registry shows an eight-fold higher incidence of skin disease than allergic respiratory disease in MWF workers. The prevalence of reported MWF OA in Finland was similar to that in the general population, which contrasts with Finnish research findings from cross-sectional studies which have found a high prevalence of respiratory symptoms in exposed workers, even in fairly clean work environments [323 324]. A Finnish study [323] suggested that skin disease may also be under-reported to FROD, which may reflect patients not seeking medical attention, or skin complaints not being identified at primary health care units. The diagnosis of irritant contact dermatitis is based on clinical assessment, as there are no gold standard diagnostic tests [323]. Allergic contact

dermatitis is demonstrated by patch testing. Therefore if a patient presents with dermatitis it can be diagnosed clinically regardless of the response to skin testing. This is in marked contrast to the diagnosis of OA, which is based on confirming the diagnosis of asthma, onset of symptoms after entering work and association between symptoms and work. Work as the cause of disease must be proven by significant work-related changes in peak expiratory flow, similar to the usual diagnostic method in the UK. In addition to this, however, an IgE mediated allergy to an agent at work needs to be identified. If either or both of these are lacking, a positive response to a specific bronchial challenge test may be required. Both testing of IgE mediated allergy and bronchial challenge test are difficult without knowledge of the actual allergen causing MWF OA [327]. MWF is a complex mixture of ingredients and each brand of MWF is slightly different. It is rarely possible to test workers with every conceivable potential allergen and it may be difficult to accurately reproduce the work environment, particularly where challenges are only performed with pristine MWFs. The level of diagnostic rigor required is therefore greater than in the UK, where challenges are rarely performed and this may be part of the explanation for lower rates of OA seen in Finland.

The reporting data from German insurance schemes shows a very different picture, with a thirty-five-fold higher reporting of dermatitis relative to respiratory disease. Without a detailed knowledge of the German reporting scheme, these figures are difficult to interpret. It seems likely that again this may partly be explained by differences in the diagnostic requirements of their 'insurance based' system (e.g. the requirement for specific inhalation challenges in asthma).

Comparison with other studies

To our knowledge, this review is the first to comprise an in depth review of published outbreaks of MWF related ill health and to include data from European reporting schemes where there has been few published incident outbreak investigations. The findings of this study regarding outbreaks are in keeping with those from a NIOSH MWF-associated hypersensitivity pneumonitis (EAA) workshop, which was held in 1997 [280]. This followed eight clusters of disease in the American automotive industry

and recognised reversible disease, which occurred despite oil mist exposures within guidance limits. This workshop reviewed the existing evidence from outbreaks of EAA and identified a range of significant knowledge gaps, including risk factors for disease, exposure-response relationships, intervention efficacy and the natural history of disease. Over the last 10-12 years, despite a great deal of further research in relation to large outbreaks of occupational respiratory disease, many of these questions remain unanswered. This is particularly true for the timing of outbreaks and the aetiology of EAA and asthma. These issues are complex and a range of factors limits the conclusions that may be reached by studying outbreaks of disease. These include resource issues, difficulties with the complexity of workplace exposures and evolving improvements, which may be implemented within the workplace during data collection.

Many of the detailed outbreak investigations have focused on EAA and it is clear that this has only occurred with the more modern water containing MWFs. These fluids readily support microbial growth and there is some evidence to implicate this contamination in the aetiology of respiratory disease. However, a consistent link between exposure and disease has not been found, with some outbreaks occurring despite relatively low exposure levels [292]. Improvements in workplace hygiene have often followed respiratory outbreaks, often by cleaning machines, changing fluids, and improving general and local exhaust ventilation. There is some limited evidence from longitudinal studies that this approach, linked with worker education, has allowed a significant proportion of workers with EAA to safely return to work [292].

Established UK guidelines for OA [42 50] highlight the importance of early case identification and removal of the worker from further harmful exposure. There is some case series evidence to support this for EAA also, where removal of affected individuals from further MWF exposure has often been associated with a good clinical recovery, with marked improvements in radiology and physiology [279 292 302 303]. It therefore follows that early case identification by health surveillance and outbreak investigation should be advocated for all MWF exposed workers and that they should be adequately educated about the health risks.

Conclusion

The main finding of this review has been the lack of a standard approach to outbreak investigations. This limits the useful conclusions which can be gained from comparing data from outbreaks, which is further hindered by the lack of uniformity between national reporting schemes. Although microbial contamination was commonly found, no unifying cause could be identified amongst outbreaks.

Chapter 2: Systematic review of the diagnostic criteria used in previous outbreaks of extrinsic allergic alveolitis associated with metal working fluids

Introduction

In clinical practice, a diagnosis of EAA is often only suspected following the identification that a symptomatic patient is in an at-risk exposure group, or following the typical high resolution CT (HRCT) features of EAA being found in a patient with unexplained interstitial lung disease [346]. Due to the non-specific presentation of the disease clinical diagnosis is often not straightforward and no single diagnostic test exists for EAA of occupational or environmental causes [215 347]. This has led to the development of a number of general diagnostic criteria for EAA [203 210 215 246 348 349], all relying on a varying combination of: clinical assessment, suitable exposure, abnormal lung physiology, the presence of specific precipitating IgG antibodies in blood tests, radiology and the demonstration of a lymphocytic alveolitis on bronchoalveolar lavage or granulomas on lung biopsy. Confirmatory evidence may also come from symptomatic, physiological and radiological deterioration with workplace exposure [246 350] and rarely specific inhalation challenges may also be performed with nebulised antigen [351].

For OA clear diagnostic guidelines have been developed and are freely available on line [41 112]. Workers suspected of having OA should be referred early to a physician with an interest in this disease and objective confirmation for UK MWF workers still in employment is usually made by demonstrating work-related changes in airway calibre by recording serial peak flow measurements. Other useful objective tests for OA may include serial assessments of airway responsiveness and in a small number of cases workplace or laboratory inhalation challenges [41 112 352]. Due to the complex mixture of MWFs and the fact that their composition evolves with usage, no specific blood IgE or skin prick test is commercially available to demonstrate sensitisation.

As described in chapter one, between 1990 and Oct 2008 there has been 25 documented outbreaks of respiratory disease, particularly OA and EAA, associated with exposure to MWFs. The majority have occurred in the USA between 1992 and 2003 [1 279 287-301 303], affecting workers manufacturing metal components, often for

motor vehicles. During outbreak investigations of large workplaces several hundred workers may need to be screened for work-related symptoms by questionnaire, with symptomatic workers requiring detailed diagnostic testing. If many workers are affected with the same condition in the same workplace it may not be diagnostically necessary for all workers to have invasive tests (such as lung biopsies) and epidemiological or clinical case definitions may be agreed [1 260 281 288 294 300 303]. Difficulties exist in processing such large numbers of individuals, particularly given the unpredictable nature and timing of outbreaks.

Following the Powertrain outbreak in Birmingham [260 281], it was suggested by WATCH and agreed by HSE, that a standard UK approach to outbreak investigations should be developed. Development of this involved a review of the EAA case definitions used in previous outbreaks and formally planning the response for future outbreaks following a multidisciplinary modelling scenario.

The aim of this part of the project was to review the respiratory case definitions used in previously published MWF investigations, in an attempt to adopt approved standards for future UK outbreaks.

Methodology

As part of a formal literature review designed to identify published MWF outbreaks, a research team, comprising two clinical staff, two microbiologists and an immunologist, agreed the search terms that are shown in table 14. Library searches for paper abstracts that included a word from list 1 and a word from list 2 were conducted in OSHROM (HSELINE, NIOSHTIC, CISDOC, RILOSH and OSHLINE) databases, Embase, Medline, Healsafe and Web of Science. Papers documenting diagnostic criteria or case definitions for respiratory ill health were then identified and reviewed.

Results

The first description of a US outbreak of MWF HP was published in 1995, based on workers investigated in 1992 [279]. Bernstein et al. named the condition machine operators lung and the investigation followed the recognition of a cluster of respiratory ill health among 6 out of 16 workers exposed to soluble MWFs, manufacturing car parts. In this outbreak, no case definitions were developed, as each case was investigated in detail. Clinical diagnoses were established based on improvements in work-related symptoms, chest x-ray appearances and lung function, following cessation of exposure.

The Kenosha diagnostic criteria

A separate outbreak of 34 cases of EAA in MWF exposed workers occurred in a large US engine manufacturing plant (Kenosha outbreak 1995-6), leading to the Wisconsin Division of Health carrying out an investigation and case-control study [1]. In the opinion of the authors, existing HP diagnostic criteria developed for all causes, were not ideally suited to the MWF environment given the lack of a clear etiological agent and the commonality of some of the symptoms of HP with MWF bronchitis. To allow a case-control study to investigate risk factors for developing HP they developed seven diagnostic criteria to allow case definitions (table 16). These were designed to facilitate an epidemiological study of workers already diagnosed with possible HP and not for a systematic plant-wide survey of all workers.

It should be noted that of the 34 workers previously clinically diagnosed with HP in the outbreak, only 20 (59%) met the epidemiological case definition of being at least a possible case. Of these, 10 were definite cases, 5 probable cases and 5 possible cases. The authors also acknowledged that their criteria had been developed by themselves for the purpose of the study and had not been validated elsewhere.

Table 16: The Kenosha diagnostic criteria

1. Physician diagnosis of hypersensitivity pneumonitis
2. Onset of at least two pulmonary symptoms (cough, wheeze, chest tightness, shortness of breath), and at least one systemic symptom (fever, weight loss) after July 15, 1995
3. Recurrence of pulmonary or systemic symptoms after 3 or more day avoidance
4. Restrictive pattern on spirometry not due to obesity
5. Impairment of pulmonary diffusing capacity less than 80% predicted
6. Interstitial or reticulonodular pattern on chest X-ray or CT
7. Biopsy evidence of non-caseating granulomas

Definite case, 6 or 7 criteria; probable case, 5 criteria; possible case 4 criteria.

Wisconsin diagnostic criteria

A further set of diagnostic criteria (table 17) were developed to investigate another US outbreak, which occurred between March 1996 and May 1997, in a Wisconsin automobile manufacturing plant [288]. It can be seen from table 17 that the diagnostic criteria for this outbreak were broadened to include OA and industrial bronchitis, as well as HP.

Table 17: Wisconsin diagnostic criteria

	Required features	Supportive features
Hypersensitivity pneumonitis		
• Workplace-related cough, dyspnea, chills, fever; or insidious onset of malaise, weight loss, or progressive dyspnea	X	
• Serum precipitins to MWF or microorganisms isolated in MWF		X
• Chest X-ray: infiltrates in a reticulonodular or interstitial pattern; occasionally normal		X
• Pulmonary function: restrictive abnormality with decreased diffusing capacity; occasionally normal		X
• Lung biopsy: non-caseating granulomas		X
Occupational asthma		
• Workplace-related cough, shortness of breath, chest tightness, or wheezing	X	
• Pulmonary function: obstruction with reversibility with normal diffusing capacity or bronchial hyperresponsiveness, using methacholine challenge	X	
• Chest x-ray: hyperinflation or atelectasis		X
Industrial bronchitis		
• Workplace-related cough and sputum production	X	
• Pulmonary function: negative methacholine challenge and normal spirometry, unless complicating disease such as COPD present	X	

The HP criteria were broadly similar to those developed for the Kenosha outbreak, but more relaxed and with the first criteria of physician diagnosis removed. Although no detail as to how these were developed or selected is given in the article, it seems likely that this reflects the two different styles of outbreak investigation. In the Kenosha outbreak, cases had been investigated by a number of different centres; whereas all of the cases in the Wisconsin outbreak were investigated at the author's centre.

Around the same time (1996-1998), concerns regarding an outbreak of HP in an Indiana plant, manufacturing car climate control components, lead to a NIOSH (National Institute for Occupational Health and Safety) survey of the workforce, comprising a notes review and questionnaire [289] . No single case definitions were used in this survey and the authors stated that diagnoses were based on symptoms, exposure history and results of clinical tests including radiology, lung biopsies and lung function testing.

Development of Hypersensitivity Pneumonitis Diagnosis Index

A further US outbreak of HP in MWF exposed workers began in 1997, in a Connecticut factory that produced precision parts for the aerospace industry [292-294]. This followed the identification of a cluster of cases of HP having been identified by a single clinician. All workers from the plant were then invited to be examined at the University of Cincinnati Occupational and Environmental Medicine Unit, where they underwent a standard clinical assessment of history, examination, spirometry before and after work, a chest x-ray, a thin-section CT of the chest, a gallium scan and full lung function tests. Workers suspected of having HP after these tests were then offered invasive tests in the form of transbronchial or thoracoscopic lung biopsies for confirmation. Clinical diagnosis of HP required symptoms consistent with the disease, including at least one systemic symptom and one respiratory complaint, in association with a positive biopsy. In addition to this, the workplace was screened with a cross-sectional survey, using a combination of three previously developed questionnaires. The first of these was designed for HP, enquiring about the presence of three respiratory and three systemic symptoms, their frequency (rarely,

sometimes, usually) and their work-relatedness i.e. whether they improve away from work at weekends (symptoms get better or do not). In addition to this, a separate questionnaire was used to record current asthma symptoms, physician diagnosis and frequency of medication. A third questionnaire was also used to document the work-relatedness of chest symptoms. Questionnaire based case definitions were then developed for HP and OA (table 18).

Table 18: Questionnaire case definitions Connecticut outbreak

	Required features
Hypersensitivity pneumonitis	
• At least one chest symptom (coughing, wheezing, dyspnea with exertion)	**X**
• At least one systemic symptom (arthralgias, chills and feverishness)	**X**
• Symptoms frequency of usually or usually/sometimes	**X**
Occupational asthma (loose definition)	
• One chest symptom	**X**
• Improvement away from work	**X**
Occupational asthma (tight definition)	
• Three or more chest symptoms	**X**
• Improvement away from work	**X**

Although the sensitivity and specificity of these criteria are not documented, an attempt to examine the validity of the questionnaire case definitions was made. This demonstrated that seven of ten biopsy proven HP cases did fulfil the above case definition for HP, but that a much looser case definition was needed to include all ten cases. In order not to have missed any of the ten biopsy-proven cases, all workers reporting that they experienced at least one respiratory or systemic symptom “sometimes” or “usually” would have had to be included and further investigated. Using a different model, with tighter HP questionnaire case definitions that only included workers reporting at least three respiratory or systemic symptoms “usually”, only 30% of the biopsy-proven cases would have been identified. The authors also

noted a significant cross-over of the questionnaire case definitions, with 60% of the HP clinical cases also fulfilling their looser definition for OA.

The investigation of this outbreak led to the recognition by the authors of the need to develop less invasive diagnostic criteria for HP than the Kenosha criteria, in an attempt to avoid the cost and morbidity of transbronchial and open lung biopsies [293]. Using regression models, clinical data from biopsy-proven cases and non-cases was compared and a non-invasive Hypersensitivity Pneumonitis Diagnostic Index was developed (table 19). The results of the index were similar in output to the Kenosha case definitions, resulting in definite, probable or possible cases, depending on number of positive criteria. In this model, the previous physician diagnosis of hypersensitivity pneumonitis was removed as was the need for invasive tests. In place of these criteria, others were added: listening for lung crackles and taking a blood sample from the patient to assess inflammatory markers (ESR). The index also included performing an extra radiological test, a radioisotope gallium scan. The authors do not state why this scan was included in their case definitions although it may simply have been a routine part of their institutions assessment of the activity of interstitial lung disease. The authors went on to attempt to validate the index with other workers from the outbreak and compared case definitions made by this index, with cases diagnosed by slightly modified Kenosha criteria. The modifications made were minor and made the definition more inclusive. They included adding chills, sweats and fatigue to the constitutional symptoms in criteria 2, adding ground glass to the CT appearances in criteria 6 and modifying criteria 7 to allow any histopathology consistent with HP (see table 19).

When case definitions were compared for 61 workers, there was a good level of agreement between the Kenosha criteria and the HP Diagnostic Index (kappa = 0.766 +/- 0.093), although they did not identify identical patients. Four patients who met the case definition by the HP Diagnostic index did not meet the Kenosha criteria and the reverse was true for two other patients.

Table 19: Hypersensitivity Pneumonitis Diagnostic Index criteria

1. Onset of at least one work-related systemic symptom (extreme fatigue or myalgias/body aches) and two work-related respiratory symptoms (cough, dyspnea, chest tightness, or wheezing) after January 1, 1995. That is, these symptoms occurred repeatedly during the work week and subsided when the patient was out of work (over long weekends, vacations, or medically restricted from work): **One point**
2. Dry crackles (typically at the bases) detected on lung auscultation: **One point**
3 Restrictive spirometry (FVC < 80% predicted and FEV1/FVC > 70%) while symptomatic, not due to obesity: **One point**
4. Evidence of decreased diffusion capacity while symptomatic: **One point** for DL_{co} (single breath) 60-80% of predicted, or an increase of the A-a oxygen gradient to > 16 mmHg **Two points** for DL_{co} < 60% of predicted, with or without an increased A-a gradient
5. Increased erythrocyte sedimentation rate while symptomatic: (≤ 15 mm/hr **= No points**, 16-60 mm/hr = **One point**, > 60 mm/hr = **Two points**)
6. High resolution chest CT scan chest X-ray interpreted as consistent with hypersensitivity pneumonitis by an expert reader: **One point**
7. Gallium scan of lung parenchyma interpreted by the nuclear medicine service as being consistent with hypersensitivity pneumonitis: **One point**

Possible hypersensitivity pneumonitis (HP) is denoted by a score of 3; probable HP is denoted by 4-5; and definite HP by 6 or more.

Ohio outbreak

In 2001 three machinists from a US automobile brake manufacturing facility in Ohio were hospitalised with HP, prompting an investigation of the records for the rest of the workforce by NIOSH [298-300]. Symptomatic workers were investigated by local health-care providers and cases were identified from their medical records. The diagnostic criteria for OA and HP used are shown in table 20.

Table 20: NIOSH diagnostic criteria for Ohio outbreak

	Required features
Hypersensitivity pneumonitis	
• One or more work-related respiratory symptoms (cough, dyspnea, wheezing, or chest tightness)	**X**
• One or more systemic signs or symptoms (fever, chills, extreme fatigue, myalgia, or night sweats)	**X**
• Infiltrate on CXR or HRCT	**X**
• Abnormal spirometry (either an obstructive or restrictive pattern)	**X**
Occupational asthma	
• One or more work-related respiratory symptoms (cough, dyspnea, wheezing, or chest tightness	**X**
• Absence of systemic signs or symptoms	**X**
• No infiltrate seen on CXR or HRCT	**X**
• Spirometry consistent with reversible airway obstruction (an obstructive pattern with ≥12% improvement in FEV_1 after administration of inhaled bronchodilators)	**X**

The diagnostic criteria used here by NIOSH both for OA and HP are again slightly different to those used in other US investigations. In this outbreak the case definitions were based purely on symptoms, radiology and spirometry, without the need for blood tests, bronchoscopies, lung biopsies or gallium scans. Again it is likely that this choice in part reflected the type of investigation, based on reviewing notes and in part the need to avoid expensive invasive tests.

In 2002 NIOSH were involved in another workplace investigation following an index case of hypersensitivity pneumonitis in a toolmaker, working for a company manufacturing automatic transmissions and transmission components [301 302]. In this investigation, medical notes of symptomatic workers were reviewed and the Kenosha hypersensitivity pneumonitis case definitions were utilised. A short symptom questionnaire was also administered to part of the workforce but this was purely to facilitate an immunological study.

Michigan State diagnostic criteria

Three further outbreaks of HP were identified from cases in 2003-2004, following an investigation in Michigan by Michigan Occupational Safety and Health Administration (MIOSH) of three separate plants manufacturing automobile parts [303]. This followed the identification of seven cases of HP, either from reports to the Michigan State Occupational Disease surveillance system, or referrals to the Division of Occupational and Environmental Medicine at Michigan State University. In this case, general diagnostic criteria for HP were used, which had previously been developed for HP of any aetiology (table 21).

Table 21: Michigan State diagnostic criteria for hypersensitivity pneumonitis

Major Criteria
• Symptoms compatible with HP • Evidence of exposure to appropriate antigen by history or detection in serum/or BAL antibody • Findings compatible with HP on CXR or HRCT scan • BAL lymphocytosis (if BAL performed) • Pulmonary histological changes compatible with HP • Positive “natural challenge” (reproduction of symptoms and laboratory abnormalities after exposure to the suspected environment)
Minor criteria
• Bibasilar rales • Decreased diffusion capacity • Arterial hypoxemia (rest/exercise)

Diagnosis is confirmed if the patient fulfils four major criteria and two minor criteria and other diseases with similar symptoms are ruled out.

These criteria were originally designed for clinical diagnosis with follow up, rather than epidemiological case definitions in cross-sectional surveys. They are therefore more stringent than some of the criteria specifically designed for MWF outbreaks and allow an assessment of whether abnormalities improve away from work and then recur with re-exposure. With these criteria an exposed MWF worker with symptoms,

a typical CT scan and abnormal lung function, would still need either an invasive test (bronchoscopy or lung biopsy) or a positive “natural challenge” to be diagnosed with HP. Of the seven cases described in this outbreak, all fulfilled four of the major criteria but only five also fulfilled the requirement of two minor criteria.

Diagnostic criteria used for Powertrain outbreak

In 2003-4 a large outbreak of respiratory ill health was identified in a UK car engine manufacturing plant [260 281]. This outbreak was investigated in detail, using a phased approach. In Phase 1 all (836) employees were provided with a screening questionnaire, enquiring about 11 respiratory and nasal symptoms. In Phase 2 symptomatic workers with at least one respiratory or nasal symptom, or reporting weight loss were invited for further assessment. This comprised a detailed self-completed questionnaire, spirometry, phlebotomy and a clinical opinion with an experienced occupational respiratory physician. Those with possible occupational asthma were also asked to perform serial peak flow measurements. In Phase 3 further detailed clinical assessments were performed including allergy tests, radiology, assessment of bronchial responsiveness to methacholine, full lung function and bronchoscopy. The case definitions for HP (table 22) were adapted from the criteria used in the Kenosha outbreak (table 16); case definitions were also developed for OA and humidifier fever. By comparing table 16 and table 22, it can be seen that criteria 1,3,4,6,7 for HP were slightly adapted and more inclusive than those described in the original Kenosha outbreak; modifying the physician diagnosis criteria; redefining the work-related criteria for symptoms; allowing a broader spectrum of compatible CT appearances and adding a less invasive test (bronchoscopy with alveolar lavage) to the biopsy criteria. The investigators in this study also accepted EAA cases with four or more of the seven criteria i.e. the outbreak included possible, probable and definite cases of EAA. This study also noted an overlap between case definitions, with eight workers meeting the criteria for EAA and OA.

Table 22: Diagnostic criteria used for Powertrain outbreak

Disease	Criteria for case definition
Extrinsic allergic alveolitis (at least 4 of the 7 criteria must be met)	1. Physician diagnosis of EAA (probable or definite) 2. Onset of at least two pulmonary symptoms (cough, wheeze, chest tightness, shortness of breath), and one systemic symptom (fever, weight loss) 3. A history of symptoms improving regularly on days away from work and deteriorating on return to work 4. Restrictive pattern on spirometry FVC <80%, FEV_1/FVC > 70% 5. Pulmonary carbon dioxide transfer factor < 80% predicted 6. CXR or CT scan showing interstitial, reticulonodular or mosaic pattern 7. Biopsy evidence of non-caseating granulomas and/or lymphocytosis on bronchoalveolar lavage
Occupational asthma	Diagnostic peak expiratory flow record in 2003-5 (ie OASYS score ≥2.67 and/or a mean day interpreted difference between work and rest days of ≥16 l/min)
Humidifier fever	Onset of disease after December 2002 and a physician diagnosis based on: • Recurrent symptoms of a flu-like illness worst on first day of exposure after a break • No weight loss or radiological infiltrates • No long-term restrictive lung disease

Discussion

Main findings

This review identified six different case definitions for EAA, four for occupational asthma and one each for humidifier fever and industrial bronchitis. In all but one of these, no information was presented as to how the case definition had been developed or validated [1 260 288 294 300 303]. Only one paper was identified where the performance of different disease case definitions was compared [293].

Limitations

This study comprised a comprehensive and systematic review of the literature based on search terms agreed by a multidisciplinary team with experience of investigating MWF outbreaks, assisted by an experienced library search team. Despite this it is possible that the review may have missed certain other outbreaks, particularly if the nature of the paper was not clear from the abstract review, or the outbreak was published in a language other than English. In addition it is possible that there have been other MWF case definitions published since October 2008, although the authors are not aware of any in the recent literature.

Comparison with other studies

A number of difficulties arise in developing an approach to investigating MWF outbreaks. The first of these are logistical as they are usually unexpected and have to be investigated with little time to plan in order to minimise further harmful exposures. It may be difficult to differentiate workers with HP and OA from those with similar symptoms due to irritant bronchitis, humidifier fever, or unrelated viral infections. No internationally agreed gold standard diagnostic criteria exist for HP [207] or OA of any cause [112 353], which therefore makes comparisons of the performance of MWF case definitions very difficult. The situation is particularly difficult for MWF associated EAA, as a case definition needs to allow for workers with very different presentations of disease including typical sub-acute EAA, as well as those with slowly progressive interstitial disease identical to idiopathic fibrosis [293]. The value of

utilising a positive biopsy consistent with HP as a gold standard during outbreaks of HP [287] [294] [354] is limited by a number of factors, including interpretation of histopathology, false negative rates, cost and patient acceptability [293].

The most commonly used MWF-EAA case definitions utilised in outbreaks have been those published by Fox et al. in 1999, which were used in their original or modified format in 4 outbreaks [1] [260] [293] [301]. In their original paper the authors acknowledged a major limitation to their study was that this case definition had been created for their case-control study without prior validation. In terms of performance, when applied to 22 workers with clinically diagnosed MWF-EAA, these criteria only identified 45% of them as definite EAA cases.

One set of MWF-EAA criteria (the HPDI) have been developed by statistical analysis of outbreak data, with some attempt at validation and comparison with another EAA case definition [293]. Despite this, since their publication in 2002, they have not been utilised in subsequent reported US or UK outbreaks [260] [303]. The HPDI includes a criteria based on the results of a gallium scan, which may limit its usefulness if this test is not routinely performed in the assessment of possible HP [207].

In one further MWF outbreak, HP diagnostic criteria were utilised, that had previously been developed for EAA of any cause [246].The level of clinical certainty required to diagnose a single isolated case of EAA, is clearly different to that required when a number of similar cases have been diagnosed from the same workplace. These criteria were not developed from outbreak data and are comparatively stringent in terms of fulfilling the case definition. This was highlighted in the outbreak report they were utilised in, as 2 of the 7 HP cases did not actually meet the full case definition that required two minor criteria. There is also some limitation for these criteria in MWF-EAA, as opposed to farmers or bird fanciers lung, as aetiological exposures are more complex, with no standardised serum or BAL antibody available. In terms of satisfying the four major criteria, a symptomatic MWF worker during an outbreak, with crackles, a CT showing classical HP and a reduced gas transfer would still need either an invasive test, or re-exposure to demonstrate deterioration during a “natural challenge”. The authors acknowledged the limitations of these criteria and also checked their cases by applying three other diagnostic criteria, one for farmers lung [210] and two developed for EAA of any cause [203] [215]. No detail of the comparison of the

performance of these criteria was provided however and according to a recent review, three of the four criteria utilised in this study [203] [210] [246] have not been previously validated [207].

The final set of criteria utilised in their study for EAA represent an evidence-based prediction rule, developed based on clinical differences between patients with suspected ILD, who did or did not have EAA as their final diagnosis [215]. The significant predictive factors for EAA included exposure to a known cause of HP, positive serum precipitins, recurrent episodes of symptoms, lung crackles, symptoms 4-8 hours after exposure and weight loss. These factors were then combined in to a model, to allow a calculation of how likely EAA was to be the underlying cause for any patient presenting with possible ILD. This prediction rule was therefore designed to differentiate EAA and non-EAA in sub-groups of hospital patients with ILD, as opposed to identifying MWF-EAA amongst symptomatic workers in an outbreak. Whether this type of prediction rule could be of value in MWF outbreaks requires further study.

It has been estimated that over 1 million US workers are exposed to MWF during machining processes [355] and the associated health concerns of increased risk of occupational lung disease, as well as dermatitis and cancer, remain relevant to all MWF exposed workers worldwide. Although no more recent US outbreaks have been identified, it is not possible to tell whether this relates to an absence of outbreaks, an absence of outbreak investigations, or an absence of related publications. An outbreak of MWF-EAA has however recently been published in French automobile workers [345], although no case definitions were reported. Cases of MWF related occupational lung disease also continue to be reported to UK surveillance schemes and between 2010 and 2012, they were the 4th most common cause of OA [4]. Recent Scandanavian cross-sectional studies of MWF exposed workers have also reported an excess of respiratory symptoms and asthma, even at relatively low average exposure levels [325] [327].

Conclusion

Despite numerous previous outbreak investigations, there are no gold standard diagnostic criteria for MWF-related respiratory ill health. Although many different criteria have previously been utilised, they have usually been developed for a specific type of investigation, often by adapting existing criteria, and with little or no validation. In some cases these criteria would not be suitable for UK investigations due to the nature of the test included [293].

There is a clear need to develop a standardised approach to facilitate clinical investigations of future UK outbreaks of respiratory ill health in MWF-exposed workers. Further research work is needed to establish reasonable, acceptable and validated case definitions for these investigations.

Chapter 3: Expert panel identification of definite cases of EAA associated with exposure to metal working fluids at the Powertrain site

Introduction

The detailed literature reviews in the previous chapters summarise the features of previously published outbreaks of MWF-related ill health, serving to highlight both a lack of consistency in approach to outbreak investigation and a lack of evidence-base for case definitions of extrinsic allergic alveolitis.

In 2003-4, a large outbreak of respiratory ill health occurred at Powertrain, in the Longbridge car engine manufacturing plant in Birmingham [260]. This outbreak is discussed in detail in chapter 1. At the time of the outbreak investigation, 10.4% of the total Powertrain workforce met the case definitions for occupational lung disease, this included 19 cases of extrinsic allergic alveolitis and 7 cases of humidifier fever [260] [281]. During the investigation, all of the clinical data collected was entered in to an SPSS database containing up to 400 data points on over 800 workers. This database could potentially be used to compare questionnaire responses etc from those workers with and without EAA, in order to assist in future diagnosis of workers with MWF associated disease. The validity of this work was dependent on identifying a group of workers with definite EAA. The aim of this chapter was therefore to review the records of those Powertrain workers initially suspected of having EAA or a related condition and unambiguously clarify which workers definitely had EAA.

Methodology

In the absence of a single standardised diagnostic test to establish the diagnosis of MWF associated EAA, an 'Expert Panel' of occupational respiratory consultants was utilised. The 'Expert Panel' reviewed the available medical information, including follow-up data after exposure had ceased, in order to identify which workers could be clinically diagnosed as definite cases of EAA.

Case Selection

During the Powertrain outbreak investigation, a three-phased approach was applied to the entire workforce. The study population for this project comprised all workers recorded as having suspected EAA and/or humidifier fever, following assessment by the Powertrain clinical team at Birmingham Chest Clinic (Phase 3 of the investigation).

Preparation of clinical information

Clinical notes, radiology and computer records were made available and reviewed. A clinical summary was prepared for each case, based on this recorded clinical information and the data documented during the outbreak investigation. This included symptoms, radiology reports, physiology, immunology, cyto/histopathology and the clinical course of each workers illness. Hard and/or digital copies of all available radiology were also sourced for the panel meeting. Data was collected during a number of visits to Birmingham Chest Clinic over a several month period.

Selection of Expert Panel

The Expert Panel comprised five physicians, all founder members of the Health and Safety Executive sponsored national Group of Occupational Respiratory Disease Specialists (GORDS), and all with a current or previous clinical interest in EAA. The panel included two members (Professor Burge and Dr Robertson) who had both

been involved in the initial Powertrain outbreak investigation and clinical follow-up of affected workers at Birmingham Chest Clinic. The third member (Professor Pickering) had taken part in the Powertrain outbreak investigation, but not the clinical follow-up of affected workers. The fourth and fifth members (Professor Hendrick and Dr Barber) had not participated in the Powertrain investigation or follow-up of workers.

Expert Panel Meeting

The Expert Panel meeting was held at East Lodge on January 13-15th 2010. Dr Burton presented clinical data to the Expert Panel on each case, with the addition of summary data projected in a Powerpoint presentation. Hard copies of chest X-rays and CT scans for each case were made available for viewing on light boxes, with digital copies of radiology available to view projected on to a separate screen.

Following the presentation of each case, there was discussion by the five members of the Expert Panel, and they were each asked their clinical opinion as to whether they felt they would be confident to diagnose EAA. Each member was only allowed to give one of the following opinions:

- Definite case of EAA
- Possible case of EAA
- Definitely not EAA

The Expert Panel was not provided with any information during the meeting relating to whether each case had met the case definition of EAA used during the outbreak investigation. A definite clinical case of EAA (i.e. sufficient to give this diagnosis to a patient in clinic) required at least four of the panel members to agree. Similarly a 'definitely not a case of EAA' (i.e. EAA excluded) required four panel members to agree. Any other combination of votes was taken as the patient being a possible case of EAA.

In addition to the clinical opinion statement, an Expert Panel Score (range 0-100%) was calculated for each case, representing how likely it was that this represented

EAA. This was calculated based on the total of five scores, one given by each panel member, where a vote of:

- Definite EAA = 20
- Possible EAA = 10
- Definitely not EAA = 0

Reproducibility

In order to assess the reproducibility of the Expert Panel opinion, the panel re-reviewed ten randomly selected cases, blinded to their initial opinion. Results from the first and second opinion were compared. Reproducibility of the Expert Panel Score was calculated using the concordance correlation co-efficient.

Expert Panel opinion and modified Fox case definitions

The Expert Panel opinion was compared graphically with the outcome of the case definition that had been used at the time of the Powertrain outbreak (modified Fox criteria).

Comparison with interleukin-2

Although the Expert Panel opinion was taken as the gold standard for a diagnosis of EAA, the Expert Panel Score was compared to a key cytokine (interleukin-2), responsible for T-cell activation in EAA. This data had previously been collected as part of a separate research project during the Powertrain investigation and was not available to the Expert Panel.

Ethical Approval

Ethics approval was granted by the Birmingham Ethics Committee, as an amendment to the existing Ethical approval for the Powertrain Research project.

Results

Participants

Following interrogation of the Powertrain database 37 workers were identified for the study.

Figure 11: The number of patients seen at each phase of the Powertrain outbreak and the selection criteria for Expert Panel review [356]

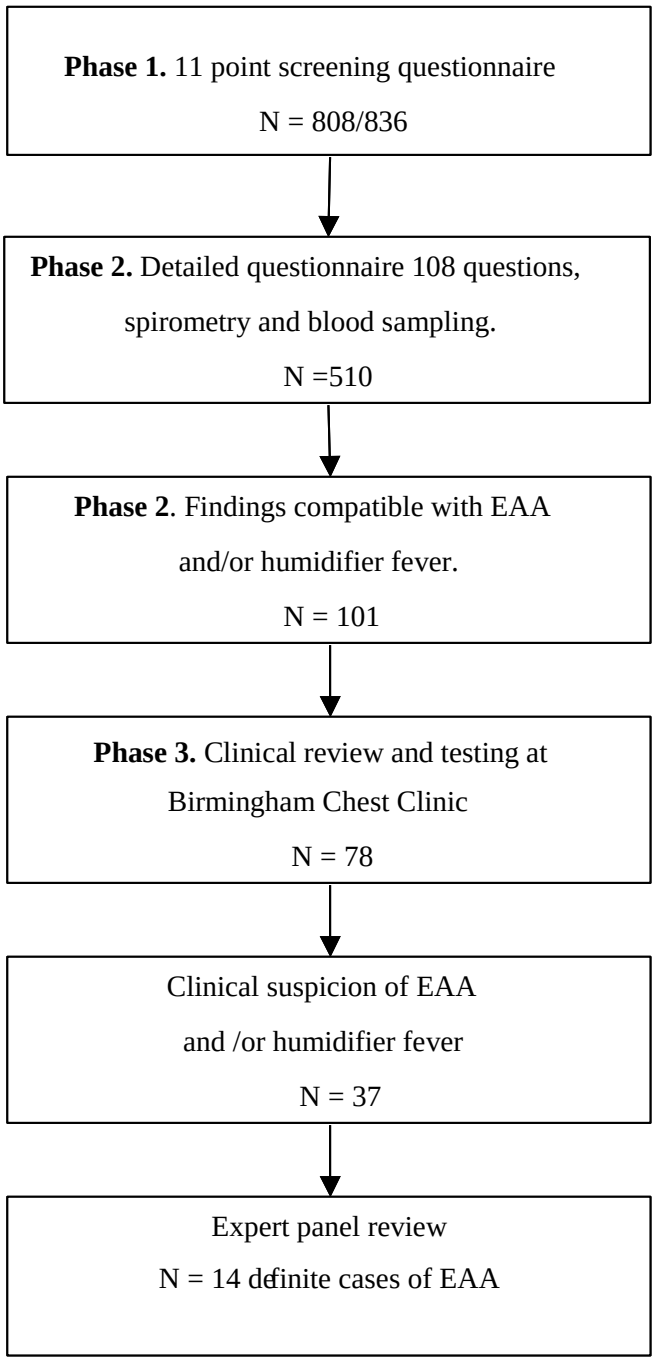


Table 23: Expert Panel results for the 37 workers reviewed, showing the panel EAA opinion, calculated panel score and original Powertrain outbreak case definition

ID	Panel opinion	Panel case?	Panel score %	Powertrain case?
1	YYYYY	Definite	100	Probable
2	YYYYY	Definite	100	Definite
3	YYYYY	Definite	100	Probable
4	PPNNN	Possible	20	Possible
5	YYYYY	Definite	100	Possible
6	YYYYY	Definite	100	Probable
7	PPPPP	Possible	50	No
8	YYYYY	Definite	100	Probable
9	NNNNN	No	0	No
10	YYYYY	Definite	100	Probable
11	PPNNN	Possible	20	Probable
12	YYYYY	Definite	100	Definite
13	YYYYY	Definite	100	Definite
14	PNNNN	No	10	No
15	NNNNN	No	0	No
16	NNNNN	No	0	No
17	NNNNN	No	0	Possible
18	PPPNN	Possible	30	Probable
19	PPPPP	Possible	50	No
20	PPPPN	Possible	40	Possible
21	PPNNN	Possible	20	No
22	NNNNN	No	0	No
23	PNNNN	No	10	Probable
24	YYPPN	Possible	60	No
25	PPPPP	Possible	50	No
26	YYYYY	Definite	100	Possible
27	YYYYY	Definite	100	Definite
28	PPPNN	Possible	30	No
29	NNNNN	No	0	No
30	NNNNN	No	0	No
31	NNNNN	No	0	No
32	YYYPP	Possible	80	Possible
33	YYYYY	Definite	100	Probable
34	NNNNN	No	0	No
35	YYYYY	Definite	100	Definite
36	PPPPP	Possible	50	No
37	YYYYY	Definite	100	Probable

It can be seen from Table 23 that in the opinion of the Expert Panel, 14 workers were definite cases of EAA, 12 were possible cases of EAA and 11 were definitely not cases of EAA. For all of the 14 definite cases of EAA, there was full agreement by all five members of the panel, i.e. a panel score of 100%. Possible cases had a range of Expert Panel Scores between 20-80% and definitely not EAA cases a range of scores between 0-10%.

Table 24: Reproducibility of panel opinion for EAA cases

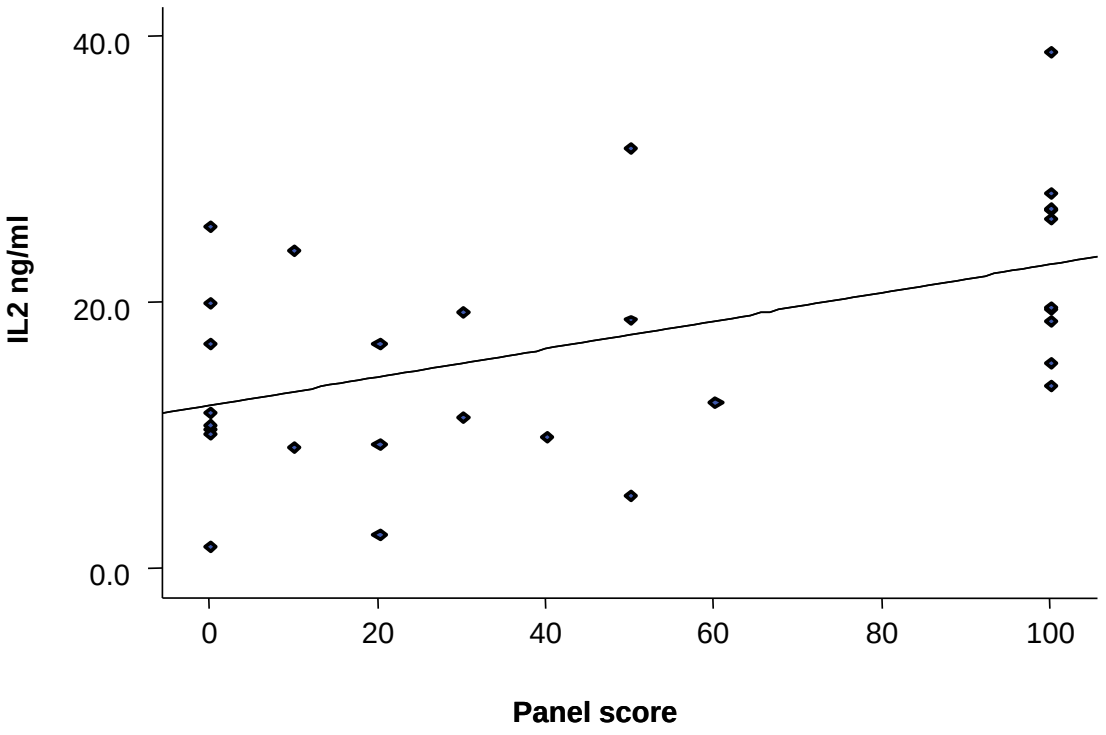
Case	Panel opinion 1	Panel opinion 2
1	Definite case (YYYYY = 100%)	Definite case (YYYYY = 100%)
2	Definite case (YYYYY = 100%)	Definite case (YYYYY = 100%)
3	Definite case (YYYYY = 100%)	Definite case (YYYYY = 100%)
4	Definitely not a case (NNNNN = 0%)	Definitely not a case (PNNNN = 10%)
5	Possible case (PPPPP = 50%)	Possible case (YYPPN = 60%)
6	Definitely not a case (NNNNN = 0%)	Definitely not a case (NNNNN = 0%)
7	Possible case (PPPPP = 50%)	Possible case (PPPPN = 40%)
8	Possible case (PPPNN = 30%)	Possible case (PPPNN = 30%)
9	Definitely not a case (NNNNN = 0%)	Possible case (PPNNN = 20%)
10	Definite case (YYYYY = 100%)	Definite case (YYYYY = 100%)

The reproducibility of the Expert Panel opinion was good and the results are shown in Table 24. The final opinion only varied in one case on repeat testing, with a definitely not a case of EAA becoming a possible case. The four definite cases re-reviewed remained definite cases. For the Expert Panel Score, the concordance correlation coefficient was 0.98, with a mean difference of 5% (range 0-20%).

Comparison with interleukin-2

There was a significant positive correlation between the serum levels of a cytokine interleukin 2 (IL-2) and the Expert Panel Score (figure 12). The Pearson correlation coefficient was 0.51 (p=0.004).

Figure 12: Scatter plot showing correlation between IL-2 and Expert Panel Score



Comparison of Expert Panel Opinion and Powertrain Case Definitions

When the diagnostic criteria utilised in the Powertrain outbreak (modified Fox criteria) [260] are reviewed for the 14 definite Expert Panel EAA cases, it can be seen that they were all classified as possible (n=2), probable (n=7), or definite (n=5) EAA cases (Figure 13). During the outbreak, any case scoring 4 (probable case) or above, on the modified Fox criteria was documented as being a case of EAA. All 14 of the definite cases identified by the expert panel had met the case definition of EAA at the time of the outbreak.

It is possible to map the modified Fox criteria scores against the Expert Panel Score, for each of the 37 workers (Figure 14). This demonstrates the range of Expert Panel clinical opinion for each level of the outbreak diagnostic criteria scores. It can be seen that, of the 37 workers reviewed by the expert panel, cases who met the 'possible EAA' criteria at the time of the outbreak (a score of 4), had a range of Expert Panel Score between 0-100%, and for 'probable cases' in the outbreak (a score of 5), the range of Expert Panel Score was 10-100%. Those who had a 'definite EAA' diagnosis at the time of the outbreak (a score of 6 or above), all received an Expert Panel Score of 100%.

Figure 13: Original case definitions (modified Fox criteria) used in Powertrain outbreak for the 14 workers with definite EAA as per Expert Panel opinion (score of 6 = definite, 5 = probable, 4 = possible case)

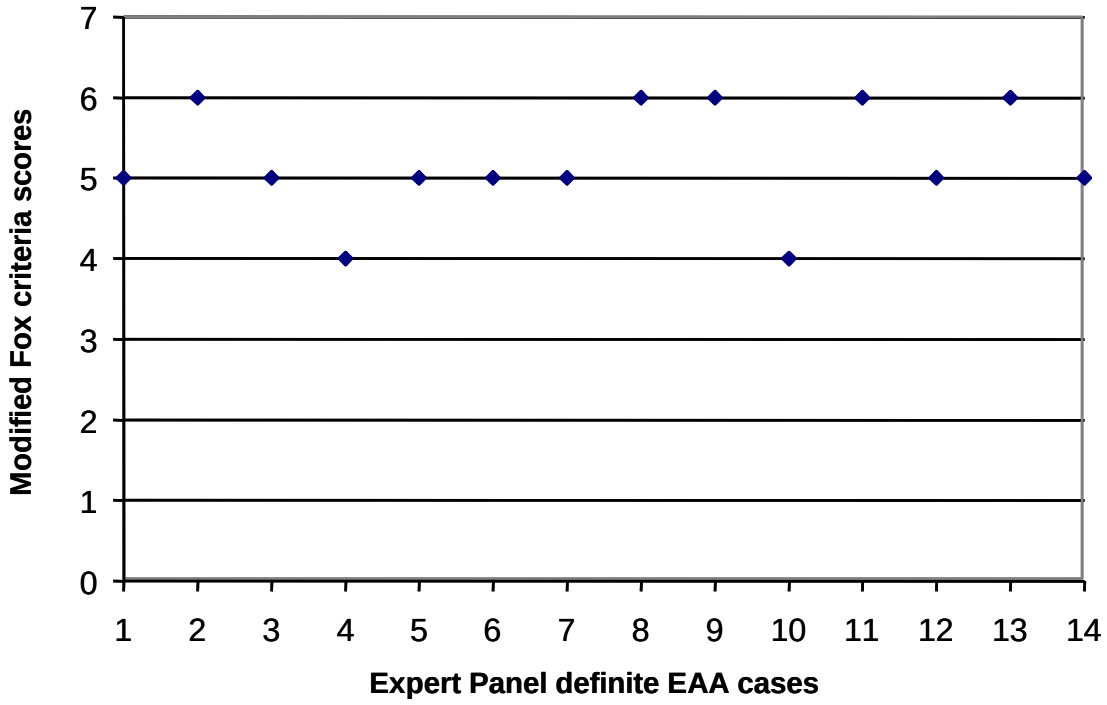
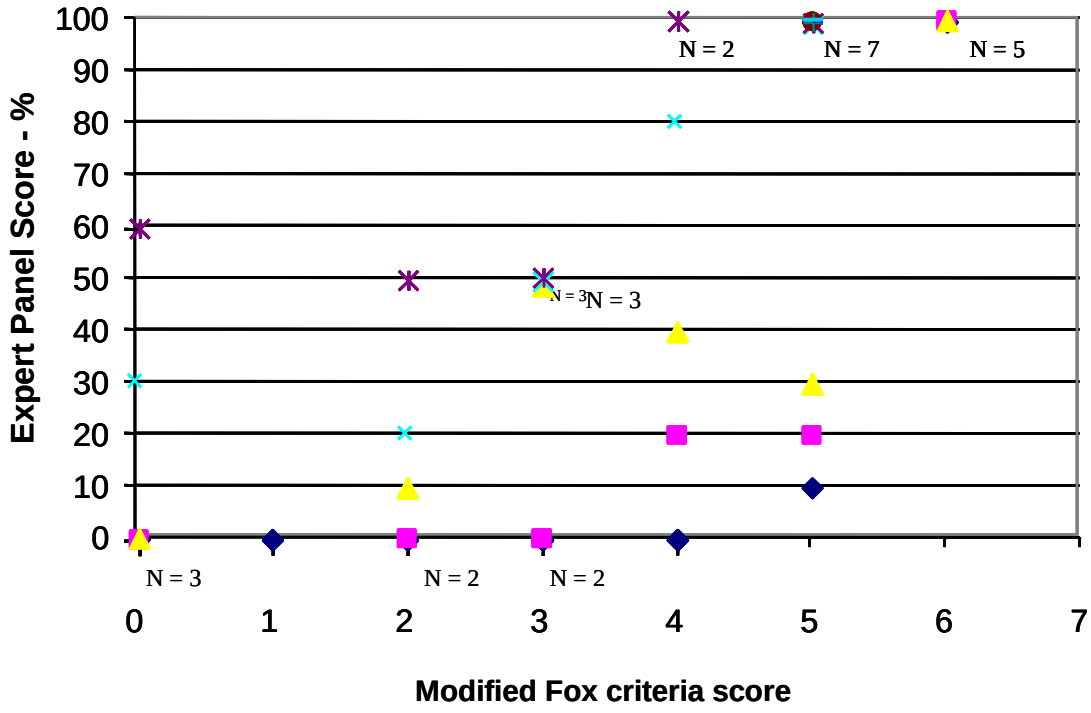


Figure 14: Comparison of Modified Fox scores and Expert Panel Scores for the 37 workers (Modified Fox case definition with score of 6 = definite, 5 = probable, 4 = possible case)



Discussion

Principal Findings

An Expert Panel of five occupational lung disease consultants from the GORDS group, reviewed the clinical case histories of 37 workers who had been suspected of having EAA due to MWF exposure during the Powertrain outbreak investigation. Information presented to the panel included summaries of work-related symptoms and the results of any diagnostic tests performed, including lung function, chest radiology, blood tests, alveolar lavage and lung biopsies. Data was provided from the initial Powertrain investigation and from subsequent follow-up visits at Birmingham Chest Clinic.

The 14 definite cases as defined by the Expert Panel had all been diagnosed as EAA using the modified Fox criteria at the time of the outbreak, but not all had been classified as 'definite EAA' i.e. had not necessarily received a score of 6 or more. Additional to those 14 workers confirmed as having EAA by the Expert Panel, the Birmingham group had diagnosed a further 5 workers with EAA at the time of the outbreak and another one case subsequently. These 6 workers were not considered to be definite cases of EAA by the Expert Panel.

Study limitations

Due to the lack of a single diagnostic test for EAA, the condition is usually diagnosed on clinical grounds, based on the results of a range of diagnostic tests. We therefore retrospectively reviewed the outbreak investigation and clinical data for 37 workers suspected of having EAA in Phase 3 of the Powertrain outbreak investigation and used the clinical opinion of five UK occupational respiratory disease specialists as a gold standard diagnosis. The Expert Panel review was designed to mirror clinical practice, reviewing available clinical information, and discussing diagnosis between clinicians who had and had not been involved in each workers clinical care and follow-up. No information was provided to the panel regarding how each worker had been classified during the Powertrain outbreak, however two panel members had been involved in the medical care of the workers. The main output from the panel was to divide workers in to two groups, dependent on whether they had definite EAA

or not, to allow comparison between these groups. We therefore adopted a stringent requirement of at least four out of five panel members to agree a worker definitely had EAA, in order to ensure this classification was as close to a clinical gold standard diagnosis as possible. The opinion of the panel was also translated in to a score, which showed good reproducibility and was significantly positively correlated with a blood test marker of T-cell activation. The results of T-cell activation were not available at the time of the panel meeting.

Many cytokines have been linked to the pathogenesis of EAA for example IFN – γ [357], IL – 17 [358 359], IL- 12, IL – 18 TNF – α [360], IL – 5, IL - 1β [361] and IL – 2 [362]. IL – 2 is used to demonstrate correlation with the panel score because this was measured by the original group investigating the Powertrain outbreak and therefore the data was available. It has not been demonstrated that this interleukin in the marker of choice and it is not an accepted gold standard for monitoring T-cell activation.

Clearly the opinion of the Expert Panel was based on the data presented to them, data collected during the investigation of an unexplained outbreak and subsequent outpatient visits, rather than from the results of a carefully designed research study. EAA is a variable disease and logistical issues within the NHS may have determined the timing of the tests, this is likely to have affected the predictive value of certain diagnostic investigations. Important examples of this include outpatient CT scanning and gas transfer estimates, where there may have been a several week interval between requesting the test and it being performed, potentially allowing time for a symptomatic worker to recover. Clearly the value of any diagnostic test in a variable disease is likely to be greatest if it is performed at the time of a worker having symptoms, which may not always be possible in an NHS outpatient setting.

There was also some missing data, as not all workers had been judged to require the full range of tests, and some workers were lost to clinic follow up. The workers rated as “possible cases” of EAA by the Expert Panel therefore are likely to represent a mixed group, with some truly indeterminate cases,and some with insufficient clinical information. Due to the retrospective nature of the panel review, diagnosis could only be based on the results of the tests that had already been performed i.e. the Expert Panel were unable to request extra tests or further question the patients.

The Expert Panel only reviewed cases where a doctor in the Birmingham Chest Clinic had previously suspected EAA or humidifier fever, during Phase 3 of the Powertrain outbreak investigation. In this highly selected group of 37 workers, there was unanimous agreement for 14 definite cases of EAA. It is entirely possible however that there were more actual cases of EAA in the outbreak, who were not identified in the earlier phases, or who did not take up the invitation to attend hospital appointments.

At the time of the outbreak, there were initially thought to be, based on clinical opinion alone, 24 cases of EAA. At the time of publication, this was reduced to 19 by using the modified Fox criteria. Emerging data after the time of publication confirmed an extra case that met the criteria, bringing the total to 20. This is reflected in graph 3 by 20 points with a modified fox score of 4 or above.

Comparison with other studies

EAA is now a well recognised complication of exposure to water containing MWF. In some outbreaks the investigators have relied on diagnosis by a physician [279 289 296]. In 1995, Bernstein reported a case series of six workers from an automobile-manufacturing site who were evaluated and treated for respiratory disease between April and September of 1992. This was the first documented outbreak of MWF related EAA. No diagnostic criteria were used, just clinical assessment including appropriate investigations. Rose et al. and Hodgson et al. relied heavily on a biopsy showing changes consistent with EAA for a diagnosis [287 294]. Other outbreak investigations have adopted a diagnostic criteria [1 260 288 302 303], the validity of these criteria are discussed in chapter 2. Other investigations have used a combination of diagnostic methods, in report HETA 2001 0303 2893 some cases of EAA were physician diagnosed and others were diagnosed based on a diagnostic criteria [299]. As far as is evident, no outbreak investigation has previously used an expert panel case review in order to decide on definite diagnosis of EAA. The use of an expert panel is time consuming and potentially costly and may be difficult to arrange in an emerging outbreak setting. However it was felt that, given the lack of gold standard test or specific validated diagnostic criteria, the consensus diagnosis of a group of

expert occupational respiratory physicians would provide the best available diagnosis of definite EAA.

In the 14 cases of definite EAA diagnosed by the expert panel there was total agreement among the panel members, creating a panel score of 100%. However in the cases when EAA was thought to be possible but not definite, there was an expert panel score range 20-80%. Clearly, even in the retrospective review of clinical cases, discrepancy still occurred between experts. This mirrored the findings of work by Baldwin et al. and Turner et al. who looked at OA and agreement in diagnosis between experts [363] [364]. In both studies, there was significant variation in diagnostic opinion. Baldwin et al provided physicians with 35 peak flow records from workers under investigation for suspected OA including details of nature of work, inter-current illness, drug therapy, predicted PEF, rest periods, and holidays. Simple plots of PEF and the Oasys-2 generated plots were available. Experts were advised that approximately 1 hour was available to review the records and were asked to score each record for evidence of asthma and occupational effect, these scores were expressed as a percentage. Cases were divided in to 2 groups depending on the scores, 0-50% and 51-100%. For occupational effect, median kappa values were 0.83 (range 0.56–0.94) for the two groups. For asthma, median kappa values were 0.58 (0–0.67). It was concluded that considerable variation in agreement was seen in expert interpretation of occupational PEF records which may lead to inconsistencies in diagnosis of OA [363].

Turner et al. sent summaries of possible OA cases to 104 occupational and respiratory physicians, to identify differences in diagnoses between the specialties. Raters assigned likelihood scores (0–100%) of OA based on case histories (phase 1) and on histories plus investigative procedures (phase 2). The difference between mean overall scores was 2.1% (52.1% occupational physicians; 50.0% respiratory physicians) in phase 1 (95% CI −2.6 to 6.8, p=0.37). In phase 2, mean overall scores were 46.1% (occupational physicians) and 41.5% (respiratory physicians); the difference in mean overall scores was 4.6% (95% CI −3.5 to 12.5, p=0.27). However, despite mean overall scores between the groups being similar, on a case by case basis, the OA scores showed limited agreement within each group of (occupational or respiratory) physicians. Raters with General Medical Council registration ≥1986

were found to be more likely to give a positive occupational asthma diagnosis. In phase 2, male raters were more likely to label cases as OA than female raters (RR 4.5, 95% CI 3.3 to 6.0) [364].

Diagnosis by the expert panel was based on clinical review of data, as this was the chosen gold standard of the research team. Other teams have chosen different methods as their gold standard, and different levels of acceptable certainty in the diagnosis. When the Birmingham team, investigating Powertrain used the modified Fox criteria, they agreed to count even possible EAA [260]. However, as the aim of our research is to identify a group of workers with definite EAA in order to compare and contrast their clinical findings, it was important to take a more stringent approach.

Study Implications

EAA has traditionally been described to have an acute, subacute and chronic form. In the acute form, respiratory and systemic symptoms tend to occur 4 -8 hours after exposure and persist for up to 12 hours. In these patients the history is often clearer, especially if exposure to a known antigen is present. In other patients the disease takes a more insidious, progressive form, with non specific symptoms such as worsening dyspnoea on exertion [201] [207]. In some workers with subacute EAA, constitutional flu-like symptoms such as fever, myalgia, malaise and weight loss are more predominant than respiratory symptoms [293]. The variable face of EAA means it can be difficult to identify the disease, in some cases leading to delayed diagnosis.

Conclusion

In an outbreak setting, it is not possible to have the wealth of follow up data that was available to the Expert panel. However by studying the cases that the panel defined as definite EAA and comparing them to those that were not, it may be possible to retrospectively isolate clinical differences that could aid diagnosis of ‘definite EAA’ in future outbreaks of EAA associated with MWF.

Chapter 4: Sensitivity and positive predictive value of questionnaire responses in the Powertrain outbreak of metal working fluid – extrinsic allergic alveolitis

Introduction

Expert panel opinion may be considered gold standard for the diagnosis of the multifaceted disease that is EAA, however the practicality of this is clearly limited. In the case of individual patients, clinical review of the patient and investigative results, perhaps with discussion in a multidisciplinary meeting, would usually be sufficient to establish a working diagnosis. In the setting of a large outbreak of respiratory disease in a MWF exposed population, the feasibility of a full clinical review of every worker would be restricted. In such scenarios, screening questionnaires have been utilised to identify workers with potential occupational respiratory problems. Little is understood about the predictive value of particular screening questions in this situation, both for occupational asthma or EAA.

For OA, it has been possible to examine the performance of questionnaire responses against specific inhalation challenge results, for patients referred to tertiary centres, although this is likely to be different in an outbreak situation. Malo et al. found that wheezing at work occurred in 88% of subjects with OA and was the most specific symptom. Nasal itching at work, and improvement in symptoms at weekends and on vacations were also significantly associated with the presence of OA [365].

Similarly, Lacasse et al. investigated which symptoms best predicted EAA in referrals to specialist centres. They concluded that dyspnoea, recognised exposure to known EAA inciting antigen, cough, recurrent episodes of symptoms and weight loss carried the highest predictive values ranging from 98% to 42% respectively [215].

The first phase of the Powertrain outbreak investigation was completed in May 2004 when 808 of the 836 workers completed a 'self reporting' symptom questionnaire, including 11 screening questions. A further, more extensive questionnaire was completed by those workers recording a respiratory or nasal symptom, or weight loss. The results of the questionnaires and further follow up data were entered in to an SPSS database.

The aim of this chapter was to compare the questionnaire responses of those workers who had a definite diagnosis of EAA, as decided by the expert panel (chapter 3) and those workers who did not. By calculating the sensitivity and positive predictive value of each question, the usefulness of the individual questions in identify cases of MWF-EAA in an outbreak setting could be established thus highlighting those questions that should be included in future questionnaire surveys.

Methodology

During the outbreak investigation at the Powertrain site, workers who complained of at least one respiratory or nasal symptom or weight loss during the initial screening questionnaire were invited to take part in phase 2 of the investigation. The phase 2 assessment included a detailed questionnaire (appendix 2), spirometry and blood tests undertaken at the factory site during June 2004. The phase 2 questionnaire involved 108 questions on worker and workplace demographics, shortness of breath, cough, ocular, nasal and throat symptoms, past illnesses, asthma symptoms, and flu like symptoms. An initial clinical opinion was then provided based on the questionnaire responses and spirometry results.

Based on the results of phase 2 assessments, employees with symptoms suggestive of occupational disease were identified and invited to enter phase 3. 161 workers were seen for more detailed investigation at Birmingham Chest Clinic, this included pulmonary lung functions, chest x-rays, methacholine challenge tests (for bronchial hyperreactivity), skin prick tests for common environmental allergens, and HRCT.

In phase four, case definitions for EAA and OA were applied to identify cases that met predefined objective criteria with onset of disease after January 2003. The case definition groups were not mutually exclusive which resulted in workers potentially being assigned to more than one group. Those workers who, at phase 3 were suspected to be suffering from EAA were discussed by the expert panel and a definitive diagnosis of definite EAA, possible EAA or not EAA was made.

All results from phase 1-4 of the investigation, follow up data and the findings of the Expert Panel were entered in to an SPSS database. This database was used to compare the questionnaire responses of workers with definite EAA, as defined by the expert panel, and those workers without definite EAA. With this information, the sensitivity and positive predictive value of each screening question was calculated.

Due to the design of the outbreak investigation, the calculated specificity and negative predictive value of questionnaire items would be artificially high, due to workers without an individual symptom being less likely to have continued in to the later phases. It is not possible to say therefore, whether a worker without a specific symptom was actually suffering from undiagnosed EAA, which could have potentially been identified based on physiology or radiological changes in later phases. For this reason, these values have not been calculated.

Table 25: Sensitivity and positive predictive value

Term	Definition
Sensitivity	The proportion of actual positives which the question correctly identified as such (i.e. the percentage of patients with definite EAA who answer positively to the question).
Positive Predictive Value	Positive predictive value is the proportion of subjects with positive test results who are correctly diagnosed (i.e. the percentage of patients who answer positively to the question that have EAA).

All responses to the Phase 1 questionnaire were used due to the binary nature of their answer i.e. yes or no. The first 18 questions of the phase 2 questionnaire are regarding the worker demographics and the responses provide continuous data, for example ‘On average, how many hours do you work in a week?’ These questions and those similar have not been included in the results as it is not possible to calculate the sensitivity and positive predictive value. The responses to the phase 2 questionnaire are subdivided in to shortness of breath, cough; ocular, nasal and throat symptoms; past illnesses, asthma symptoms, and flu like symptoms.

Results

This is a results summary, see appendix 2 and 3 for full details.

Phase 1 screening questionnaire

Table 26: Phase 1 responses

Question: In the last 18 months have you had any...	Sens%	PPV%
1 wheeze or chest tightness	93	4
2 treatment for chest	100	8
3 woken at night with cough or tightness	100	5
4 episodes of breathlessness	93	5
5 time off with chest disease	100	13
6 tightness/breathlessness post exercise	93	4
7 difficulty breathing	93	7
8 eye irritation	64	3
9 stuffy nose	64	2
10 soreness of nose, lips or mouth	43	3
11 unexplained weight loss	79	25

The phase 1 questionnaire was the initial survey of the workforce, aiming to identify any worker who may be suffering from a respiratory problem. The question with the greatest positive predictive value was Qu 11: In the past 18 months, have you had any unexplained weight loss? with a PPV of 25%.

Both Qu 2: Have you taken any treatment for your chest? and Qu 5: Have you had any time off work with any chest illness? refer to previous medical illness related to chest disease in the preceding 18 months. Both questions have a sensitivity of 100%, showing all workers with EAA, as defined by the expert panel, had had either treatment or time off due to chest disease before the investigation took place. They have a positive predictive value of 8% and 13% respectively, which suggests that there were high numbers of workers with significant respiratory symptoms other than those diagnosed with EAA.

Qu7: Have you developed difficulty breathing? is a very broad respiratory question and would be expected to detect most cases of EAA. This is illustrated with a sensitivity of 93%. However, as it is also a common symptom of most respiratory disease so the positive predictive value is only slightly raised at 7%.

Questions 8-10 refer to ocular, nasal and oral symptoms. These are not symptoms usually associated with EAA and therefore showed low positive predictive values of 3, 2 and 3% respectively.

Phase 2 screening questionnaire

Table 27: Shortness of breath (SOB)

Question: On your worst day in the last 12 months...	Sens%	PPV%
20 SOB hurrying on flat or walking up hill	100	6
21 SOB walking with peers	100	11
22 Stop for breath walking on own on flat	93	22
23 SOB washing and dressing	64	39
25 SOB waking	50	13
26 SOB during day	100	11
27 Woken from sleep SOB	71	18
28 SOB worse at beginning of week	8	7
29 SOB worse at end of week	79	16
30 SOB no different through week	25	2
31a SOB better on days away from work	85	9
31b SOB same on days away from work	15	2
31c SOB worse on days away from work	0	0
32a SOB better on holiday	85	7
32b SOB same on holiday	15	3
32c SOB worse on holiday	0	0
34 SOB at present	86	8

Questions 20 –23 ask about shortness of breath at decreasing levels of exertion, from hurrying on level ground or walking up a slight hill, to washing and dressing. As the disability through breathlessness increases, the sensitivity of the question decreases but the positive predictive value increases. For Example, Qu 20 On your worst day in the last 12 months, did you get SOB when hurrying on level ground or walking up a slight uphill? has a sensitivity of 100 % and a positive predictive value of 6% but Qu 23 On your worst day in the last 12 months, were you short of breath washing or dressing? has a sensitivity of 64 % and positive predictive value of 39%.

The time of day that a worker is most affected by their breathlessness was investigated by questions 25 – 27. Of the three questions, the one with the greatest positive predictive value is Qu 27 On your worst day in the last 12 months, were you woken from your sleep? (sensitivity of 71% and positive predictive value of 18%).

Qu 28 On your worst day in the last 12 months, was your breathlessness worse at the beginning of the working week? has a sensitivity of 8 % and a positive predictive value of 7% and Qu 29 On your worst day in the last 12 months, was your breathlessness worse at the end of the working week? had a sensitivity of 79 % and a positive predictive value 16%. These values show that more cases of EAA felt short of breath at the end of the week compared to the beginning, and more of the respondents complaining of worse shortness of breath at the end of a week rather than the beginning had EAA.

Qu 31a On days away from work, is your breathlessness better? and Qu 32a On holidays is your breathlessness better? are both questions aiming to identify whether the worker is less short of breath when not at work. These questions validate each other's answers, by confirming that workers are less short of breath away from the workplace, having almost identical sensitivities (85%) and positive predictive values. Interestingly, the positive predictive value of these questions, 9% and 7% respectively, is approximately half that of Qu 29 (16%), despite all three questions referring to the temporal relationship of the shortness of breath. This suggests that workers at Powertrain who identified deterioration in their breathing through a working week are more likely to have EAA than those who only notice an improvement when away from work/on holiday.

Table 28: Cough and sputum

Question	Sens%	PPV%
35 Cough	93	4
38 Cough on waking	62	7
39 Cough during day	92	5
40 Woken by cough	43	8
41 Cough worse at beginning of week	7	6
42 Cough worse at end of week	50	9
43 Cough same all week	43	3
44a Cough better away from work	69	7
44b Cough same away from work	23	2
45a Cough better on holidays	69	5
45b Cough same on holidays	23	3
45c Cough worse on holidays	0	0
46 Cough up sputum	86	5
47 Sputum 3 months per year	77	6
48 Sputum 3 months per year for 2 yrs	34	3
50 Sputum on waking	62	7
51 Sputum during day	71	6
52 Sputum worse at beginning of week	0	0
53 Sputum worse at the end of week	43	8
54 Sputum no different throughout week	43	4
55a Sputum better away from work	46	5
55b Sputum worse away from work	38	4
56a Sputum better on holiday	62	6
56b Sputum same on holiday	23	3

The question regarding cough and sputum with the highest sensitivity was the opening question, Qu 35: Do you cough? with a sensitivity of 93%. Because of the all encompassing nature of the question it has a low positive predictive value of 4% as many of the workers responding positively to this question had conditions other than EAA resulting in a cough.

Deterioration in symptoms throughout the working week and improvement away from work/on holiday, as seen in the shortness of breath questions, are echoed but not as extreme in the cough and sputum question responses. A positive response to Qu 41: Is your cough worse at the beginning of the week? has a sensitivity of only 7% and a positive predictive value of 6%. Qu 42: Is your cough worse at the end of the week? has a much higher sensitivity of 50% and slightly higher positive predictive value of 9%. A higher sensitivity (69%) but similar PPVs of 7% and 5% respectively can be seen in Qu 44a Is your cough better away from work? and Qu 45a Is your cough better on holiday? This suggests that patients with EAA are less likely to complain of temporal changes in cough rather than shortness of breath but if anything, they notice improvement away from work/on holiday rather than notice deterioration throughout a working week.

As regards to the sputum production in Powertrain workers, the question with the greatest sensitivity is the opening question, Qu 46 Do you cough up phlegm (sputum) from your chest? (sensitivity 86%). Sputum production is not specific to EAA and this is reflected in the low positive predictive value (5%). For those workers with EAA who do expectorate, the responses demonstrate an increased production at the end of the week compared to the beginning of the week. Qu 52: Is your phlegm production worse at the beginning of the week? and Qu 53 Is your phlegm production worse at the end of the week? Show sensitivities of 0% and 8% and positive predictive values of 0% and 43%. These values indicate that none of the EAA cases produced more sputum at the beginning of the week.

In summary, 100% of the EAA cases had shortness of breath, 93% had cough and 86% had sputum. All 3 of these symptoms are relatively common in the general population at Powertrain so the positive predictive value is low ranging from 5% for sputum production to 9% for shortness of breath. A temporal relationship associating these symptoms to work was most evident with shortness of breath being described as worse at the end of a working week in 79% of definite EAA cases, with a PPV of 16%.

Table 29: Ocular and nasal and throat

Question: In the past 12 months have you had...	Sens%	PPV%
58 2 x episodes of eye irritation or watering	64	4
60a Eyes better away from work	36	3
60b Eyes same away from work	29	4
60c Eyes worse away from work	0	0
61a Eyes better on holiday	43	4
61b Eyes same on holidays	21	3
61c Eyes worse on holidays	0	0
62 Blocked or stuffy nose	79	3
64a Nose better away from work	36	3
64b Nose same away from work	43	3
64c Nose worse away from work	0	3
65a Nose better on holiday	64	0
65b Nose same on holiday	14	2
66c Nose worse on holiday	0	0
66 Dry or sore throat	71	3
68a Throat better away from work	50	4
68b Throat same away from work	21	2
68c Throat worse away from work	0	0
69a Throat better on holiday	57	4
69b Throat same on holiday	14	2
69c Throat worse on holiday	0	0

The questions with the highest sensitivities are the two lead questions, Qu 58: In the past twelve months have you had more than two episodes of irritation or watering of the eyes? (64%), Qu 62: In the past twelve months have you had more than two episodes of blocked or stuffy nose? (79%) and Qu 66: In the past twelve months have you had more than two episodes of a dry or sore throat? (71%).These

sensitivities indicate that a high proportion of workers with EAA suffered with ocular, nasal and throat symptoms. However, the PPVs range from 3-4% suggesting that the symptoms are common throughout the workforce who completed phase two of the questionnaire. What is apparent is that workers with definite EAA consistently denied symptoms being worse out of work and generally felt that their ocular, nasal and throat symptoms were worse at work.

Table 30: Past illness

Question	Sens%	PPV%
71 Previous chest illness	50	4
72 Treatment for chest	79	15
73 Lymphoma	0	0
74 Weight loss	64	9

In the past illnesses section of phase two, the question with the highest positive predictive value is Qu 72: Are you taking any treatment for your chest? This indicates that 79% of the definite cases of EAA were already taking treatment for chest disease at the time of the outbreak. It is not possible to know whether those patients had been diagnosed with EAA and were consequently taking appropriate treatment. In many cases, EAA is initially misdiagnosed as conditions such as infection or asthma, and this was certainly noted to be the case for some workers when preparing the clinical reviews for presentation to the expert panel (chapter 3). The positive predictive value of this question is 15%, suggesting that 85% of the workers who responded positively to this question were not in the 14 that were ultimately diagnosed as having definite EAA, thus demonstrating a high burden of other chest disease within the population.

Table 31: Asthma

Question	Sens%	PPV%
75 Previous asthma diagnosis	43	8
In the last 12 months...		
76 Chest tightness or breathing difficulties	100	5
79 Chest or breathing difficulties on waking	50	8
80 Chest or breathing difficulties during day	93	6
81 Woken from sleep by chest or breathing	50	10
82 Chest or breathing worse at beginning of week	0	0
83 Chest or breathing worse at the end of week	75	14
84 Chest or breathing same throughout week	25	2
85a Chest or breathing better away from work	77	8
85b Chest or breathing same away from work	23	2
85c Chest or breathing worse away from work	0	0
86a Chest or breathing better on holidays	92	8
86b Chest or breathing same on holidays	8	1
86c Chest or breathing worse on holidays	0	0

100% of the workers with definite EAA suffered with chest tightness or breathing difficulties, although a PPV of PPV 5% suggests that a large proportion of the other workers also complained of these symptoms. As regards the temporal relationship, this follows the same pattern as that demonstrated with the shortness of breath,

cough and sputum questions, with a 92% of the EAA cases stating an improvement during holidays (PPV 8%), 77% stating an improvement away from work (PPV 8%) and 75% complaining of worsening symptoms throughout the working week. The progression of symptoms throughout the week has the highest PPV, 14%.

Question: In the past 12 months have you had...	Sens%	PPV%
87 Wheezing or whistling (WW)	86	5
90 WW on waking	54	8
91 WW during the day	86	7
92 Woken from sleep by WW	54	13
93 WW worse at beginning of week	7	10
94 WW worse at end of week	57	13
95 WW same throughout week	23	2
96a WW better away from work	62	8
96b WW same away from work	23	2
96c WW worse away from work	0	0
97a WW better on hols	77	8
97b WW same on hols	8	1
97c WW worse on hols	8	1

The temporal association of wheeze mirrors that identified by earlier respiratory symptoms. Waking at night due to difficulty in breathing or a tight chest (sensitivity 50% PPV 10%) or wheeze (sensitivity 54% PPV 13%) in the previous 12 months was documented by at least half of the cases of definite EAA. This compares to 100% of the cases when asked in phase one if in the past 18 months, they had woken at night with a cough or chest tightness? This is a symptom traditionally associated with asthma rather than EAA.

Table 32: Flu

Question: In the past 12 months have you had...	Sens%	PPV%
98 Recurrent flu like symptoms	62	4
99 Fever	38	5
100 Shivering	38	5
101 Tiredness	62	4
102 Weakness	62	5
103 Joint/muscle pains	54	4
106 More freq after particular job	25	17
107a Flu at beginning of week	15	11
107b Flu at the end of the week	31	11
107c Flu same throughout week	17	1
108a Worse back at work after weekend	46	13
108b Worse back at work after holiday	46	11

Phase two questionnaire illustrated that flu like symptoms in general are common in workers with and without definite EAA. Qu 106: Do these symptoms occur more freq after doing a particular job? aims to associate the flu like symptoms to a particular activity. Although this question is not particularly sensitive, in that only a quarter of the workers with EAA felt that they had flu like symptoms that occurred more frequently after doing a particular job, the positive predictive value was relatively high at 17%.

Qu 107-108, look more generally at the association between work and flu like symptoms, rather than a specific activity. The style of the questions is slightly different than that seen in previous sections of phase two. Qu 107a asks 'Do these symptoms occur at the beginning of the working week?' rather than whether they are worse at the beginning of the week. The temporal relationship is not as clearly evident as seen previously with the respiratory symptoms. Qu 108 refers to a worsening of flu like symptoms when returning to work after a weekend break or holiday (sensitivity 46% PPV 11% and 13%). This question maybe included due to

the typical increase in symptoms after a return to work post break seen in humidifier fever.

When analysing a work health survey for responses typical of workers with EAA, the PPV of the question would be an important factor to consider. Those questions with the highest positive predictive value are listed in Table 2.

Table 33: Questions in the Powertrain questionnaires with the highest positive predictive value

Question number	**Question**	**Positive predictive value (%)**
Phase one:11	In the past 18 months, have you had any unexplained weight loss?	25
Phase two: 22	On your worst day in the last 12 months, did you have to stop for breath walking at your own pace on level ground?	22
Phase two: 23	On your worst day in the last 12 months, were you short of breath washing or dressing?	39
Phase two: 27	Are you woken from sleep by your breathlessness?	18
Phase two: 29	Is your breathlessness worse at the end of the working week?	16
Phase two: 72	Are you taking any treatment for your chest?	15
Phase two: 106	Do these symptoms (recurrent flu like symptoms) occur more freq after doing a particular job?	17

Discussion

Main Findings

This study aimed to identify the most useful questions for recognising MWF-EAA during an outbreak. By comparing the questionnaire responses of those workers with definite EAA to the responses of those workers without definite EAA, the sensitivity and positive predictive value of each question was calculated.

Three of the phase one eleven screening questions had 100% sensitivity; all the MWF-EAA cases had had time off work due to chest problems, treatment for chest conditions and had been woken with cough or chest tightness in the preceding eighteen months. The positive predictive values of these questions for EAA however were variable however, ranging from 5-13%. Question 11 of phase one asked 'In the past 18 months, have you had any unexplained weight loss?' had a lower sensitivity of 79% but a higher PPV of 25%.

During Phase 2 of the Powertrain outbreak, a very detailed questionnaire was utilised, with over 100 questions. As regards respiratory symptoms, 100% of the EAA cases had shortness of breath and difficulty breathing or chest tightness, 93% had cough and 86% had sputum and wheeze. All of these symptoms are relatively common in the general population at Powertrain, so the positive predictive values are low ranging from 5% to 9%. A temporal relationship associating these symptoms to work was most evident with shortness of breath being described as worse at the end of a working week in 79% of definite EAA cases, with a PPV of 16%. The question with the highest PPV (39%) was Qu23: On your worst day in the last 12 months, were you short of breath washing or dressing? This suggests that although shortness of breath when hurrying on level ground or walking up a slight hill had a low PPV of 6%, the greater the disability, the greater the proportion of positive respondents having definite EAA.

Phase two questions relating to eyes, nose and throat had low PPV, which maybe expected as these are not symptoms typical to EAA. They were however common symptoms in the workforce in general. The question relating to flu like symptoms with the most significant PPV was that referring to increasing symptoms following completing certain task within the work place (PPV 17%).

Limitations

The limitations in this chapter largely relate to its design, in terms of interrogating an existing database from an investigation of an unexplained health outbreak, with no facility to collect further data. The questionnaires were designed as part of an evolving outbreak investigation, not as part of a research study. A possible limitation is that only one constitutional symptom (unexplained weight loss) was included in the Phase 1 screening questions. It is possible therefore that some cases of MWF-EAA, for example those suffering recurrent flu-like symptoms in the absence of weight loss or respiratory symptoms, will have been classed as asymptomatic and not invited to take part in Phase 2 of the study. Consequently, they would have remained undiagnosed by the investigative team and their disease would not be included in the findings. It is possible to look at positive predictive value and sensitivity (as these calculations look at those workers with definite EAA, as defined by the expert panel), but it is not accurate to look at negative predictive value and specificity as we cannot guarantee that other additional workers at Powertrain did not have EAA that went unidentified by the researchers and so the total number of workers without EAA cannot be calculated.

The response rate for this outbreak investigation was high, although not 100 percent. 808 of 836 workers completed the first phase of the screening questionnaire. In the second phase, the detailed questionnaire was completed by 454 of the 481 symptomatic workers. Both questionnaires were self-reporting and as a consequence not all were completed in their entirety. As the questionnaire responses were used by the investigating team to identify potential cases of occupational lung disease, missing data obviously leads to the potential of cases being over looked.

The number of definite EAA cases in the analyses is the number diagnosed as definite cases by the expert panel. The limitations in the Expert Panel can therefore also be applied to any further analysis using the definite 14 cases as a reference point. The true number of cases of EAA caused by MWF exposure at the Powertrain site can never actually be calculated for certain and the limitations of the methodology of using an expert panel as a gold standard for diagnosis is discussed in Chapter 3. At expert panel review, there were other workers judged to be possible

cases of EAA, some of whom were lacking definitive investigation results, and others were lost to follow up.

Symptoms enquired about in phase one were often the subject of questions in phase two, and the sensitivity and PPV values were not always consistent. In phase two, workers were asked whether, in the previous 12 months they had experienced waking at night due to difficulty in breathing or a tight chest (sensitivity 50% PPV 10%) or wheeze (sensitivity 54% PPV 13%). Unlike the 100% sensitivity seen in phase one, only half of the cases of definite EAA responded positively to the phase two questions. The difference could be accounted for the extra 6 months covered by the phase one question. Nocturnal waking is a symptom traditionally associated with asthma rather than EAA.

Question 11 of phase one asked 'In the past 18 months, have you had any unexplained weight loss?' This received a positive response from 11 of the 14 definite cases, producing a sensitivity of 79%. 1 in 4 of the workers reporting weight loss in phase one went on to be diagnosed with MWF-EAA by the expert panel (PPV 25%). Question 74 of phase two asked 'Have you lost weight since January 2003?' received a positive response from only 9 of the definite EAA cases and a much lower PPV (sensitivity 64% PPV 9%). 33 workers who did not receive the diagnosis of EAA responded positively to the phase one question and 92 to the phase two question regarding weight loss. The reason for almost 3 times as many non EAA cases, but less of the EAA cases, reporting weight loss in phase two of the questionnaire is not evident. It is possible that this relates to improvements in the workplace between the questionnaires or the phrasing of the question.

Comparison with other work

Comparison with the findings from other studies is limited by a lack of standardisation, in terms of type and extent of investigation and exact method of symptom identification. In the Powertrain outbreak, initial screening of the workforce found that symptoms were common with 60% of workers reporting at least one respiratory symptom and a further 18% having eye or nasal symptoms. This is in keeping with previously published outbreaks in large workplaces which have been

reviewed in detail in Chapter 1. For example, in a large automobile factory where there had been 8 reported cases of EAA, Trout et al. [299] found symptom prevalence to be 74% for unusual shortness of breath, 72% for wheezing and whistling, 68% for chest tightness, 51% for fever or sweats, and 34% for chills or shivering. In another study, HETA 99-0177-2828, in 1999, 43% of workers exposed to MWFs complained of unusual tiredness of fatigue [310].

Eye, nose and throat symptoms are commonly reported in MWF outbreaks, and in Phase 1 of Powertrain nasal stuffiness was the most commonly reported symptom. Although these symptoms are not traditionally associated with EAA, they were reported by approximately two-thirds of workers with MWF-EAA. Their positive predictive value however was low and this may reflect a non-specific response in the workplace to high levels of fume or dust, or other allergic responses to MWF allergens. For identifying subjects with OA, Vandenplas et al., found that the most useful questionnaire items in tertiary centres were wheezing at work, nasal and eye irritation [365]. The high prevalence of nasal and eye symptoms in the Powertrain workforce suggests that they would not be discerning questions in an outbreak setting.

The findings from our study can be compared with general EAA research findings outside of MWF outbreaks. Lacasse et al. reported a range of symptom prevalence for 116 patients with EAA, predominantly farmers and bird fanciers [215]. He found breathlessness (98%) and cough (91%) to be the commonest symptoms of EAA, but unlike our study, found a much lower prevalence of chest tightness and wheezing (31-35%). In the Powertrain study, 79% of workers with EAA reported unexplained weight loss in Phase 1 (64% in phase two), this was higher than in Lacasse's report where the corresponding figure were 42%. However the number of EAA cases describing shivering/chills was very similar with 38% in the Powertrain outbreak and 34% reported by Lacasse et al and Trout et al [215 299].

In addition to recording the presence or absence of symptoms, it is also usual for questionnaires to enquire about the work-relationship of symptoms, often by asking whether symptoms improve at weekends or on holidays [294]. A number of existing general diagnostic criteria for EAA include variability in symptoms as a case criterion, but there is little published research relating to how exactly to ask about work-

relatedness. In the Powertrain outbreak, questions regarding respiratory symptoms, especially shortness of breath that was worse at the end of the working week, had a greater positive predictive value than questions relating to symptoms that improved on weekends and holidays. A difference in symptom intensity associated with days at or away from work was not identified for constitutional symptoms, where the question with the highest PPV was for symptoms after a particular work task. The reasons for this variation are not clear from this study, although variation in working patterns, differences in disease phenotype, and confounding factors such as humidifier fever may be relevant. Because of these factors, some groups have removed the requirement for work-relatedness in their diagnostic criteria. For example, during the investigation of a large outbreak of EAA in Connecticut, the temporal patterns of symptoms were ignored, as it was believed that the variable nature of the disease and the long working hours of the employees rendered the work relatedness of symptoms unreliable [294].

Implications

When analysing questionnaire data from an outbreak of MWF-EAA, certain questions were found to have a relatively high PPV for EAA. Recent weight loss, extreme shortness of breath including nocturnal symptoms, breathlessness worse at the end of the working week and flu like symptoms associated with particular work tasks are all symptoms that should be noted with a high level of suspicion. These questions and also whether the worker is being treated for chest disease presently should be included in any screening questionnaire designed to detect MWF-EAA in an outbreak setting.

When discussing work relatedness of symptoms, physicians should be aware that simply asking if symptoms improve while away from work, may not be sufficient and that patients should also be asked how their symptoms change throughout the working week. Due to the potential difficulties in establishing a temporal relationship, some researchers have decided to dispense with the need for this in their diagnostic criteria.

Conclusion

This study illustrates the difficulties in developing a questionnaire for use in MWF outbreak investigations where symptom prevalence is high compared to actual cases of disease, and individuals with occupational asthma and alveolitis need to be accurately and rapidly identified to avoid further harm. This chapter has highlighted a number of simple questions which have a higher PPV for MWF-EAA and could, in conjunction with other diagnostic procedures, form the basis of future outbreak investigation survey.

Chapter 5: Development and validation of evidence-based case definitions for extrinsic allergic alveolitis due to metalworking fluid exposure

Introduction

After reviewing the outbreaks of MWF EAA and further discussing the different diagnostic criteria used to define EAA, it became clear that there is no consistent, evidence based diagnostic criteria available for use in an outbreak scenario. The majority of criteria have utilised some combination of symptoms, lung function, radiology, blood tests and/or biopsies.

Fox et al. investigated the US Kenosha outbreak of MWF EAA which occurred between 1995-97 [1]. They were the first to develop and publish case definitions for EAA for the purposes of their study, although these had not been validated prior to their usage. Their seven point diagnostic criteria was based on (one point for each), a previous physician diagnosis of EAA, at least two respiratory and one constitutional symptom, a recurrence of symptoms after a three or more days break from work, restrictive spirometry, a reduced gas transfer, abnormal radiology, and granulomas on lung biopsy. It was these criteria in a slightly modified form that were later used in the Powertrain investigation [260].

Dangman et al. developed an evidence-based non-invasive hypersensitivity pneumonitis (EAA) diagnostic index (HPDI) for outbreak investigations, in part to avoid the morbidity and expense of lung biopsies, which had been previously used for case definition in other outbreaks [293]. They also recognized the clinical variability of EAA, and noted that EAA may present as chronic fibrotic lung disease, mimicking idiopathic pulmonary fibrosis or sarcoidosis. They compared data by logistic regression from 16 cases of biopsy proven EAA, with that from 14 workers thought least likely to have EAA. This found that workers with EAA had more symptoms, higher ESRs, lower gas transfers, higher alveolar-arterial oxygen gradients, lower vital capacities, more abnormal HRCTs, and more abnormal gallium scans, than those without EAA [293]. In practice in the UK, as alveolar-arterial oxygen gradients and gallium scans are not routinely available, the HPDI is not a useful tool.

By using the definite cases of EAA, as defined by the Expert Panel, the sensitivity and PPV of the questions making up phase one and two of the Powertrain investigation have been calculated (chapter 4). This provided insight in to which questions would be useful in future outbreaks of respiratory ill health associated with MWF and have provided the basis of further analysis of the database, in order to formulate an evidence based diagnostic criteria for use in an outbreak setting of MWF associated EAA.

Methods

Comparison of Expert Panel definite EAA cases versus cases reviewed but not diagnosed as definite EAA versus cases not review by expert panel

Chapter 5 divides workers into, those reviewed by the panel and diagnosed with definite EAA (n=14), those reviewed by the panel and not diagnosed with EAA (n=23), and those not reviewed by the panel i.e. those not considered in phase 3 to warrant further investigation for EAA or humidifier fever. This differs from chapter 4, which divides workers in to just two groups, those with definite EAA and without definite EAA, so grouping the latter two groups together. Between the three groups, comparisons are made regarding basic demographics, responses to the eleven phase 1 screening questions, the major symptoms recorded in the phase 2 questionnaire, lung function test results, blood test results, radiological findings, and histopathology and statistical analysis. Continuous data was compared using Student t-tests and categorical data was compared using Fisher's Exact tests.

Case definition development

Utilising the clinical differences found during the comparison between those workers reviewed by the expert panel with and without definite EAA, and with knowledge of existing EAA diagnostic criteria, a new diagnostic case definition (MWF EAA Score) was developed. This was designed to fit as closely as possible with the Expert Panel opinion, whilst remaining clinically valid and inclusive. The new scoring system was then applied to the Powertrain workers, and compared with the Expert Panel Score. Suitable cut offs for definite, possible and definitely not EAA were chosen, to best match the opinion of the Expert Panel.

The performance of the MWF EAA Score and other published case definitions were compared by applying each of the case definitions to the 37 Powertrain workers reviewed by the panel. Performance was assessed by comparing the proportion of workers correctly identified as definite, possible and definitely not EAA, against Expert Panel opinion. Cohen kappa scores for agreement between the Expert Panel and the different case definitions for definite EAA cases were also calculated.

Validation of MWF EAA Score

In an attempt to externally validate the MWF EAA Score, the scoring system was also applied to all available previously published case reports of workers developing definite EAA due to MWF exposure.

Results

Demographics of workers reviewed by Expert Panel

Workers with EAA were on average slightly older, had a shorter employment history prior to the Powertrain outbreak, and were less likely to be current smokers than the other groups. These demographic factors were not statistically significantly different however, and there were no significant gender or atopy differences. The high level of atopy in the workers who had skin prick tests, but were not reviewed by the Expert Panel for suspected EAA, is likely to be explained in part by their having this test as part of investigation for possible allergic occupational asthma.

Table 34: Comparison of demographics for workers who were or were not reviewed by the Expert Panel

Demographic	**Reviewed by Expert Panel (N=37)**		**Not reviewed**
	definite EAA	**not definite EAA**	**(n=473)**
Mean age (SD)	47 (8)	43 (8)	45 (9)
Male	86%	91%	84%
Smoker	7%	26%	25%
Atopic	38%	35%	50% (n=118)
Year first employed	1996	1992	1992 (n=464)

Analysis of Phase 1 screening questionnaire responses

Responses to the Powertrain Phase 1 screening questionnaire responses can be compared between workers with definite EAA, workers reviewed but not thought to have EAA, and the remaining workforce, this data is shown in table 4.

Table 35: Comparison of Phase 1 screening questionnaire responses for workers who were or were not reviewed by the Expert Panel (*significant p<0.05)

Question	Reviewed by Expert Panel (N=37) definite EAA	not definite EAA	Not reviewed (N=771)
Episodes of wheeze or chest tightness	93%	87%	40%
Chest treatment	100%*	39%*	19%
Woken with cough or chest tightness	100%	74%	31%
Episodes of breathlessness	93%	78%	28%
Time off with chest illness	100%*	32%*	11%
Chest tightness or breathlessness after exercise	93%	87%	36%
Difficulty with breathing	93%	64%	19%
Eye irritation	64%	39%	40%
Stuffy nose	64%	83%	61%
Soreness of nose/lips/mouth	43%	44%	28%
Unexplained weight loss	79%*	9%*	4%

For workers with suspected EAA reviewed by the Expert Panel, the largest difference in terms of symptom prevalence between those with and without definite EAA was seen for unexplained weight loss. Significant differences were also seen for previous chest treatment, and previous time off with chest illness.

The positive predictive values of questionnaire responses are shown in Table 36. In the first column these relate to the likelihood of respondents answering yes to each question, later going on to be clinically suspected of having EAA when assessed at Birmingham chest clinic (i.e. and therefore being reviewed by Expert Panel). Similarly, the second column shows the likelihood of workers answering yes to each

question, later being considered definite cases of EAA by the Expert Panel review, as previously discussed in chapter 4. It can therefore be seen that 1 in 4 workers who on initial screening reported unexplained weight loss, and 1 in 8 workers who reported having had time off with chest problems, went on to be diagnosed as a definite case of EAA.

Table 36: Positive predictive value (ppv) of Powertrain screening questions

Screening question	ppv clinical suspicion EAA	ppv definite EAA
Have you had any episodes of wheeze or chest tightness?	10%	4%
Have you taken any treatment for your chest?	14%	8%
Have you woken at night with a cough or chest tightness?	12%	5%
Have you had any episodes of breathlessness?	12%	5%
Have you had any time off work with any chest illness?	20%	13%
Have you developed chest tightness or breathlessness after exercise?	11%	4%
Have you developed difficulty with breathing?	15%	7%
Have you had irritation or watering of the eyes?	5%	3%
Have you had a stuffy nose?	6%	2%
Have you had any soreness of the nose, lips or mouth?	7%	3%
Have you had any unexplained weight loss?	30%	25%

Analysis of Phase 2 questionnaire responses

Table 37: Comparison of Phase 2 detailed questionnaire responses for workers who were or were not reviewed by the Expert Panel (* p<0.05) showing the prevalence of self-reported symptoms

Question	Reviewed by Expert Panel (N=37) definite EAA	not definite EAA	Not reviewed (N ~ 473)
Cough	93%	87%	55%
WR cough	77%	70%	31%
Progressive cough	50%	50%	13%
Wheeze	86%	70%	42%
WR wheeze	77%	57%	21%
Progressive wheeze	57%	41%	10%
Chest tightness	100%	87%	43%
WR chest tightness	86%	61%	25%
Progressive CT	64%	48%	10%
Shortness of breath MRC 2 MRC 3 MRC 4 MRC 5	 100% 100% **93%*** 64%	 83% 70% **39%*** 22%	 42% 20% 7% 2%
WR SOB	92%	57%	27%
Progressive SOB	79%	38%	10%
Recurrent flu	62%	74%	39%
WR flu	50%	43%	11%
Progressive flu	29%	17%	7%

When the prevalence of the main symptoms from the Phase 2 questionnaire is compared between the groups of workers (Table 37), the majority of symptoms were more common in the workers who were reviewed by the Expert Panel i.e. those with suspected EAA. This reflects the design of the Powertrain investigation, where those workers with symptoms in Phase 2, were invited to attend Birmingham Chest Clinic for further tests in Phase 3. It can also be seen that the prevalence of work-related

and progressive wheeze, chest tightness and shortness of breath were higher in workers judged to have definite EAA by the Expert Panel (although these differences did not reach statistical significance), as opposed to those judged not to have definite EAA. The high prevalence of symptoms is to be expected, as the Expert Panel only reviewed workers with clinically suspected EAA, based on their having reported compatible symptoms during the outbreak investigation.

All of the definite EAA cases reported shortness of breath on exertion, with the majority suffering from severe breathlessness of MRC Grade 4 or 5. MRC Grade 4 breathlessness (having to stop for breath when walking at your own pace on level ground) was significantly more prevalent amongst workers with definite EAA than workers without definite EAA.

In terms of constitutional symptoms, recurrent flu-like symptoms were more commonly reported in workers reviewed by the expert panel but not diagnosed with definite EAA than those with definite EAA, where as the reverse was true for work-related and progressive flu-like symptoms. It is likely that this reflects the distinction between workers with EAA, whose constitutional symptoms worsened through the working week, and workers with humidifier fever whose symptoms improved through the working week. Although not statistically significantly different, the largest difference in symptom prevalence was for progressive flu-like symptoms i.e. workers with flu-like symptoms that became progressively worse over the working week.

Analysis of Phase 2 respiratory physiology

In addition to symptom prevalence, similar comparisons can also be made for the results of the respiratory physiology tests. The majority of workers in Phase 2 performed simple spirometry in the workplace, resulting in measurements of FEV_1, FVC, and FEV_1/FVC ratio. Although mean per cent predicted values for both FEV_1, and FVC did not differ between those with and without definite EAA, mean levels were significantly lower in both of these groups as compared to the rest of the workforce. Again this is to be expected by the nature of patients selected for Expert Panel review. The mean FEV_1/FVC ratio was similar between all three groups.

Table 38: Comparison of physiology for workers who were or were not reviewed by the Expert Panel (* p<0.05)

Lung function	Reviewed by Expert Panel (N=37) definite EAA	not definite EAA	Not reviewed (N=473)
FEV_1 % pred	84%	85%	98%
FEV_1 < 80% pred	29%	35%	12%
FVC % pred	85%	91%	105%
FVC < 80% pred	21%	26%	5%
FVC < 70% pred	14%	9%	1%
FEV_1/FVC	81%	80%	78%
Tlco % pred	**68%***	**80%***	N/A
Tlco < 80% pred	79%	56%	N/A
Tlco < 60% pred	**29%***	**0%***	N/A
Kco	**1.43***	**1.71***	N/A

More detailed respiratory physiology was only performed in workers with suspected occupational lung disease, with measurements of carbon monoxide gas transfer (Tlco) and transfer co-efficient (Kco) performed in the hospital respiratory function unit. Mean percentage values for both of these were lower in the group of workers with definite EAA versus not definite EAA, and having a gas transfer less than 60% predicted was only seen in the former group.

Analysis of Phase 2 blood tests

Blood tests were also performed in a large number of workers as part of the Phase 2 investigation. Workers with definite EAA had significantly higher mean levels of neutrophils and total white blood counts, as compared to workers reviewed by the Expert Panel but without definite EAA . No significant differences were seen for the other types of white blood cells, such as lymphocytes or eosinophils. Serum levels of alpha 1 antitrypsin (an acute phase protein with a half-life of 4.5 days) were measured in 31/37 workers reviewed by the Expert Panel, with mean values being significantly higher in the definite EAA group. The other inflammatory mediator measured in the Powertrain investigation was another acute phase protein, c-reactive

protein (CRP), which has a much shorter half-life of 5-7 hours. This was only measured in 18 Of the Expert Panel reviewed workers and although this did not reach statistical significance, was higher in four workers with definite EAA, than in 14 workers without definite EAA. No significant differences were seen for the results of the other blood tests measured, immunoglobulin G or M, or serum ACE.

Table 39: Comparison of blood test results for workers reviewed by the Expert Panel, who did and did not have EAA (* p<0.05)

Blood test	Definite EAA	Not definite EAA
CRP – mg/L	11 (13)	4 (3)
WBC – $x10^9$/L	**8.1 (2.0)***	**6.64 (1.5)***
Neutrophils – $x10^9$/L	**5.9 (2.5)***	**4.1 (1.3)***
Lymphocytes – $x10^9$/L	2.1 (0.8)	2.2 (0.6)
Eosinophils – $x10^9$/L	0.2 (0.1)	0.18 (0.1)
IgG – g/L	9.5 (3.0)	11.4 (1.9)
IgM –g/L	1.1 (0.7)	1.1 (0.5)
ACE – U/L	31 (25)	38 (14)
Alpha -1 antitrypsin –mmol/L	**1.4 (0.11)***	**1.21 (0.15)***

Analysis of Phase 3 investigations

In Phase 3 of the Powertrain investigation, workers with suspected EAA were investigated as clinically indicated. Further tests included chest radiology, CT scans, bronchoscopy with alveolar lavage lymphocyte counts, and transbronhial or surgical lung biopsies. Table 9 shows the results of these further tests, with the prevalence of positive results for those with and without definite EAA. The figures in brackets show that not all workers had all tests.

Workers with definite EAA were more likely to have abnormal chest X-rays, CT scans, and BAL lymphocytosis, than those without definite EAA. These differences were only statistically significantly different for CT changes and positive biopsies in this small group.

Table 40: Comparison of radiological findings, bronchoalveolar lavage lymphocyte counts and lung biopsy results in workers reviewed by Expert Panel (*p<0.05)

Symptom	Definite EAA	Not definite EAA
CXR nodularity, alveolar infiltrate interstitial change	54% (7/13)	29% (4/14)
CT nodularity, ground glass, mosaic change or interstitial fibrosis	**86% (12/14)***	**32% (6/19)***
BAL lymphocytes ≥ 20%	78% (7/9)	40% (2/5)
Biopsy compatible with EAA	**62% (8/13)***	**0% (0/5)***

Development of diagnostic criteria from Powertrain data

Utilising the clinical differences between those workers with and without definite EAA as defined by the Expert Panel review and the relative positive predictive value of each of the diagnostic elements from previously published MWF diagnostic criteria, it was possible to develop diagnostic criteria from the outbreak data. This is shown in Table 41, where the highest score from each of the five sections is applied, and then added together up to a maximum of 41 points. It would have also been possible to use a combination of questions to try and predict the diagnosis of EAA, for example by using logistic regression analysis, although this was not carried out for this thesis.

Each of the sections is based on the usual groupings in other diagnostic criteria, comprising respiratory and constitutional symptoms, with abnormalities of lung function, radiology, clinical examination, biopsy and blood test results. Only those diagnostic elements that were collected in the Powertrain outbreak have been included.

The weighting of each score in each section is based on the positive predictive value of being a definite EAA case, whilst having that feature, in workers with a clinical suspicion of EAA. An example of this is that 14 out of 21 workers with unexplained weight loss went on to be diagnosed with definite EAA by the Expert Panel, i.e. a positive predictive value of 67%. This is then divided by ten, and rounded up or down to the nearest whole number, equating to a score of 7 in the diagnostic criteria. The content of each section has been selected with the intent of best separating the workers who were and were not thought to definitely have EAA by the Expert Panel.

Table 41: MWF EAA Score during MWF outbreaks based on weighting scores by positive predictive value

Respiratory symptoms	
Work-related cough/wheeze/sob/chest tightness	+4
Stopping for breath when walking at own pace on level ground	+6
Previous time off work with any chest illness	+7
Constitutional symptoms	
Recurrent flu-like symptoms worse at the end of the working week	+5
Unexplained weight loss	+7
Physiology	
FVC < 80% predicted	+3
FVC < 70% predicted or Tlco < 80% predicted	+5
Tlco < 60% predicted	+10
Radiology/clinical examination	
Abnormal CXR (diffuse ground glass or nodularity)	+6
Abnormal HRCT (ground glass, nodularity, mosaic, or UIP fibrosis)	+7
Fine end-inspiratory crepitations on auscultation	+7
Evidence of inflammation	
Neutrophilia > 7 or CRP ≥ 10	+5
BAL lymphocytosis ≥ 20%	+8
Lung biopsy typical of EAA (granulomatous or UIP)	+10
Maximal score	41

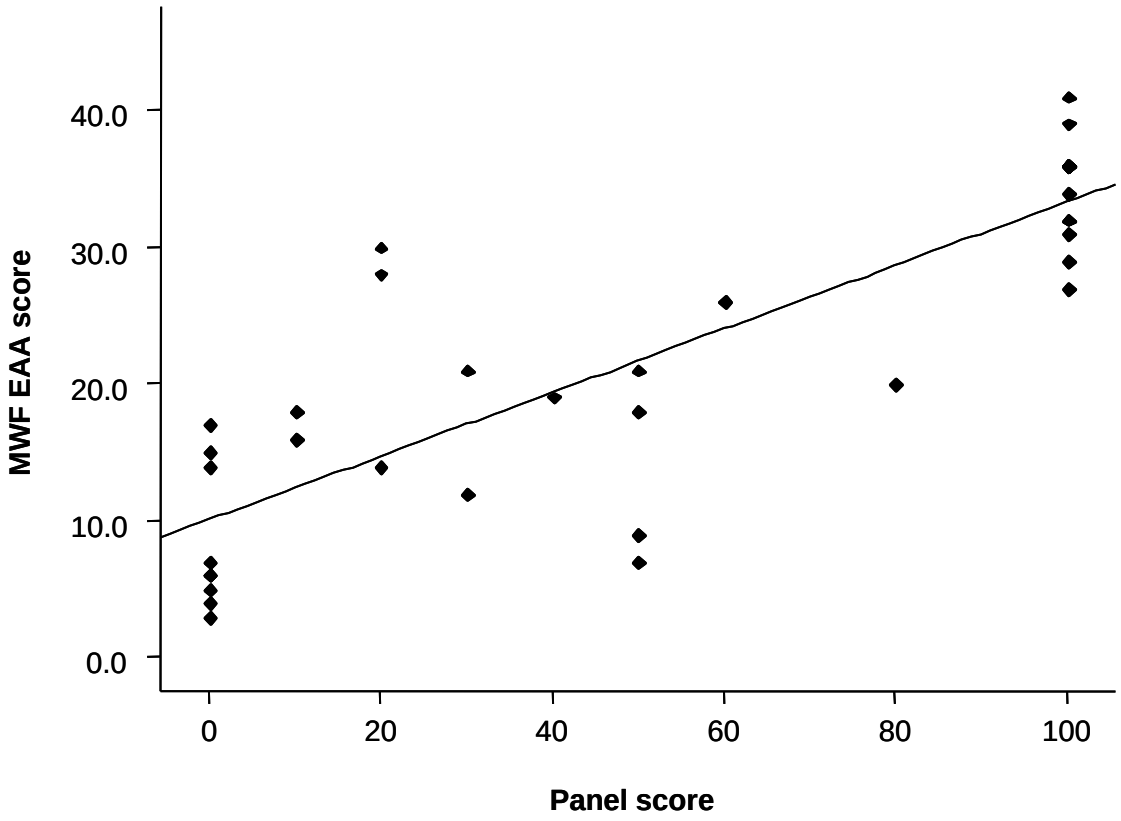
The calculated and total MWF EAA Score for each of the 37 workers is shown in Table 42. The first 14 workers were those felt to be definite EAA cases (EAA) by the Expert Panel (EP), and their MWF EAA scores ranged between 27-41. The next 12 workers were cases of possible EAA (Poss), having scores between 7-30. The final 11 workers were not thought to have EAA by the Expert Panel (Not), and had scores between 3-18.

Table 42: MWF EAA scores for the 37 workers reviewed by the Expert Panel

EP	Respiratory	Constitutional	Physiology	Radiology/ex	Inflammation	Total
EAA	7	7	10	7	5	**36**
EAA	7	0	10	7	10	**34**
EAA	7	7	3	7	8	**32**
EAA	7	7	5	7	10	**36**
EAA	7	7	5	0	8	**27**
EAA	7	7	5	7	10	**36**
EAA	7	7	10	7	8	**39**
EAA	7	5	5	7	8	**32**
EAA	7	7	5	7	10	**36**
EAA	7	7	5	7	5	**31**
EAA	7	7	5	7	10	**36**
EAA	7	7	10	7	10	**41**
EAA	7	7	0	7	8	**29**
EAA	7	7	5	7	10	**36**
Poss	7	7	5	7	0	**26**
Poss	4	3	5	7	5	**21**
Poss	4	7	3	6	8	**28**
Poss	6	7	5	0	0	**18**
Poss	4	0	5	0	0	**9**
Poss	6	7	5	7	5	**30**
Poss	7	0	0	0	0	**7**
Poss	7	5	0	0	0	**12**
Poss	7	3	0	7	0	**14**
Poss	7	7	5	0	0	**19**
Poss	0	0	5	7	8	**20**
Poss	4	7	5	0	5	**21**
Not	0	0	3	0	0	**3**
Not	4	0	5	7	0	**16**
Not	6	0	5	7	0	**18**
Not	4	5	5	0	0	**14**
Not	4	0	0	0	0	**4**
Not	7	0	0	0	0	**7**
Not	6	0	0	0	0	**6**
Not	0	0	5	0	0	**5**
Not	6	0	0	0	0	**6**
Not	4	0	5	6	0	**15**
Not	7	5	0	0	5	**17**

There was a good level of correlation between the derived MWF EAA score, and the Expert Panel score, with a Pearson correlation coefficient of 0.85 ($p<0.01$).

Figure 15: Graph comparing Expert Panel score and MWF EAA score for 37 patients considered by Expert Panel



Comparison of Expert Panel Opinion and MWF EAA Score

By using suitable cut offs of MWF EAA Scores, that were defined manually, (definite case > 26, possible case 19-26, and definitely not a case < 19), it is possible to show agreement (shown in bold) with the Expert Panel opinion in 30/37 (81%) of cases (Table 43). The performance of the MWF EAA diagnostic criteria against the Expert Panel opinion, can then be compared to the performance of other published diagnostic criteria, which have categorized workers in to similar groups (shown in Tables 44 - 47.)

Table 43: Comparison between MWF EAA case definitions, versus Expert Panel opinion (81% agreement)

		Expert panel opinion		
MWF EAA Score		Definite	Possible	Not a case
	Definite	**14**	2	0
	Possible	0	**5**	0
	Not a case	0	5	**11**

It can be seen from Tables 44 - 47, that the proportion of correctly classified workers was 65%, 59%, and 43% for the three other published case definitions utilized [1 260 293].

Table 44: Comparison between modified Fox case definitions (as used in Powertrain Outbreak) [260], versus Expert Panel opinion (65% agreement)

		Expert panel opinion		
Modified Fox score		Definite	Possible	Not a case
	Definite/probable	**12**	2	1
	Possible	2	**3**	1
	Not a case	0	7	**9**

Table 45: Comparison between original Fox criteria (as used in Kenosha outbreak) [1], versus Expert Panel opinion (59% agreement)

		Expert panel opinion		
Original Fox score		Definite	Possible	Not a case
	Definite/probable	**10**	2	0
	Possible	3	**2**	1
	Not a case	1	8	**10**

Table 46: Comparison between Hypersensitivity Pneumonitis Diagnostic Index case definitions [293], versus Expert Panel opinion (43% agreement)

	Expert panel opinion			
HPDI score		Definite	Possible	Not a case
	Definite/probable	**6**	1	0
	Possible	5	**1**	2
	Not a case	3	10	**9**

In addition, it is possible to compare the Cohen kappa levels of agreement between the Expert Panel definite cases, and the definite cases as rated by other case definitions (Table 47).

Table 47: Levels of agreement between outbreak case definitions of definite EAA cases versus Expert Panel opinion

Outbreak (year published)	**Cohen kappa agreement with Expert Panel definite cases**
Zacharisen 1998 (Wisconsin) [288]	0.44 (moderate)
Fox 1999(Kenosha) [1]	0.68 (substantial)
Hodgson 2001 (Connecticut) [294]	0.34 (fair)
Dangman 2002 (HPDI) [293]	0.55 (moderate)
Weiss 2002 (Ohio) [300]	0.49 (moderate)
Gupta 2006 (Michigan) [303]	0.68 (strong)
Modified Fox 2007 (Powertrain) [260]	0.71 (strong)
MWF EAA Score 2010	0.94 (very strong)

Validation of MWF EAA Score from Published Case Reports of EAA Due to MWF exposure

In addition to comparing the MWF EAA score with the opinion of the Expert Panel's review of UK Powertrain cases, it is also possible to apply the criteria to fifty other previously published American cases of EAA due to MWF exposure (Table 48- 56).

Table 48: MWF EAA Scores for Bernstein cases 1995 [279]

Case	Respiratory	Constitutional	Physiology	Radiology/ex	Inflammation	Total
1	4-7	7	5-10	7	0-10	**23-41**
2	4-7	5	10	6-7	0-10	**25-39**
3	4-7	0	5-10	6-7	0-10	**15-34**
4	4-7	0-5	10	0-7	0-10	**14-39**
5	4-7	0	0-10	0-7	0-10	**4-34**
6	4-7	7	10	6-7	0-10	**27-41**

Table 49: MWF EAA Scores for Trout cases 1996 [289]

Case	Respiratory	Constitutional	Physiology	Radiology/ex	Inflammation	Total
1	4-7	5	3	7	10	**29-32**
2	4-7	0	5	7	0-10	**16-29**
3	4-7	0	10	7	0-10	**21-34**
4	4-7	0	0-10	7	10	**21-34**
5	4-7	7	5	7	0-10	**23-36**
6	4-7	0	5	7	10	**26-29**
7	4-7	0	3	7	0-10	**14-27**
8	4-7	5	5	7	0-10	**21-34**
9	4-7	0	5-10	7	10	**26-34**
10	4-7	5	5	7	10	**31-34**
11	4-7	0	5-10	7	0-10	**16-34**
12	4-7	0	3	7	10	**24-27**
13	4-7	5	5	6-7	10	**30-34**
14	4-7	0	5	7	10	**26-29**

Table 50: MWF EAA Scores for Rose cases 1996 [287]

Case	Respiratory	Constitutional	Physiology	Radiology/ex	Inflammation	Total
1	7	7	5	7	10	**36**
2	4-7	7	5	6-7	10	**32-36**
3	4-7	5	10	7	10	**36-39**
4	4-7	5	5	7	10	**31-34**
5	4-7	5	0-10	7	10	**26-39**
6	4-7	0	10	6-7	10	**30-34**
7	4-7	7	5	7	10	**33-36**

Table 51: MWF EAA Scores for Zacharisen case 1998 [288]

Case	Respiratory	Constitutional	Physiology	Radiology/ex	Inflammation	Total
1	7	5	5	6-7	10	**33-34**

Table 52: MWF EAA Scores for Fox cases 1999 [1]

Case	Respiratory	Constitutional	Physiology	Radiology/ex	Inflammation	Total
1	4-7	5-7	5	7	0-10	**21-31**
2	4-7	5-7	10	7	10	**36-41**
3	4-7	5-7	5	6-7	0-10	**20-36**
4	4-7	5-7	10	6-7	10	**35-41**
5	4-7	5-7	5	6-7	0-10	**20-36**
6	4-7	5-7	10	6-7	0-10	**25-41**
7	4-7	5-7	10	6-7	10	**35-41**
8	4-7	5-7	5	7	10	**31-36**
9	4-7	5-7	5	7	0-10	**21-36**
10	4-7	5-7	5	6-7	0-10	**20-36**

Table 53: MWF EAA Scores for Hodgson cases 2001 [294]

Case	Respiratory	Constitutional	Physiology	Radiology/ex	Inflammation	Total
1	7	5	5	0-7	10	**27-34**
2	0-7	0-7	10	0-7	10	**20-41**
3	7	0-7	0	0-7	10	**17-31**

Table 54: MWF EAA Scores for Weiss case 2002 [300]

Case	Respiratory	Constitutional	Physiology	Radiology/ex	Inflammation	Total
1	7	0-7	5-10	7	0-10	**19-41**

Table 55: MWF EAA Scores for Trout case 2003 [301]

Case	Respiratory	Constitutional	Physiology	Radiology/ex	Inflammation	Total
1	7	5	3	7	7	**29**

Table 56: MWF EAA Scores for Gupta case 2006 [303]

Case	Respiratory	Constitutional	Physiology	Radiology/ex	Inflammation	Total
1	7	5	10	7	0-10	**29-39**
2	4-7	0	10	7	0-10	**21-34**
3	4-7	0	10	7	10	**31-34**
4	4-7	5	5-10	7	10	**31-39**
5	7	5	10	7	10	**39**
6	4-7	5	5-10	7	0-10	**21-39**
7	7	7	5	7	10	**36**

Where a range of score is shown for a criterion, this reflects data not provided in the case report or case series. The total MWF EAA Score provided in the final column, ranges from the lowest possible value (presuming that the missing data elements would all have been negative), to the highest possible value (presuming the missing data would all have been positive). For the fifty cases, there were only three cases where a definite MWF EAA Score could be calculated from the data provided and all of these would have been rated as definite cases (MWF EAA Score > 26.) A further eighteen cases would also have been rated as definite EAA cases using the MWF EAA Score, as the minimum of the range of possible scores were all greater than 26. In all of the remaining twenty-nine cases, the range of possible MWF EAA scores includes a score of 27, i.e. they may have been definite cases if more data were available. If the mid-range of these scores is taken as an approximate value, twenty of the twenty-nine would also have had MWF EAA Scores of at least 27.

Discussion

Study Findings

By calculating the relative positive predictive value of the diagnostic elements for a diagnosis of EAA, combined with knowledge of previous EAA diagnostic criteria [1], it was possible to develop a new evidence-based EAA diagnostic score (the MWF EAA Score). This scoring system was designed to be a simple and reproducible tool, which would show high levels of agreement with the Expert Panel opinion and provide an evidence-based case definition suitable for use in future UK outbreaks.

By applying the MWF EAA Score to the Powertrain data it was possible to demonstrate agreement with the Expert Panel Opinion in over 80% of the cases, with a greater number of workers correctly classified than with other published diagnostic criteria [1 260 293]. In order to attempt to externally validate the new EAA rating system, the score was also applied to fifty previously published case series of workers diagnosed with MWF EAA from a number of different US outbreaks. The MWF EAA Score appeared to perform well, and there was sufficient data provided in twenty-one of these published cases, to establish that the MWF EAA Score would have shown agreement (i.e. MWF score greater than 26 equating to a definite case). In the remaining cases, there was not sufficient data provided in the publications to ascertain this for certain, although all cases had a range of MWF EAA Scores that included the score needed to be a definite case.

Study limitations

As the study was developed based on the Expert Panel review of Powertrain cases, the MWF EAA Score fits the Powertrain data very well, agreeing with expert clinical opinion in over 80% of cases. The MWF EAA Score did however identify two workers as having definite EAA (scores of 30/41 and 28/41) who were not identified by the Expert Panel as definite clinical EAA cases (both with Expert Panel Scores of 20%). Both of these workers had been identified as cases of EAA by the modified Fox case definitions used in the Powertrain investigation (one possible and one probable).

Although it is not possible to ascertain why the Expert Panel did not rate these as definite EAA cases, it is possible that these were false negatives i.e. cases missed by Expert Panel, reflecting the difficulty of diagnosis from a retrospective notes review. Alternatively they may have been truly negative cases i.e. other similar lung diseases that could only be separated from EAA with more detailed clinical input and follow-up.

In order to attempt to externally validate the MWF EAA Score case definition it was applied to all previously published case series and case reports of definite EAA from other MWF outbreaks. Although this process was limited by the lack of detail provided in some of the case reports (particularly exact symptoms, examination findings, and results of blood tests), the scoring system seemed to perform well. In 42% of these definite clinical cases, the MWF EAA Score would also have rated them as definite EAA. In the remaining cases it is not possible to tell this, although the mid-point of the range of possible MWF EAA Scores was at least 27 in a further 40% of cases.

Comparison to other studies

Dangman et al. used the differences they had found between cases of EAA and controls to derive a hypersensitivity pneumonitis diagnostic index (HPDI) based on scoring points for, symptoms (one work-related systemic and two work-related respiratory), crackles on auscultation, abnormal pulmonary physiology (restrictive spirometry, reduced gas transfer, or increased A-a gradient), raised inflammatory markers (ESR), and abnormal radiology (on CXR, CT and gallium scan) [293]. This formed the basis of an HPDI score out of 9, with 6 being a definite case, probable 4-5, and possible 3. Unlike the Fox criteria, Dangman et al. applied some weighting to gas transfer and ESR, so that more abnormal results scored double points. For example, an ESR greater than 60 mm/hour scored double the points (2 points) of a CT consistent with EAA (1 point). The HPDI was then validated in a separate subgroup from the same outbreak, comparing the findings from 20 patients who were EAA cases on HPDI (at least possible cases) with 11 who were not.

Dangman et al. went on to compare the HPDI case identification with the original Fox criteria [1 260] which agreed in 55 of 61 cases [293]. Our study was broadly similar, but

each diagnostic criterion was weighted based on its positive predictive value giving each a possible score of 3-10. The diagnostic elements selected were chosen to be as inclusive of cases as possible, and to allow for the variability of EAA presentation and diagnosis. An example of this is that the respiratory symptoms included workers with progressive shortness of breath on exertion, in the absence of work-related symptoms, in an attempt to include chronic progressive EAA. Workers requiring time off work with recurrent acute EAA episodes, even if unrecognized as such, would also be included in the criteria. In addition, our criteria were developed from the Expert Panel review of suspected EAA and humidifier fever cases, an inclusion based on the similar constitutional symptoms that occur in these conditions. We therefore modified the recurrent flu-like symptom category to be more specific for EAA, being worse at the end of the working week (typical of EAA), rather than better (typical of humidifier fever). The remainder of the diagnostic elements in the MWF EAA Score are common to EAA investigation in general and other previously published case definitions [1 215 260 293 366].

The main difference between our criteria and those previously published was that our criteria were relatively weighted in importance based on how predictive the positive symptom or test was in a real UK outbreak. An example is that in the MWF EAA Score, a positive lung biopsy consistent with EAA (score=10) has twice the diagnostic value of a raised blood inflammatory marker (score=5). By including a range of possible scoring elements in each category, the scoring system should allow a wider range of workers, investigated in different ways, to still meet the EAA case definition. By setting the diagnostic score around that best fitted the Expert Panel opinion it was possible to correctly classify 80% of definite, possible and definitely not EAA cases. As the criteria were generated by the data, as expected, this result was better than when any other published criteria were applied to the data outbreaks [1]. Our study is the first to our knowledge to have developed evidence-based diagnostic criteria from one outbreak and apply it to cases from other outbreaks. Although limited by the detail provided in published case series the MWF EAA Score performed well during this external validation process, as applied to 50 cases of MWF EAA from nine US outbreaks published between 1996-2006 outbreaks [1].

Study Implications

Investigating any ill health outbreak in large workplaces is logistically challenging due to the unexpected nature of the outbreak and the need to screen and diagnose large number of workers in a short period. Accurate and early diagnosis of allergic occupational lung diseases is key to improve prognosis in affected workers and prevent inappropriately disadvantaging symptomatic workers without disease. No single diagnostic test exists for EAA, and the diagnosis may be complex due to this and a number of other associated factors. Firstly, EAA may present as three different forms, acute, sub-acute or chronic disease, and symptom complexes and diagnostic test findings may differ markedly [246]. Secondly, the respiratory and constitutional symptoms of EAA are non-specific and may be ignored or misdiagnosed as recurrent chest infections [293]. Thirdly, due to the variable nature of acute and sub-acute EAA, the diagnostic value of certain tests varies based on the timing of that test. Lastly, particular difficulties exist in diagnosing EAA in MWF exposed populations where workers may also develop other forms of occupational lung disease with similar symptoms, OA, and humidifier fever [260]. It is this variability in EAA, linked with unpredictable nature of MWF occupational lung disease outbreaks in large workforces, which has made case recognition so difficult and led to a variety of American MWF EAA case definitions being developed, often with little or no validation outbreaks [1].

The MWF EAA Score provides a tool that can be used in future outbreaks of MWF EAA. By using a cut off of 19, all possible cases of EAA should be identified and these workers could then be clinically assessed as to their need for further investigations. The MWF EAA Score was developed using a cohort of MWF exposed workers, however future development of the scoring system to demonstrate its use in other groups of patients with EAA, particularly those without a measurable precipitin, could potentially expand the benefit of this research.

Conclusion

This work has developed and validated an evidence based diagnostic scoring system in order to investigate future outbreaks of MWF-EAA in a consistent and evidence based manner.

Conclusions

Impact of occupational lung disease

Occupation related illness was first documented in the 4th century BC. Despite a change in industries, scientific understanding and legislation, it remains an important and preventable cause of disease. In 2012 there were 1770 new cases of occupational respiratory disease recorded by consultant chest physicians within the SWORD reporting scheme (Surveillance of work-related and occupational respiratory disease) [367]. The incidence of occupational disease identified by reporting schemes such as SWORD is thought to be significantly under estimated [35 39]. This burden of ill health comes at a personal and socioeconomic price. In 2011/12, Work related respiratory disease was responsible for the loss of 667 000 working days and accounted for around 2% of the total number of days of sickness absence certified due to all occupational illnesses [367 368]. It is estimated that the annual cost to the UK, of OA alone, maybe be as large as £95-135 million [369].

MWF continues to be an important cause of occupational lung disease. In 2012, there were 56 reported cases of occupational EAA compared to an annual average over the past 10 years of 41. Of the total occupational EAA burden, 39% is associated with MWF exposure. Between 2010 and 2012, MWF were the 4th most common cause of OA [4].

Causative agent

Despite reviewing outbreaks and collecting international data this research found no clear causative agent for MWF-EAA. Cases of MWF-EAA were found in factories using all different categories of soluble MWFs and many different contaminants were detected. Mycobacteria have been highlighted by some research groups as a likely inciting agent, however despite *Mycobacterium sp.* being a known cause of EAA, for example in hot tub lung [344], we did not find enough evidence to establish this.

Muilenberg et al. were the first researchers to identify mycobacteria in MWF, *M.chelonae*, during an investigation involving 10 machinists in 1993 [370]. Bacterial

analysis of MWF led to the identification of a new species, *M. Immunogenum* [371]. Wallace et al. found that the majority of mycobacteria isolates from MWF grew *M. Immunogenum* [372]. Other studies have found a more equal split between *M. chelonae* and *M. immunogenum*, suggesting that both species are similarly prevalent [373].

Tille LeBlond et al. conducted a study at a car engine manufacturing plant implicated in MWF-EAA, in order to identify the responsible antigen (Ag). Almost half of used fluids were confirmed to be contaminated with *M. immunogeum*, and a similar percentage grew *Bacillus* spp., with an additional smaller percentage isolating Gram-negative bacteria, fungi and *Aspergillus* spp. Measurements made using electrosyneresis were interpreted by Tille LeBlond et al. as being indicative that *M. immunogenum* is the inciting agent in MWF-EAA. They went further, to calculate a threshold for differentiating MWF-associated HP patients from asymptomatic exposed workers [345].

The difficulties of interpreting immunological findings in EAA were demonstrated in a detailed immunological investigation performed on workers in a MWF-EAA outbreak in the USA, where *Mycobacterial* contamination was identified. Measurements of immunity to *M. immunogenum*, such as interleukin 8 and tumour necrosis factor, were able to distinguish between MWF exposed and unexposed workers, but not between workers with and without MWF-EAA [301].

Our study found, despite a thorough review of outbreaks of ill health associated with MWFs, although mycobacteria were identified in over half of outbreaks, it only comprised a small percentage of identified microbiological isolates. In outbreaks prior to the initial identification of mycobacteria as a potential contaminant of MWF, it is possible that it went undetected due to the necessary prolonged incubation time compared to that of a routine bacterial culture. However, for example, in Powertrain, the largest UK outbreak of respiratory disease associated with MWF, *Mycobacterium* sp were not identified either from culture or DNA extraction, despite specific investigation. Analysis of MWF samples from two other workplaces associated with UK MWF-HP outbreaks also found no detectable mycobacterial DNA. In addition, extracts from cultures including *M. immunogenum, M. chelonae* and *M. fortuitum* were used to look for the presence of precipitating antibodies in Powertrain UK workers, including cases of MWF-HP, OA and asymptomatic exposed controls. Over

half of the EAA patients had positive results for at least one microbial species, compared to only 5 % of asymptomatic controls. Precipitating antibodies to *Mycobacterium* spp, however were not detected in any workers. Further evidence against a mycobacterial cause came from specific challenges performed in two workers, where positive responses were seen after controlled exposure to used MWFs that did not contain mycobacteria [260 281].

It is undeniable that mycobacteria are prevalent in some MWF systems, however this research study suggests that its presence is not ubiquitous and that it has been absent at sites where there have been large outbreak of EAA. Therefore, naming mycobacteria as the causative agent in MWF-EAA is unfounded at present. Thorough investigation of any plant using MWF where workers are diagnosed with EAA is essential, in the continuing research necessary to validate any hypothesis on the potential inciting agent in this form of EAA.

Increasing incidence of idiopathic fibrosis

Based on data from the Office of National Statistics, mortality rates from EAA show little variation, from 0.04 per 100 000 person years in the 1968-1972 calendar period to 0.08 per 100 000 person years in the 2005-2008 period. Between the same dates, the mortality of EAA rose slightly from 0.12 per 100 000 person years to 0.22 per 100 000 person years, an increase of approximately 9% a year [374]. This contrasts with the rising mortality of IPF, with death certification suggesting a six fold increase in the past two decades. Current findings suggest that the number of new diagnoses of idiopathic pulmonary fibrosis clinical syndrome (IPF-CS) increased by over a third between 2000 to 2008, with more than 5000 new cases being diagnosed each year [375]. Hubbard et al. studied national secondary care data to determine trends in hospital admissions in England and found that the number of hospital admissions from IPF-CS increased at an annual rate of approximately 5% [376]. The highest incidence was found to be in older men, with a mean age of 71 yrs, particularly in the northwest of England [375 376]. IPF is therefore an important health problem in the UK in terms of morbidity and mortality.

The diagnosis of IPF depends on the exclusion of other known causes of interstitial lung disease including occupational and environmental exposures, causing diseases such as EAA. The radiological and histopathological findings of EAA frequently overlap those of usual interstitial pneumonitis, which in the absence of an identifiable cause would be diagnosed as IPF [221]. Previous work by Hubbard et al. looked specifically at the occupational risk of IPF (then referred to as cyptogenic fibrosing alveolitis CFA), collecting occupational histories from hundreds of patients and matched controls. It was concluded that occupational exposures to metal or wood dust are independent risk factors for CFA and could account for 20% of cases. The American Thoracic Society note, in their guidelines on IPF diagnosis and management, that an increased risk for IPF has been found to be associated with a variety of environmental exposures (ATS) [377] [378]. A significantly increased risk has been observed after exposure to metal dusts and wood dusts [379-381].

IPF has also been significantly associated with farming, raising birds, hair dressing, stone cutting/polishing, exposure to livestock and vegetable dust/animal dust [382] [383]. With many of these agents being known to cause EAA [203], it is possible that a significant number of patients diagnosed with IPF actually have chronic EAA. Increased numbers of inorganic particles have been detected at autopsy, in lymph nodes of patients with pulmonary fibrosis, further supporting an environmental aetiology [384]. If this is the case, the improved detection of EAA is of paramount importance to enable the correct identification of these workers and where possible, the cessation of exposure to the causative agent. It is well established that the prognosis in EAA can be improved where this can be achieved [198] [207].

Morell et al. studied a group of patients previously diagnoses with IPF and by using a questionnaire and then further immunological testing as appropriate, found that 43% of the patients actually had chronic EAA [385]. It is clear that more research is needed in this area to verify the hypothesis that EAA could be accountable for at least some of the increasing incidence of IPF. The potential misdiagnosis of these conditions, although understandable due to the clinical, radiological and pathological similarities, would have potentially significant repercussions on not only the individual patients, in terms of treatment options and antigen avoidance, but also on presently undiagnosed exposed workers. Increased awareness of an enlarging health risk would hopefully

lead to an increase in health surveillance and subsequent faster disease identification. As an emerging cause of EAA, the early detection of respiratory symptoms in the MWF exposed population is an area which needs highlighting.

Health Surveillance

Secondary health prevention includes health surveillance which aims to identify disease at a pre-symptomatic stage or early stage. In a multi-centre hospital study, Fishwick et al. found that in a group of patients with inadequate or no annual health surveillance there was a mean delay of 4 years between the onset of symptoms and a confirmed diagnosis [148]. Mackie et al. found a mean delay of nine months in those whose symptoms were detected at health surveillance and who attended for subsequent investigations [149]. Although it is difficult to dissociate the effects of health surveillance from the effects of other risk management procedures it is felt that outcome is improved in workers who are included in a health surveillance programme [150].

This research has focused on the investigation of an outbreak of MWF associated respiratory disease, specifically EAA, by identifying the symptoms with a high sensitivity and positive predictive value and thus formulating a new case definition. In doing so we have highlighted several key areas that are likely to be useful for developing health surveillance for workers exposed to MWFs. In addition to the existing HSE guidance requiring questions relating to work-related respiratory symptoms such as cough, wheeze and chest tightness, our research has identified other more specific questions that might improve the value of secondary prevention screening in this group of workers. Presently, any employer browsing the HSE website for guidance on health surveillance for workers using MWFs, is directed to Control of Substances Hazardous to Health (COSHH) information for prevention of OA but not other lung conditions [386].

When analysing questionnaire data from an outbreak of MWF-EAA, certain questions were found to have a relatively high PPV for EAA. One in four workers at Powertrain who complained of unexplained weight loss were found to have definite EAA, suggesting that a simple question referring to weight loss might be a useful addition

to the standard respiratory questionnaire. As well as weight loss, extreme shortness of breath including nocturnal symptoms, breathlessness worse at the end of the working week and flu like symptoms associated with particular work tasks are all complaints that should be noted with a high level of suspicion. It would seem sensible that questions referring to these symptoms should be included in any health screening questionnaire designed to detect MWF-EAA in exposed workers. The importance of identifying workers having time off with chest problems, or treatment for chest conditions (often thought to be recurrent chest infections) was also noted, as this may actually represent recurrent bouts of undiagnsosed EAA. Recognising that chronic EAA may present with slowly progressive ILD, it is also important to identify patients with gradual onset exertional breathlessness, to ensure they are picked up even in the absence of work-related respiratory symptoms.

The development of a bespoke screening questionnaire for use in MWF exposed workers would require further research. If the screening was to include questions aimed at identifying MWF-OA and other respiratory disease associated with MWF exposure, this research could include extended analysis of the database to identify those questions with a high sensitivity and perhaps PPV for these conditions. This of course would limit the screening questions to those initially asked by the Birmingham group at the time of the outbreak, as retrospective addition of questions is not possible.

Although HSE guidelines [387] would advocate spirometry as part of health surveillance for a MWF exposed population due to the risk of OA, it is difficult to advocate regular spirometry simply for EAA surveillance, as the FVC measurements in those Powertrain workers with definite EAA were often within the normal range. Although measuring gas transfer appeared more useful, it is unlikely that this more costly hospital-based test would provide a suitable alternative form of objective health surveillance. Whether serial estimates of spirometry looking for excessive annual declines are more predictive of early disease requires further study. Again, if the surveillance was designed to incorporated early detection of other respiratory conditions associated with MWF exposure, regular spirometry maybe validated.

Additional to health surveillance measures, a high index of suspicion among exposed workers and medical staff is required, with clear referral pathways for workers

developing respiratory or constitutional symptoms at work. If future outbreaks are to be avoided, new cases must be detected early, allowing improved control measures to be put in place to protect the remaining workforce.

Future Outbreak Planning

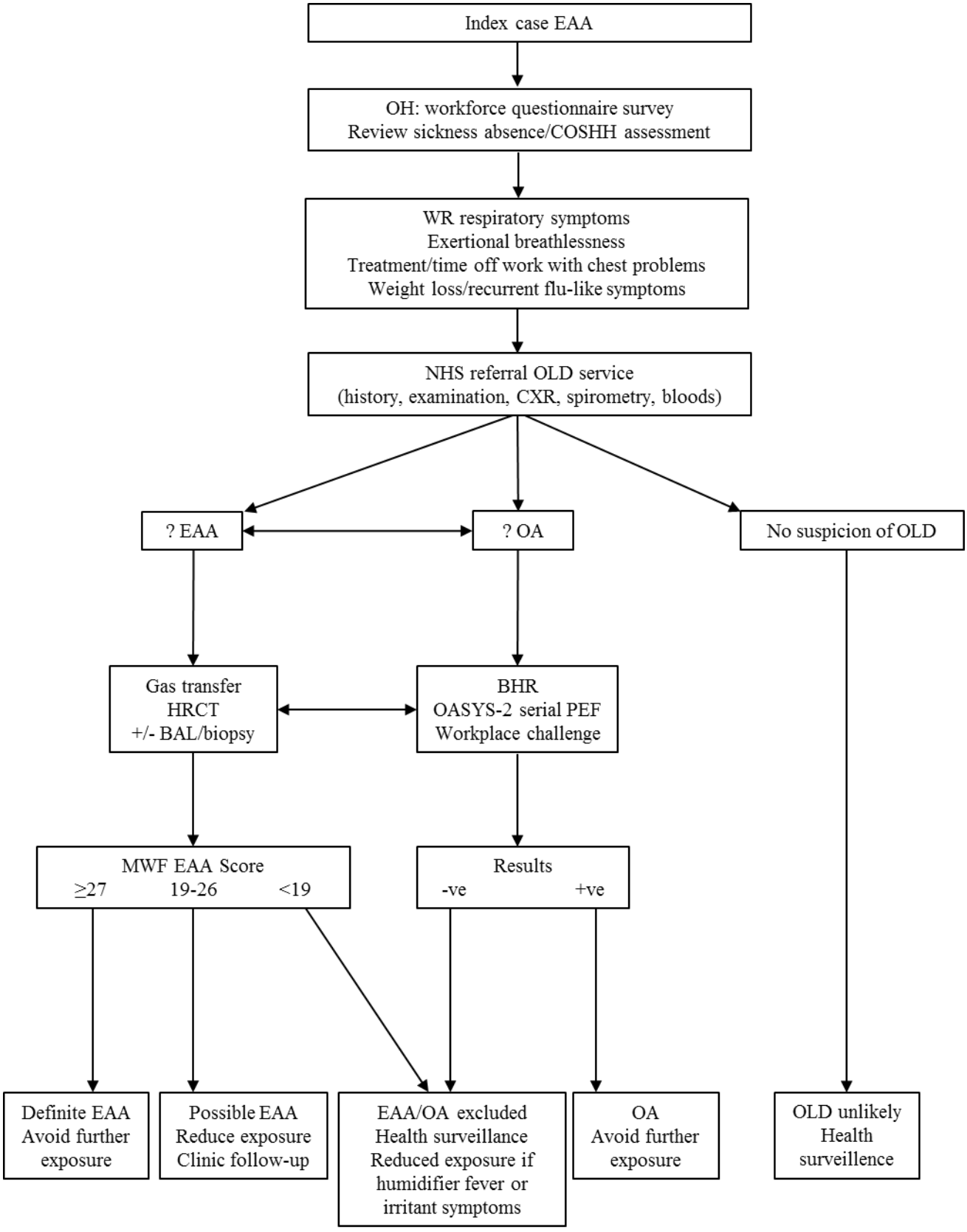
One possible approach to MWF outbreak investigation is shown in Figure 16. A single sentinel case of EAA in a workforce would prompt the occupational health provider to screen the other MWF exposed workers. In addition to questionnaire screening of the entire at risk workforce, there would be a review of sickness absence records, and the existing exposure control measures for MWF mist. All symptomatic workers would then be referred to an NHS occupational lung disease centre for an initial simple assessment, followed by further more detailed diagnostic tests where indicated. All workers with a definite diagnosis of OA or EAA (after applying the MWF EAA Score) would ideally avoid further exposures by relocation wherever possible. Workers with possible occupational asthma or EAA would have a reduction in exposure and regular clinical follow-up. Workers without EAA or occupational asthma would be reassured, and return to work with reduced exposures where possible, and continued occupational health surveillance. Ideally, this suggested approach and the EAA MWF case definitions need testing prospectively in future outbreaks.

We have produced evidence-based diagnostic criteria specifically for EAA in workers exposed to MWFs, suitable for assessing the respiratory ill health of symptomatic workers in future UK outbreaks. Unlike certain other criteria [288 303], this does not rely on obtaining invasive lung biopsies in all workers, or complex radiological tests which are not routinely available in the UK [293]. With knowledge of the predictive value of different diagnostic tests, it should be possible to streamline future investigations, minimizing the impact of the outbreak in terms of health and therefore also socioeconomic disadvantage to the patient. In addition to being applicable to future EAA outbreaks due to MWF, it may be possible to utilise the MWF EAA Score when investigating similar outbreaks due to other organic agents such as in lifeguard lung [354] and EAA due to water-damaged buildings [388] or contaminated humidifiers [389]. In

such circumstance, when EAA is secondary to a known antigen, serum immunological testing has traditionally played a key role, therefore the MWF EAA Score although useful, may need adaptation in other settings. Equally, if further research identifies the causative agent or agents in MWF-EAA, additional criterion may need to be added to the diagnostic tool.

MWF related ill health is still a relatively new and emerging problem. As industry continues to strive to improve the function of MWFs and consequently the formulations evolve to containing different chemical compounds, new potential health risks are a constant threat. Continuing research in to the cause of MWF-EAA, early identification and the measures that can be taken to reduce its incidence are clearly essential to reduce the incidence of this potentially preventable yet life threatening condition.

Figure 16: Health investigations precipitated by a sentinel case of EAA in a MWF exposed worker



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Appendices

Appendix 1

Outbreaks of respiratory ill health associated with MWF reported in USA

The literature review identified twenty separate NIOSH studies that met the selection criteria for an outbreak making up 20 of the 25 reports of outbreaks of respiratory ill heath attributed to MWF in the USA. These reports are briefly summarised in date order

Studies of respiratory disease:
Fourteen of seventeen outbreaks that investigated respiratory disease alone were from the USA and nine of these were NIOSH investigations. The investigations of respiratory disease were typically large and involved the collection of clinical, environmental, and exposure data.

Bernstein, D. I. et al. 1995 [279]

Background

Bernstein et al. were amongst the first investigators to identify MWF as a potential cause of EAA amongst machinists.

Methods and results

They reported a case series of six workers from an automobile-manufacturing site, exposed to a synthetic MWF (introduced in October of 1991) from machines with an open and shared sump. The six workers were evaluated and treated for respiratory disease between April and September of 1992, and all had symptoms that improved on removal from the workplace. Five of the six workers had pulmonary restriction (as measured by simple spirometry), and four of the six had interstitial shadowing on chest X-ray. One worker had a bronchoscopy to rule out infection. *Mycobacterium chelonae* was identified in a sputum culture from one of the group but all others showed normal bacterial flora. For the four workers with abnormal chest X-rays, removal from exposure was associated with marked improvement in lung function, with an average 55% increase in forced vital capacity from baseline.

Two samples of used MWF were analysed and these contained less than 10 colony forming units (CFU) of fungi and approximately 1.3 $x10^6$/mL of bacteria. When cultured these samples grew eight microbial isolates, including *Pseudomonas* spp*, Aspergillus* spp*, Staphylococcus* spp and *Bacillus* spp. No air monitoring was performed in this investigation. Serum precipitins to one or more of the microbial isolates were found in all six workers, most commonly to *Pseudomonas fluorescens.* Positive precipitins were only present in blood samples taken from one out of nine non-exposed control subjects

Conclusions

The authors concluded that in their opinion the presence of positive precipitin reactions in all the EAA cases indicated an immunologically mediated response to aerosolized microbial antigen. They recommended environmental monitoring and medical surveillance for MWF exposed workers, as well as advocating further research in this area.

Rose, C. et al. 1996 [287]

Background

The occurrence of cases of EAA prompted physicians to request NIOSH investigate occupational exposures at three different automobile manufacturing plants.

Methods and results

During 1994 – 1995, six cases of EAA were confirmed on biopsy and after a review of medical records of plant employee's fourteen additional 'probable' cases (not biopsy proven) were also discovered. Of the six biopsy proven cases, all but one reported recurrent respiratory and systemic symptoms that they attributed to working with MWF. The symptoms of one worker permanently resolved after his exposure to MWF ceased. One worker died after a myocardial infarction, but had a background of eighteen months of interstitial lung disease with work-related cough and shortness of breath. Autopsy showed chronic granulomatous lung disease suggestive of a diagnosis of chronic EAA. For two workers, serum precipitin tests to a standard antigen panel (including bacteria, fungi and avian proteins that had been associated with EAA in other settings) were all negative. Four workers had abnormal spirometry, two showing a restrictive pattern, and two a mixed pattern of restriction with

obstruction, all of which improved with removal from exposure. Three workers had a measurable reduction in the gas transfer capacity of their lungs.

Conclusions

This report summarised the six biopsy proven cases of EAA, but did not document any investigation of the workplaces (i.e., hygiene assessment, or diagnostic evaluation of other illness). The report concluded that ongoing medical surveillance and exposure assessment is required for workers potentially exposed to MWFs.

Fox, J. et al. 1999 [1]

Background

The 'Kenosha' outbreak occurred in an engine manufacturing plant, which employed 1592 workers. Between July 1995 and April 1997, eighty-one of these staffs complained of respiratory symptoms to the company medical staff. A synthetic MWF had been in use since 1989, but this was changed to a soluble MWF between May and August of 1996 in response to an earlier outbreak of respiratory ill health. In August 1996, the company had also installed new ventilation, steam cleaned sumps, and improved local exhaust ventilation.

Methods and results

All workers who had complained of respiratory symptoms, and a group of case controls who were asymptomatic were offered medical review. Seventy-one of eighty-one staff with symptoms agreed to this review. The medical officer then assessed these workers carrying out tests for serology, spirometry, radiological and in some cases biopsy of the airways. Case definitions for EAA were developed as either 'definite', 'probable' and 'possible' based on seven diagnostic criteria. These criteria have subsequently been used for other investigations.

Thirty one percent (twenty two cases) of the seventy-one symptomatic staff investigated were diagnosed by a physician as meeting their criteria for EAA (with symptoms starting after July 1995). Only twenty of the twenty-two cases met the criteria for EAA set by the investigators (ten definite cases, five probable cases and four possible cases). Of these twenty, sixteen had interstitial infiltrates on radiological imaging. All definite cases of EAA had a reduced diffusion capacity (TLCO) and

restrictive spirometry. Four workers underwent biopsy, all showing non-causeating granuloma and lymphocytic infiltrates. Interestingly, two of the four workers biopsied were initially diagnosed with sarcoidosis (an idiopathic granulomatous lung disease), and only after long-term follow up was their diagnosis changed to EAA. This illustrates the difficulty with EAA, where there is no single gold standard diagnostic test. Even when lung tissue was biopsied and examined histologically, the findings were interpreted in conjunction with symptoms, exposure history, and the results from other diagnostic tests.

Eighteen of the twenty cases of EAA, and fifty-one controls subjects also provided blood samples to analyse precipitating IgG antibodies. With the exception of two weak reactions, no positive precipitin results were found to any of seven unused MWFs, seven detergents, three hydraulic oils, or two biocides in use in the factory. When serum precipitin reactions to used MWFs were compared however, EAA cases had elevated odds ratios for 3 of the fluids; two synthetic, and one oil-soluble. Thirty-four demographic factors were also compared between cases and controls, but no statistically significant differences were found.

In addition to the EAA cases, OA was diagnosed in three employees, and a further twelve were diagnosed with occupational bronchitis (or potentially EAA despite not meeting the minimum diagnostic criteria). Six workers were diagnosed with non-occupational bronchitis, three with chronic obstructive pulmonary disease (COPD) and ten with other diagnoses.

The company records were examined to assess previous environmental monitoring data, and where biocide use was recorded this was taken as surrogate evidence that bacterial contamination of the MWF had occurred. When compared to typical amounts of biocides used from January 1994 to March 1996, the use of biocides peaked (two standard deviations above the average use) during May and June of 1995. This peak preceded the outbreak of respiratory symptoms, which occurred from October to December 1995. According to the plant records, oil mist concentrations measured between January 1994 and March 1996 had not exceeded the OSHA permissible exposure limits (PEL) of 5 mg/m^3 and no total particulate measurements exceeded the OSHA total particulate PEL of 15 mg/m^3. No statistical

difference was seen in oil mist levels when comparing the values at workstations of workers with and without EAA.

Conclusions

The relative risk of EAA was 3.2 times higher in the exposed workers compared to unexposed and the authors suggested that the cause of the EAA was not MWF itself (as demonstrated by the lack of serum precipitin reactions to unused MWF) but a response to increased bacterial contamination of the MWF. The addition of large amounts of biocide prior to the outbreak was taken as an indication that bacterial contamination had preceded the outbreak of illness although no specific 'lead' pathogen was identified [1].

Zacharisen, M. C. et al. 1998 [288]

Background

A spectrum of respiratory diseases was recorded amongst workers at an automobile manufacturing plant commencing in 1995. A total of 1600 workers were employed, and 800 were exposed to MWF. Seven different MWFs were used, six were synthetic and one was a soluble oil water mix.

Methods and results

Thirty workers presented to an 'Asthma and Allergen' centre because of work-related respiratory problems, and seven were diagnosed with EAA. The investigators devised their own criteria for EAA, which included evidence of work-related symptoms, and supportive features for example positive precipitins, chest x ray findings, pulmonary function tests, and biopsy results. These workers had been employed at the site for between two and thirty eight years. All EAA patients had positive precipitins to used water soluble and synthetic MWF, none had positive precipitins to *Mycobacterium chelonae*. All had decreased lung function and borderline low gas transfer (TLCO). After seven months out of the work place, four workers were able to return to work using personal protective equipment, one failed to return, and a further two were unable to return due to persistent symptoms.

Twelve workers were diagnosed with OA and their average length of employment was seventeen years. OA was diagnosed on the basis of work-related symptoms,

reversible obstruction, or a positive methacholine challenge, and the presence of hyperinflation or atelectasis on chest X ray. Eleven of these workers were tested for precipitins and ten showed positive precipitin reactions to used MWF or bacterial extracts. Spirometry in five of the workers showed a reduced FEV_1 with reversibility. One in four of the workers who underwent skin prick testing for inhalant allergens had a positive result. All workers with OA had a chest X ray, of which eight were normal, three demonstrated hyper-inflated lung fields, and one showed atelectasis.

Six workers were diagnosed with occupational bronchitis based on work-related symptoms (including sputum production), and a normal methacholine challenge. Their average length of employment was 18.1 years. Three of the six workers with occupational bronchitis were unable to go back to work because of their symptoms. Five workers were diagnosed with unclassified respiratory symptoms of short duration.

Air monitoring was performed, and MWF samples were collected. Airborne bacterial counts (taken in December 1995) revealed high levels of Gram-negative bacteria in areas close to areas where MWF was used. Concentrations ranged from 525 to 4200 CFU/m^3. Bacteria cultured included; *Bacillus sps, Xanthomonas sps, Pseudomonas sps, Citrobacter sps, Acinetobacter sps* and *Klebsiella sps.* Acid-fast bacilli identified as *M.Chelonae* were found in seven samples, six from synthetic MWF and one from water based MWF. The authors of this study concluded that a 'lead' pathogen in the outbreak could not be identified.

Conclusions

This outbreak demonstrated the occurrence of multiple occupational respiratory conditions (EAA, OA and bronchitis) associated with exposure to MWFs. The outbreak seemed to end spontaneously in 1996 with no clear temporal relationship to improvements made to the factory environment.

Trout, D. R. et al. 1996 [289]

Background

This NIOSH investigation (HETA 96-0156-2712) involved a large factory producing automobile parts. The factory had an area of 1.7 million square feet and used semi

synthetic and soluble mineral oil-based MWFs in the compressor plant where 265 staff worked. Workers suffering from recurrent respiratory complaints requested that NIOSH carry out the investigation.

Methods and results

The medical records of all workers diagnosed with EAA, or EAA like conditions, and all the workers restricted from work in the compressor area were reviewed. Shortness of breath and cough were common symptoms and twelve out of fourteen patients had crepitations on auscultation. Spirometry was abnormal in all cases showing a restrictive or mixed picture, which is a combination of obstructive and restrictive abnormalities. Ten of the cases underwent HRCT scans, all of which were abnormal. Eleven had abnormal chest X rays, and only one had normal radiology. Eight workers had lung biopsies, six of which showed histological evidence of non-causeating granuloma and two showed lymphocytic alveolitis. Both pathologies are consistent with the diagnosis of EAA. Thirteen of the fourteen workers diagnosed with EAA had worked full time in the compressor room and were exposed to MWF; one of the other cases had visited this area frequently.

Questionnaires were completed by 165 MWF exposed, and 87 non-exposed workers. Six of the fourteen workers who had recently been diagnosed with EAA were also included. The mean length of employment of these workers was ten years. Respiratory symptoms were more common in those workers who had worked in the compressor room, and fatigue with recurrent flu like symptoms were commonly reported.

Mycobacterium immunogenum was the major microbiological contaminant (between 1.4×10^3 and 1.0×10^7 CFUs/ml) of all the bulk MWF samples taken from the site. Endotoxin levels ranged from non-detectable to 44,375 EU/ml. It should be noted here that endotoxin are derived from Gram negative bacteria, not mycobacteria, therefore this suggests that bacteria other than mycobacteria were also present.

Serum from participating workers was analysed using an enzyme linked immunosorbent assay (ELISA) and a precipitin assay to detect specific IgG to five different bacteria. *Mycobacterium chelonae* antigen was prepared from organisms

isolated from MWF used in the compressor area. Twenty four percent of the employees who reported exposure to MWF had a positive precipitin reaction to *Mycobacterium* spp, and when an enzyme linked immunoassay (ELISA) forty-two percent of the serum sample were found to contain specific mycobacterium IgG suggesting that ELISA was a more sensitive tool to detect sensitisation.

An additional site visit was carried out in 1997 and those employees previously diagnosed with EAA were asked to participate. The aim of this second study was to carry out challenge tests using isolated mononuclear blood cells in an *ex vivo* challenge with *M. chelonae* antigen. Seven workers with EAA and six asymptomatic workers agreed to participate. The potential for *M. chelonae* antigen to provoke an immune reaction was assessed by measuring cytokine expression comparing the reaction in workers diagnosed with EAA to that observed in the asymptomatic workers. No statistically significant difference in cytokine expression was found between the EAA versus the asymptomatic patients for any of the antigens tested.

Twenty-one personal breathing zone (PBZ) samples and five general air (GA) samples were collected to measure total particulates. In addition, twenty-four real time particulate measurements were made using a real time light scattering aerosol spectrometer. The average PBZ exposure was 0.40 mg/ m^3, with only three samples above the total particulate NIOSH REL for MWF of 0.5 mg/m^3. In 1997, ventilation changes were made in the factory and NIOSH returned to re sample the PBZ. In many cases the same individual workers were used to collect personal exposure data. Of the nine PBZ samples taken post ventilation, six had concentrations of particulate above the NIOSH REL.

Conclusions

NIOSH concluded that although *M. immunogenun* was the predominant microorganism in the MWF sumps supplying the compressor area; there was no proof that mycobacterium was the causative agent of EAA. It was recommended that ongoing evaluation of the MWF environment and the exposed workers be carried out and that exposures be reduced below the NIOSH REL. Workers exposed to levels greater than this were also advised to wear respiratory protection.

Kiefer, M. T. et al. 1998 [290]

Background

NIOSH commenced an investigation (HETA 98-0030-2697) at a large, 1,000,000ft^2 factory manufacturing aircraft parts following complaints of flu like symptoms, skin problems, and irritation of the eyes. Of the total 1600 workers, eighty were exposed to a water based oil emulsion MWF.

Methods and results

The company's log of reported illnesses was reviewed for the years 1995-1997. During this period there had been 29 entries, one regarding skin disease, one regarding sinus complaints and one regarding gastrointestinal upset, the others had been due to minor injuries.

Seventy-seven exposed and eighty-four control workers completed symptom questionnaires, with an average employment time in the factory of 22.4 years. The results of the survey suggested that there was a much higher illness burden than that reported in the log and reported symptoms were more frequent in the exposed workers compared to the controls. Sinus problems were reported by 57% of exposed workers compared with 43% of the controls; 29% of the exposed group complained of having a tight chest compared to 13% of the controls; 40% of exposed workers complained of generalised aches compared to 23% of the controls; 30% reported trouble breathing compared to 19% of the controls; and 39% reported having a cough compared to 26% of the controls.

Skin rash was reported in similar frequencies in the exposed and control group, 36% of the exposed workers complained of a rash compared with 32% of the controls. No attempt was made to determine if the control group was exposed to any specific irritants that increased their rate of rash. NIOSH recommended that despite similar prevalence of reported skin symptoms in the exposed and control groups, that there were measures that should be taken to reduce skin exposure to MWFs, for example wearing protective gloves.

Environmental measurements were taken, which included air sampling for MWF and endotoxin, and bulk sampling of MWF from various points in the central distribution

system. In the PBZ samples for MWF, all but one was well below the NIOSH REL of 0.5 mg/m^3. No viable bacteria were identified in any of the bulk samples, however endotoxin was identified at concentrations of up to 7.5 x 10^4 EU/ml. Endotoxin levels were much higher in air samples from the workplace of the exposed workers compared to the areas where the non-exposed control group worked.

Conclusions

NIOSH concluded that skin problems were high in both groups, but not significantly higher in the workers exposed to MWF. Respiratory symptoms did however show a consistent trend towards exposed workers, with a statistical significance for increased prevalence of chest tightness and sore throat. Recommendations were given to generally lower exposure to MWF, monitor exposure of MWF especially for the machinists, and to encourage employees to report all potential work-related ill health.

Trout, D. et al. 1996 [291]

Background

A NIOSH investigation (HETA 97-0118-2664) at a large factory covering 1 million square feet that used semi synthetic MWF in the production of firearms, was started following complaints from workers of headaches, sore throats, bloody noses, respiratory symptoms, skin irritation and rashes. The factory employed 1100 employees with 450 being exposed to MWF.

Methods and results

Symptom questionnaires were given to all employees that agreed to participate in the study, and 950 employees took part. The mean length of employment of those workers exposed to MWF was eighty-one months compared to the unexposed workers whose mean length of employment was one hundred months. The prevalence of self-reported symptoms was more common in the exposed compared with the unexposed workers. Eye nose and throat irritation was documented in 26% of the exposed compared to 10% in the unexposed; shortness of breath was reported in 11% compared to 5% of the controls; dry cough in 26% compared to 11% of the controls; chest tightness in 11% compared to 6% of the controls; fatigue in 19%

compared to 10% of the controls; and wheeze in 15% compared to 8% of the controls.

Eighty-four of the nine hundred and fifty employees responding to the questionnaire had previously been assessed by a physician, and diagnosed with a respiratory, skin or infectious conditions. The 'physician diagnosed' conditions were not reported any more frequently in the MWF exposed workers compared to those not exposed to MWF. Nine employees were randomly chosen and interviewed; six of these denied any work-related health problems, and three complained of work-related upper respiratory symptoms. An additional five workers chosen by the union were interviewed and of this group four complained of upper respiratory symptoms, three of eye symptoms and one had previously suffered a rash.

Bulk samples of MWF were collected and analysed. Four samples yielded fungal colonies (yeast, *Fusarium sps*, and *Candida* spp) and ten samples yielded bacterial growth. Eight different gram-negative bacteria were identified including *Pseudomonas* spp*, Burholderia* spp and *Acinetobacter* spp*, and Mycobacteria chelonae* was identified in three samples. The concentration of bacterial contamination varied from $<10^1$ to $>3x10^7$ CFU/ml.

Air sampling was not carried out during the initial investigation, but at a follow up review the results of sampling carried out by the company were reviewed. This showed all results below NIOSH REL for mineral oil mist of 5 mg/m^3.

Conclusions

The authors concluded that there was a small but consistent increase in symptoms in the MWF exposed population compared to those workers not exposed. The significance of any particular bacterial contamination was difficult to assess. They recommended an improved health and safety program, maintenance of sump cleanliness and minimising where possible, generation of aerosols.

Hodgson, M. J. et al. 2001 [293]

Background

Three papers were published which described different aspects of an outbreak of respiratory illness that started in 1997 in a relatively small factory fabricating precision titanium and stainless steel parts for the aerospace industry. The factory covered 67,000 square feet and employed 120 workers, 105 involved in component production. A combination of semi synthetic, synthetic water soluble and straight oil MWFs were in use. The investigation was initiated after the Division of Occupation and Environmental Medicine (DOEM) diagnosed an employee with EAA in the autumn of 1997. Unlike most of the outbreaks of ill health due to MWF in the USA, this investigation was not undertaken by NIOSH. It led to in-depth study of the aetiological factors rather than a report of workers symptoms and working conditions.

Methods and results

Symptom questionnaires were distributed to all the employees at the outbreak plant and to employees in two control areas; one where there was exposure to MWF and one where there was not. There were one hundred responders from the outbreak site. The results indicated that 79.6% of workers had respiratory and systemic complaints. Overwhelming fatigue was the predominant feature. The investigators ignored temporal relationships of symptoms due to the chronic nature of EAA and the fact that most workers worked a six or seven day week, which meant there was not a sufficient recovery period away from work to note a change in symptoms. This is contrary to many investigations for which evidence of work-related provocation of symptoms plays a critical role in recognising occupational risk factors as well as recognising the symptoms of work-related EAA.

All symptomatic workers were offered further clinical assessment. Three workers had already been assessed elsewhere, and diagnosed on biopsy as having EAA. One had initially been diagnosed with usual interstitial pneumonitis (UIP), which is an idiopathic form of interstitial lung disease. The diagnosis of UIP was changed to EAA in view of the clinical setting. Another had been diagnosed twice with pneumonia before the final diagnosis of EAA was made. This illustrates how easily, and potentially frequently the diagnosis may be missed or at least delayed. The four

cases of 'biopsy confirmed' EAA were recognised even before the remaining symptomatic workers (identified from the questionnaire) had been investigated.

In the first six months of the investigation, a physician reviewed sixty-one workers and forty-nine described systemic and respiratory symptoms consistent with EAA. There was no significant difference in the age or duration of work at the plant in those reporting symptoms compared to those workers who did not. The clinical evaluation included a combination of history taking, physical examination, pulmonary function testing, laboratory tests and radiology. On the bases of these results diagnoses of EAA, asthma, bronchitis, sinusitis, rhinitis or 'other condition' were made. If the results were inconclusive a biopsy was considered. Biopsies were carried out on twenty patients, including the four previously mentioned who had a biopsy prior to the outbreak investigation. The histological appearance of the biopsies from sixteen workers was consistent with a diagnosis of EAA.

Some workers refused biopsy, and because of private health care costs some workers were unable afford to have a biopsy. The report authors suggested that the sixteen cases of EAA were likely to have been an underestimate of the true number of cases at this stage of the investigation. Ultimately thirty-eight out of forty-nine workers with symptoms consistent with EAA had the diagnosis confirmed and reported to the department of public health. Of the sixty-one workers reviewed, twenty-three did not receive a diagnosis of EAA. Ten out of the twenty three were lost to follow up before EAA was completely ruled out, seven were found to have work-related asthma or asthma exacerbation; another four were found to have upper respiratory tract problems. Demographic data showed that the workers with a diagnosis of EAA were more likely to be older and 'non smokers' compared to the general population at the plant.

Exposure assessment included bulk MWF samples and air samples. *Moraxella spp, Bacillus* spp and *Pseudomonas* spp were isolated from the bulk samples. *Mycobaterium* spp was also identified in MWF from one sump. In some sumps there was a low concentration of fungal species including *Acremonium* spp*, Cladosporium* sps*, Penicillium* sps and *Fusarium*. Serum samples from 10 of the workers being investigated for respiratory symptoms and twelve asymptomatic controls were tested

for antibodies against isolates of bacteria and fungi found in the MWF samples, including *Pseudomonas* spp and *Moraxella* spp. The serological testing did not implicate any specific agent in the disease process. Bulk samples were also tested for endotoxin, and this correlated with sump bacterial concentrations. Air samples were tested for microbial growth, endotoxin content and levels of oil mist and at the time of sampling all measures were below recommended standards [293 294].

Conclusions

The authors concluded after the initial six months of investigation that there were no clear relationships between contamination and airborne exposure, and no single organism (and in particular *M. Chelonae*) could be attributed as the causative agent for development of EAA. The author's key conclusions from this study were three fold. In order to ensure cases of respiratory disease secondary to exposure to EAA are detected, physicians must have a high index of suspicion. The long-term consequence of EAA is not clear; although the progression of clinically identifiable disease often resolves as exposure is controlled but low-grade disease may remain unidentified. Apparent compliance with current health and safety standards does always prevent the development of disease, perhaps suggesting the present standards may need revising [294].

On completion of the first stage of this investigation (and when the size of the outbreak was apparent) it was agreed that future diagnosis of EAA would be on the based on symptoms and 'non invasive' tests avoiding expense and potential complications of biopsy investigations. For the next stage of the study a diagnostic index for EAA was developed to reduce uncertainties in case definition. Clinical findings from workers likely to have EAA (i.e., the sixteen 16 biopsy confirmed cases) were compared to the clinical findings of cases categorised as not having EAA (based upon response to the symptom questionnaire) to develop Hypersensitvity Pneumonitis (HP) Diagnostic Criteria. The final version of this diagnostic index was validated by applying the criteria to thirty workers, some of whom had been diagnosed as cases of EAA and others who had not been diagnosed with EAA. The same sample of workers was also assessed using the Kenosha epidemiological case criteria [1]. All four workers who were suspected clinically to have EAA, but whose biopsies were negative were diagnosed with EAA using both criteria [293].

After workers were diagnosed with EAA, the decision for them to return to work was a multidisciplinary team decision. After the initial environmental sampling had occurred, the investigators continued to collect longitudinal data to assess symptom changes following the implementation of the recommended interventions. In January 1998, four months after the beginning of the outbreak, several workers attempted to return to work but experienced a prompt recurrence of their symptoms and a decline in their lung function. Further interventions were implemented, including a comprehensive MWF management program, machine enclosure with improved local exhaust ventilation, worker training and a reduction in overtime hours. After these interventions a statistically significant reduction in MWF sump bacteria and fungi was observed compared to levels at the start of the outbreak (October 1997). Whilst samples did not show any significant reduction in bacterial or fungi concentrations oil mist levels were consistently lower than previously measured [292].

A cross sectional survey in November 1998 identified two further possible cases of EAA, but the onset of their symptoms was prior to the implementation of the major interventions. In November 1999, over two years into the outbreak, 51% of the workers who had been clinically diagnosed with EAA successfully returned to work [292].

Trout, D. et al. 1998 [295]

Background

Trout led an investigation (HET ALA-98-0050-2733) at a 17.5-acre site where workers were drilling boring and milling truck axles. In total there were 1000 employees, of which 338 were machinists. Semi synthetic, soluble and straight oil MWF were used at this site. After a case of EAA was documented in 1997, NIOSH was invited to carry out an investigation.

Methods and results

A symptom and exposure questionnaire was distributed to all employees and 111 of the 131 respondents (81%) reported systemic symptoms. Thirty-nine of the 131 (30%) complained of work-related respiratory symptoms and of these thirty-five had been exposed to MWF. Eleven of the 131 (28%) had changed job due to their

symptoms. Those workers identified by questionnaire as being exposed to MWF, having work-related respiratory symptoms and more than one systemic symptom, were offered a physician review. Of ten workers offered this review, all declined the invitation. Despite the evidence that staff had relevant symptoms for EAA no further clinical investigation took place.

Nine PBZ air samples for MWF were collected and total particulate mass concentrations ranged from 0.33 to 1.29 mg/m^3; five samples had levels over the 0.5 mg/m^3 NIOSH REL. Seventeen bulk samples of MWF were collected for analysis of bacteria, fungi and mycobacteria and several isolates were identified including *Mycobacterium.chelonae*. Some samples of MWF had bacterial concentrations ranging from 10^5 to 10^7 CFU/ml.

Conclusions

The clinical conclusions from this study were limited by the poor compliance with the clinical evaluations, however the respiratory symptoms reported were comparable to those observed during other investigations. The airborne exposure to MWF mist was above NIOSH REL and it was recommended that the company reduced exposure to MWFs and institute a health surveillance program.

Shelton, B. G. et al. 1999 [296]

Shelton et al. published a paper containing three case reports describing outbreaks of EAA amongst MWF exposed workers at three different sites. Case report one describes a single case of EAA, case report two describes two cases of EAA in a population of 700 machine workers, and case report three describes five cases of EAA in a site under investigation at the time of publication. Two of the three outbreaks were in engine manufacturing sites. Detailed clinical data was only available for case one. In all factories, including the one under investigation, *Mycobacterium.chelonae* was identified in samples of the used MWF, at concentrations up to >10^7 CFU/ml. The authors hypothesised that *Mycobacterium* spp in MWF was the cause of EAA in these cases..

Trout, D. H. et al. 2000 [297]

Background

This involved an investigation of an automobile manufacturing plant where 250 workers were exposed to semi synthetic water soluble MWF containing a Triazine biocide (HETA 99-0311-2790). NIOSH were asked to review the establishment due to concerns about respiratory health reported by ninety-three workers. The initial reports were made in June of 1999, with intermittent ‘outbreaks’ of symptoms from this date to the subsequent NIOSH investigation. The reports of ill health came from one of three manufacturing departments, although all three sites used the same type of MWF.

Methods and results

Symptom questionnaires were completed by 229 of the 462 workers, spread over the three sites and sixty-six of the 229 worked at the site under investigation. The questionnaire data was used to compare reported symptoms of workers at the site under investigation, with those from the other sites included in the study. Sixty two per cent of the workers at the site under question had cough compared to 28% at the other sites and there were complaints of increased shortness of breath in 52% of the workers at the site of investigation compared to 24% at the other sites.

The medical records of seventy-one workers who had consulted the occupational physician were reviewed. Seventy two per cent of these workers complained of a cough, 45% of shortness of breath, 39% of chest tightness, 13% of wheeze, 17% of general fatigue, 6% of dermatitis, 39% of headache and 23% suffered dizziness. How the occupational physician then investigated these cases was not documented in the report but two workers were diagnosed as cases of 'new onset' asthma with work-related symptoms, two as having exacerbations of previously asymptomatic asthma, and six as having "asthma like conditions".

Area air sampling revealed trace amounts of volatile organic contaminants, none of which were thought to be significant. Seventy PBZ samples were collected to assess the level of MWF mist but only four of these showed levels either equal to or exceeding the NIOSH REL. Of note, three of these samples were from the other company sites, and only one from the department where the ill health had been

reported. Samples of bulk MWF contained gram-negative bacteria up to 10^8 CFU/mL and endotoxin levels were on average 10^5 EU/mL.

Conclusions

NIOSH concluded that the MWF did not appear to be solely responsible for the respiratory symptoms but noted that bacterial contamination was a continuing problem. It was recommended that the company continue to systematically monitor the health of its employees and to ensure good maintenance and cleaning of machinery and MWF.

Trout, D. et al. 2002 [298-300]

Background

This study was of an outbreak of respiratory ill health in a factory manufacturing automobile brake calipers and drums (HET ALA 2001-0303-2893). An additional report on aerosol sampling at the same site followed [32], adding to the depth of information available about this outbreak. The factory site covered an area of 200,000 ft^2 and the company used a semi synthetic MWF containing a Triazine based biocide. The assembly and machining departments were separated by a wall and had separate ventilation systems; therefore the assembly workers should not have been exposed to high level of MWF mist. Approximately 150 workers were based in the machining area with a further 250 workers based elsewhere on site.

Methods and results

Initial respiratory symptoms and illness were reported in October 2000 and five patients were diagnosed with EAA between December 2000 and April 2001. In response to the reported ill health, the company cleaned the sumps, replaced the used MWF, installed new biocide, improved the ventilation, and provided medical screening for the workers. NIOSH were requested to investigate the workplace to further assess the cause of the ill health.

NIOSH circulated a symptom questionnaire to all the employees, which was completed by 305 of the 335 workers. The results of the questionnaire were then compared for workers in high exposure jobs to those workers in low exposure jobs. This showed that all the reported symptoms were higher in prevalence amongst the

high exposure category workers, with prevalence ratios for symptoms ranging from 1.2 to 2.2.

Medical records of thirty-two of the workers who had complained of respiratory ill health were examined; for these workers, the mean length of employment in the factory was eighteen years. In the year preceding the NIOSH investigation, 107 workers had had their work restricted due to respiratory problems and at the time of the investigation, thirty-seven workers remained on sick leave.

Industrial hygiene evaluations were undertaken. These included bulk sampling of MWF, a review of hygiene records, and personal breathing zone (PBZ) and area air sampling during typical operations. Initially the central MWF system was found to contain up to 10^7 CFU/ml of total bacteria and 10^5 CFU/ml of *Mycobacterium sps*. Three months later, after the introduction of a biocide, no bacterial or fungal growth was identified in the used MWF. Personal breathing zone air sampling showed a range of total particulate between 0.14 to 0.68 mg/m^3 (NIOSH REL for thoracic particulate mass= 0.5 mg/m^3).

As part of the clinical investigation, workers had a combination of tests including blood tests, lung function tests, and radiological tests. It was not documented whether any patient underwent lung biopsy. In total, thirty workers were diagnosed with EAA, fourteen with OA and six with work-related chronic bronchitis. Those patients with OA met the investigators defined criterion of one or more work-related symptom (cough, wheeze or chest tightness); an absence of systemic symptoms/signs; no infiltrates on the chest radiology; and spirometry pattern consistent with reversible airways obstruction (i.e., an obstructive pattern with > 12% improvement in forced expiratory volume in one second after administration of inhaled bronchodilators).

The physician diagnosed eighteen of the total number of cases of EAA without using the chosen criteria. The remaining twelve were diagnosed using the following criterion: one or more work-related symptom (cough, wheeze or chest tightness); one or more systemic signs/symptoms (fever, chills, fatigue, myalgia, night sweats);

infiltrate on radiology and abnormal spirometry (either an obstructive or restrictive pattern).

As well as the questionnaire data that categorised workers into 'high' or 'low' mist levels, the mist concentrations were measured objectively using mist collectors. Out of the thirty cases of EAA, six cases occurred amongst the low exposure category jobs (4% of the exposed), fourteen cases amongst the medium exposure jobs (19% of the exposed), and ten cases amongst high exposure jobs (34% of the exposed).

Conclusions

The conclusion was that higher MWF mist levels were associated with a higher reported prevalence of symptoms and a higher incidence of respiratory disease.

Trout, D. et al. 2002 [301 302]

Background

This study involved a NIOSH investigation (HETA 2002-0155-2886) of another large automobile manufacturing site (with an area of 1.5 million square feet), employing 2000 production workers using a semi synthetic water mix MWF containing a Triazine biocide with. This investigation addressed the use of serological tests to aid diagnosis of EAA and to aid identification of these pathogens causing respiratory allergy.

Methods and results

NIOSH were asked to investigate respiratory complaints in sixteen workers and in response one hundred and fifty questionnaires were sent out, of which one hundred and forty were completed, and one hundred and four of the workers agreed to further assessment. The aim of the questionnaire was to identify symptomatic and asymptomatic groups of employees who would take part in immunological testing to *Mycobacterium immunogenum*. The respondents were divided into four groups; workers exposed to MWF who had previously been assessed for respiratory problems (group 1); fifteen who were exposed and symptomatic but had not previously been assessed (group 2); thirteen exposed and asymptomatic (group 3) workers; and fourteen unexposed and asymptomatic (group 4). In those groups containing more than fifteen potential workers, fifteen were randomly selected so all

four groups contained the same number of workers. The fifty-six workers within these groups consented to donate blood to assess cytokine expression involved in regulating cell mediated and humoral immunity.

Nineteen workers previously assessed for respiratory disease had medical records that were reviewed as part of the health hazard evaluation (HHE). Using the diagnostic criteria previously used by Fox et al. in the Kenosha outbreak [1], seven workers were diagnosed with either definite (3), probable (2) or possible (2) EAA. Some of the medical records were incomplete and more cases may have been recognised had the required information been documented. A further eight workers had work-related respiratory symptoms. Six out of seven possible cases of EAA and five out of eight with respiratory symptoms were found in group 1. The symptom questionnaire identified a further twenty out of one hundred and four exposed workers who complained of respiratory symptoms.

The one significant difference in cytokine expression was an increased IL-8 secretion (expressed as a percent of LPS induced cytokine secretion) in MWF exposed workers. No other significant relationships between secretion of the cytokines tested and either the presence of EAA or exposure to MWF was found. Antibody levels against both *M. immunogenum* and *M. fusarium* antigens were greater in those with EAA compared to those without a diagnosis, however based on this test alone it was not possible to determine the causative agent.

Conclusions

A number of interventions were made by the company in response to the outbreak of EAA, after which some workers previously diagnosed with EAA were able to successfully return to their place of work suggesting that improved control of exposure to the causative agent(s) had been achieved. NIOSH recommended that the firm continue health surveillance and that workers should wear appropriate respiratory protection.

Gupta, A. et al. 2006 [303]

Background

Using data gathered by the state Occupational Disease Surveillance system and the Division of Occupational and Environmental Medicine (DOEM) seven cases of EAA were identified and assessed by a physician. These came from three different automobile manufacturing sites and the initial index case was diagnosed in 2003. The workers had been exposed to MWF for a mean of 6.2 years before their diagnosis and at the time of the investigation were using mainly semi synthetic MWF.

Methods and results

The Michigan Occupational Safety and Health Administration (MIOSHA) conducted an industrial hygiene investigation at the workplaces, with financial assistance from NIOSH. There were 2825 employees over the three sites. There was no health survey of the workers, the only clinical investigation was a review of those workers already diagnosed with EAA, and no additional symptomatic workers were identified. All seven workers demonstrated an improvement in lung function (FEV_1) and radiology (HRCT) when their exposure to MWF ceased.

EAA was identified using diagnostic criteria as defined by Schuyler and Cormier [246], which specified that the worker should meet four major and two minor criteria. In the seven cases assessed in this investigation, although all of them met four of the major criterion, only two cases met at least two of the minor criterion.

Microbial analysis of MWF samples taken from the MWF system, demonstrated the presence of *M. immunogenum* at one site, an unclassifiable *Mycobacterium* at another site and no bacterial or fungal growth at the third site. Personal air monitoring data conducted by management at two of the three sites was reviewed. This revealed that the level of MWF in the air was well below the MIOSHA permissible exposure limits for mineral oil mist and total particulates.

Conclusions

At the end of the investigation, the management were recommended to continue monitoring levels of MWF in the air, and to regularly assess contamination with *Mycobacterium* spp.

Studies in the USA that investigated outbreaks of respiratory and skin disease

Eight of the twenty-nine outbreaks identified by the literature review involved cases of workers with skin disease and workers with respiratory disease. Seven of these investigations were based in the USA, and one in Croatia (see section 3.4). In these investigations the respiratory disease was mostly documented alongside skin disease (as an obstructive disease process) but without a detailed investigation.

Daniels, W. D. et al. 1988 [305]

Background

This investigation by NIOSH was of an outbreak of skin disease (HETA 88-268-L1980) in a factory producing aluminium alloy pistons for automobiles for which water based soluble MWF was used. Part of the industrial process involved tin plating. Out of the one hundred and fifty two exposed workers, thirteen were chosen for interview, but the report did not specify whether these were chosen randomly or because they had complained of skin symptoms. Their mean length of employment was 9.5 years.

Methods and results

No microbiological or immunological investigations were reported. Airborne concentrations of MWF were measured and were well below the recommended NIOSH levels for oil mist (5mg/m^3). Of the thirteen workers that were interviewed, ten complained of recurrent rash and on examination two had an eczematous like eruption with lichenification, suggesting chronic dermatitis. The general opinion of the workers was that the skin rashes were work-related.

The workers also reported suffering from work-related cough and shortness of breath, specifically related to the MWF fumes. This was not investigated further.

Conclusions

Recommendations were made to the company to continue to maintain the local exhaust ventilation systems to keep exposure as low as possible to encourage good hygiene practice, to maintain employee education, and implement a medical surveillance program for early detection of MWF related skin disease.

Filios, M. B. et al. 1994 [306]**.**

Background

In 1990 NIOSH received a request to investigate a plant processing aluminium ingots, where staff had expressed concern about skin, eye and throat irritation as well as respiratory problems (HETA 90-0286-2428). One hundred and fifty employees were exposed to MWF, although the exact type was not documented.

Methods and results

Seventy-eight staff agreed to take part in a survey and these had an average duration of employment of fourteen years. The health survey consisted of a symptom questionnaire, cross shift spirometry, and serial peak flow monitoring. Eleven participants with work-related respiratory problems were identified. Six of these reported at least one work-related respiratory symptom, and one participant had a cross shift decrease in FEV_1 of more than 10%. Four participants had a greater than 20% work-related change in peak flow detected using serial peak flow analysis, but this was not associated with a particular work area. Seventy percent of the participants reported experiencing eye irritation on more than two occasions over the preceding year, and 44% complained of skin irritation.

The industrial hygiene portion of the survey consisted of collecting PBZ and 'area' air samples, as well as microbiological examination of bulk liquid samples. The bacterial counts were very low in both the bulk and air samples.

Piacitelli, C. W. et al. 1999 [307]

Background

This involved a health and hygiene investigation (HETA 96-0232-2776) of a factory involved in the manufacturer of steel roof bolts. The factory employed sixty-six workers and approximately fifty were reported as exposed to an oil water mix MWF used in the manufacturing process. The range of symptoms reported in the study were similar to that described in an earlier report (HETA 90-0286-2428). The main symptom described was a burning sensation in the eyes, and secondary to this heartburn, coughing, upper respiratory tract problems, headaches and shortness of breath.

Methods and results

Thirty-seven of the fifty exposed workers completed a symptom questionnaire and spirometry tests. These employees had an average duration of employment of 7.5 years. Fourteen of those completing the survey reported having a rash on exposed body areas, and eight of these attributed the rash to exposure to MWF. Only one worker had sought medical attention and they were diagnosed with a skin infection. Sixty-five percent (24/37) complained of irritation of the eyes and seventeen of these attributed this irritation to their work.

Of the thirty-seven workers who participated in the survey, twenty-seven reported moving to other workstations since their initial assignment, mainly because of respiratory complaints. Three of the thirty-seven surveyed complained of a dry cough, four of a cough productive of sputum, eight had wheeze and shortness of breath, and thirteen of symptoms of chronic bronchitis. Physician diagnosed bronchitis was documented for eight of the participating workers, and abnormal spirometry was noted for four of the participants, with an obstructive pattern in three and restricted pattern in one. Thirty-six of the participants performed cross shift spirometry measurements but this was negative in all cases.

Twenty of the fifty current workers were interviewed and most of these complained of rashes and irritation of skin and mucous membranes, heartburn, as well as respiratory symptoms. None had constitutional symptoms or had sought medical attention for their complaints.

Sampling to determine 8-hour time weighted average (TWA) concentrations of airborne MWFs found none to be in excess of the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PEL) and American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) of 5 mg/m^3. However all the personal sample measurements taken at two of the three presses were above the NIOSH REL of 0.4 mg/m^3 for thoracic aerosol. This finding of increase thoracic aerosol corresponds to the workers statements that they suffered symptoms when working at the presses.

Area sampling for endotoxin generally found levels below two endotoxin units per cubic meter of air (EU/m^3) and none exceeded 11.5 EU/m^3. *Pseudomonas sps* were predominant in the MWF supply system at concentrations of 2.5 x10^6 to 2.5x10^8 colony forming units. Endotoxin contamination of the same fluids ranged from about 68 to 537 thousand endotoxin units per milliliter (EU/ml).

Conclusions

The report noted that there appeared to be a high prevalence of chronic respiratory symptoms, and work-related skin and eye irritation within the workforce. Slightly more than a third of the participants met the definition of chronic bronchitis, although no specific investigations of EAA was instigated. It was recommended that methods to reduce the exposure of workers to MWF should be adopted.

Kiefer, M. G. et al. 1999 [308]

Background

This involved an investigation of a large (500 000 square feet) factory manufacturing automobile parts using semi synthetic or straight oil based MWFs. The plant employed 850 workers (HETA 98-0246-2747). The investigation followed complaints of allergy, and irritation of the respiratory tract, skin and eyes. The investigation focused on one area of the factory (area 109) where thirteen employees (twelve machine operators and one inspector) worked. The mean length of employment of staff working in area 109 was 7.4 years compared to an average of 11 years for staff in the factory as a whole. Twelve of the thirteen workers in area 109 completed a self administered symptom questionnaire, of whom five complained of shortness of breath, four of wheeze and five of a rash. There were no controls subjects questioned for comparison.

Methods and results

Full shift PBZ air samples were collected with a size selective device to collect the thoracic particulate fraction of MWF. Two of the seven PBZ samples for MWF were higher than the NIOSH REL (0.4 mg/m^3). Both these results were from machine operators using semi synthetic MWFs. Other chemicals such as petroleum naphtha were also monitored and these were all found to be below the NIOSH REL of 350 mg/m^3. A microbiological assessment was not made.

Conclusions

Recommendations were made to reduce the workforce's exposure to MWF particularly by improving ventilation controls. A comprehensive health and safety program was also recommended, specifically addressing the needs of workers exposed to MWF.

Roegner, K. T. 2001 [310]

Background

This involved an investigation at a factory manufacturing airplane parts, which employed nine hundred and twenty workers of whom two hundred and four machinists were exposed to MWFs. The initial request NIOSH received was for a Health Hazard Evaluation based on three employees who reported several health effects including respiratory and skin disease, which they considered due to synthetic MWF used in the machine shops. Four machinists had been diagnosed with new onset asthma in the year prior to the investigation, so the medical evaluation focused on respiratory effects rather than skin disease.

Methods and results

Prior to the NIOSH investigation, twelve machinists had complained of respiratory symptoms and were reviewed by the company's occupational physician. Four of the twenty were referred for pulmonary function testing, and one was diagnosed with occupational asthma based on bronchial hyper responsiveness (BHR), two had work-related respiratory symptoms, and the other saw a private physician who diagnosed OA on the basis of a positive BHR test.

Symptom questionnaires were given to all employees in the machining area, and two hundred and eighty four questionnaires were completed and returned. Of the two hundred and eighty four, one hundred and eighty eight were considered as exposed to MWFs. Ninety-five percent complained of shortness of breath and twenty-three percent of asthma like symptoms. Of the sixteen workers referred to the occupational physician, fifteen had been exposed to MWFs, fourteen had work-related respiratory symptoms and ten had a rash. Workers were investigated depending on their symptoms; with sixty-six having spirometry tests and a smaller number undergoing

BHR tests. For a diagnosis of OA, the workers needed appropriate symptoms, a positive BHR test and peak flow variability showing work-related effects. Using this criteria only one case of OA was found, but there were eight workers who had recently diagnosed asthma with work-related symptoms.

Environmental investigations were carried out which included collecting bulk samples of MWF. Microbiology tests demonstrated the presence of *Bacillus* spp and *Pseudomonas* spp but no fungi. MWF aerosol samples were also taken and the particulate mass for each sample was measured. With one exception all but one of the fifty-five PBZ samples measured below the NIOSH recommended limits of 0.4 mg/m^3.

Conclusions

The conclusion of the report was that despite the levels of MWF mist, there was a high incidence of respiratory symptoms and skin complaints in those workers exposed to MWF, and it was therefore recommended that efforts should be made to further lower exposure where possible.

Achutan, C. N. 2003 [311]

Background

This involved an investigation (HETA 2003-0175-3033*)* of a workplace manufacturing steel bars and coils, which employed 50 staff in the production area. The NIOSH investigation was in response to concerns expressed by Union representatives about poor ventilation in the factory. Two different MWFs were used at this plant; a straight oil, and an oil water mix, which also contained 3% triethanolamine.

Methods and results

Fifty workers were identified as exposed to MWFs with some additional workers (for example forklift truck drivers) also considered as having limited exposure to MWFs. Thirty five of the exposed workers participated in a medical review and their median length of employment was 18 years. Respiratory symptoms were present in 66% of the interviewed workers (23/35) of which fourteen complained of upper airways problems, six suffered from bronchitis, three had been diagnosed with pneumonia, and two workers reported that their asthma symptoms had deteriorated since working

for the company. Thirty one percent of those interviewed (11 of the 35) complained of skin rashes.

Environmental monitoring included area and personal breathing zone samples for detection of respirable particulates from soap powder, crystalline silica, MWF, and acid mists. Four bulk samples were taken for microbiological examination and *Burkholderia* spp, *Enterobacter* spp and *Pseudomonas* spp were identified but no *Mycobacteria sps*. Endotoxin levels of 4.2 x 10^5 EU/ml were measured in these MWFs.

Conclusions

The report concluded that the employees were exposed to excessive levels of MWF mist, and recommended reductions in mist levels, linked with medical surveillance.

Tapp, L. et al. 2005 [312]

Background

This investigation (HETA 2005-0227-3049) was of a large factory producing bicycle chains. The factory site covered 600,000 ft^2 and employed five hundred and twenty staff, with approximately 40 exposed to MWF. NIOSH started the investigation after receiving a request from union representatives to investigate complaints of skin rash among the staff. Medical records of two employees were reviewed and documented a previous diagnosis of allergic dermatitis, and irritant dermatitis, which had patch tested positive to colophony resin, abeitic acid and bioban.

Methods and results

Thirty-four workers were identified for interview, and twelve reported that their rash had appeared when the MWF was changed three years previously. All twelve had a diagnosis of dermatitis but only six had an active rash on examination. Two of the twelve also reported respiratory problems but these were not investigated further.

Industrial hygiene investigations included bulk samples of used and unused MWF and of the biocides in use. Several of the MWFs were found to contain formaldehyde and formaldehyde producing chemicals (e.g. triazines), which are known to cause skin irritation and for some workers, allergic reactions. Improper work practices

leading to dermal exposure were observed and these were thought to have contributed to the high numbers with skin disease.

Conclusions

NIOSH recommended that poor maintenance and training were leading to excessive dermal exposure and therefore skin complaints.

Outbreaks of skin disease associated with MWF reported in the USA

Four outbreaks of skin disease with no documented respiratory disease were identified in this review of the literature. Three of these investigations were undertaken by NIOSH. The estimated number of exposed workers in each factory was documented in only one of these reports where there was an exposed population of one hundred and forty workers. Two of the four factories manufactured car parts, one made hydraulic pumps, and the fourth produced air compressors. The NIOSH medical investigations were based on interviewing a selection of the workers. In the one independent investigation a larger proportion of the work force was asked to report symptoms using a questionnaire. Across these four plants different MWFs were used, straight oils, soluble oil, semi synthetic and synthetic MWFs, although one report did not identify the type of MWF used.

Gupta, S. L. et al. 1989 [313]

Background

In December 1986 NIOSH were asked to evaluate a factory manufacturing hydraulic pumps (HETA 87-092-1967*)*. The request was prompted by cases of dermatitis thought to be due to MWFs, although the type of MWF used was not specified in the report.

Methods and results

There were one hundred and forty workers who were exposed to MWFs and of these fifty-five were interviewed and examined. Thirty-four of the fifty-five reported having dermatitis and of these thirty had reported their skin complaint during the preceding four months. Most of the dermatitis was located on the workers' hands, neck and

face. Examination identified chronic changes of lichenification and acute inflammatory eczema.

Patch tests were carried out on twenty-six symptomatic workers. One worker tested positive to one of the MWFs used in the factory, another tested positive to one of the biocides used in the MWF, and two subjects reacted weakly to a different type of MWF. It is not clear whether new or used MWF samples were used in the patch testing. At the time of the outbreak of skin disease, the MWF was noted to be green/brown and foul smelling, but there were no environmental or microbiological investigations.

Conclusions

The authors concluded that most of the workers were suffering irritant dermatitis rather than allergic dermatitis. It was felt that this was most likely due to exposure to bacterial contamination and decomposition of various coolants. NIOSH advised improved fluid maintenance, employee education, hazard communication, personal protection and a medical program designed to decrease the incidence of dermatitis.

Donavan Reh, B. et al. 1995 [314]

Background

This was an investigation of a plant that manufactured automotive aluminum castings. The number of workers employed was not documented. The investigation was initiated by skin complaints of irritation and infection, along with upper and lower respiratory tract symptoms. These were attributed to the use of water mix MWF (HETA 95-0153-2549).

Methods and results

After reviewing work practices, air samples were taken to monitor levels of oil mist and formaldehyde. Formaldehyde samples were all less than 0.06 ppm. The oil mist samples had a total particulate weight of 0.27 mg/m^3 and 0.47 mg/m^3 (below the NIOSH REL of 0.5 mg/m^3). Microbiological tests for the MWF samples identified gram-negative bacteria, specifically *Pseudomonas* spp and related species. Bacteria counts in bulk samples ranged from 9.8×10^5 to 9.8×10^7 cfu/ml.

Eight workers were randomly selected for interview but the method of randomisation was not detailed in the report. All of the interviewed workers complained of rashes on exposed areas such as hands, arms and face, but none of them complained of respiratory symptoms. Injury and illness records for the previous year collected by OSHA identified only sprain injuries and one reported case of rash. Of the eight workers that reported rash, five presented with visible evidence of a rash on the day of the survey. No further medical assessment of the rashes was documented.

Conclusions

Recommendations from the investigation were to reduce dermal contact with the MWF and to use protective clothing.

Donovan Reh, B. P et al. 2000 [390]

Background

This investigation (HETA 2000-0356-2851) involved a large company with three hundred and fifty employees who produced air compressors and who were using a combination of straight, synthetic, semi synthetic and water soluble MWFs. The investigation was instigated when several employees reported skin problems to the management. The company then consulted an occupational dermatologist who recommended that exposure to potential skin irritants be reduced. Despite these recommendations workers continued to report problems with their skin and so NIOSH were contacted and began their investigation in August 2000.

Methods and results

The investigating team selected twelve workers for interview, and this group had a mean duration of employment at the plant of thirteen years. Five of this group were selected because they had reported dermatitis and a further seven participants were identified by the Union. At the time of interview five of the twelve participants had a skin rash and two of these were diagnosed with eczema and one with folliculitis. Two of the five workers, both of who were assemblers, had dermatitis on their forearms. Based on rashes observed on the day of the site visit, it was thought that the type and aetiology of the eruption might vary. It was concluded that a single cause of the rashes was unlikely but that limiting contact of skin with MWFs would minimize work-

related exacerbations of dermatitis. The report did not mention whether the staff had reported respiratory symptoms.

Environmental sampling was undertaken which included air and personal breathing zone (PBZ) sampling. The total particulate count, thoracic particulate and extractable MWF content were analysed and real time particulate concentration was also determined, along with PBZ to determine content of volatile organic compounds (VOC). Over half of the MWF particulate samples concentrations were over the recommended NIOSH limit (REL) of 0.5mg/m^3 and the real time data suggested that a large percentage of the particulate mass concentration was in the respirable range. Bulk fluid samples also were collected for microbiological analysis and *Pseudomonas spp* and *Citrobacter* spp were identified, without any evidence of fungi or mycobacteria.

Conclusions

The NIOSH report concluded that a single cause for the different skin diseases was unlikely but they advised staff to minimise their dermal exposure to MWFs, washer detergents and rust inhibitors. They also recommended workers with skin problems to consult a dermatologist

Awosika-Olumo, A. L. 2003 [316]

Background

This investigation was of a car component factory in Ohio that used water mix synthetic, and semi synthetic MWFs. The size of the workforce was not documented. This investigation was precipitated by two cases of dermatitis and was a cross sectional study. The date of the sentinel case was not reported, but the publication was in 2003.

Methods and results

A self-administered questionnaire was given to forty-five workers considered as exposed to MWFs and to a group of thirty-six non-exposed controls. A trained field investigator examined all of the workers involved in the production operations. Seventy-one staff adequately completed the questionnaire, and twenty-one (26%) of

these complained of skin symptoms. Twenty of the twenty-one complaining of skin disease were exposed to MWFs.

Workers exposed to MWFs were more likely to suffer from allergies than the non-exposed workers ($p<0.001$). Twenty-two percent of the exposed workers had a past medical history of allergy, compared to 3% of the unexposed. Five workers with dermatitis underwent patch testing against a panel of chemicals including alcohols, isocyanates and a number of substances from the workplace. All five had negative results, suggesting that the dermatitis was not allergic. Exposure to MWF was a significant predictive factor for dermatitis, with 60% of the exposed manifesting symptoms but only 6% of the unexposed. The odds ratio for exposure to MWF was 11.9 ($df=1$; $p<0.001$).

Bacteria and yeasts were isolated from environmental samples but the same species were not isolated from the skin of affected workers. It was noted that nine of the twenty one workers used a plastic abrasive cleaning pad to wash their hands, and that workers with higher exposures to MWF had a higher incidence of skin disease with the hands being the most commonly affect dermal site.

Conclusions

Recommendations were made to limit dermal exposure using good hygiene practice.

Outbreaks of ill health associated with MWF reported in the UK

Three UK outbreaks of respiratory disease were identified in the literature review, but these three incidents were very different. The initial report involved several cases of occupational asthma associated with exposure to MWF. This report preceded the reported outbreaks of EAA associated with MWFs but did involve the use soluble water mix MWF and not straight oil [261 278]. The second report was of a large outbreak of 'mixed' respiratory disease that involved a thorough investigation [260]. The later report was a minimal investigation of a site using MWFs where the prevalence of respiratory symptoms was high [304].

Robertson, A. S. et al. 1988 [261]

Background

Hendy, M. S. et al. described one of the first reported cases in the UK of OA secondary to MWF in 1983 [278]. Subsequently in 1998, Robertson et al. included this case report in a collection of twenty five patients occupationally exposed to MWFs and who had been referred to an occupational respiratory clinic with work-related asthmatic symptoms [261]. The report did not clarify whether these papers referred to an outbreak from one particular site, or whether they have been included as a collection of separate cases of MWF exposed workers with respiratory disease.

Methods and results

The twenty-five patients included in the case series had been identified following clinic referral. They were assessed using history taking, clinical examination, spirometry, skin prick testing, and serial two hourly peak flow analysis. All but one worker was exposed to water-soluble MWF rather than straight mineral oil. Six of the patients undertook bronchial provocation tests to used and unused MWFs. The bronchial provocation testing with clean MWF showed a progressive deterioration in peak flow in three of the six subjects. Deterioration after only one day of bronchial provocation was seen in only one subject and only to used MWF. One subject one reacted to a pine reoderant used in the MWF.

Of the twenty-five patients assessed, thirteen had definite work-related asthma and equivocal evidence for work-related asthma was found in another seven staff. A

further three staff had asthma unrelated to work and the remaining two staff were normal.

Conclusions

This study concluded that OA due to oil mist was common, and that the agent responsible was variable.

Roberston A. S et al. 2005 [391 260]

Background

This paper summarised the largest reported outbreak of respiratory disease in the UK due to MWF at a car manufacturing plant in Birmingham. This part of the plant investigated (120,000 m^2) was involved in the production of aluminium alloy or cast iron car engine parts as well as the assembly of engines. The machining process used MWF (oil water emulsions with chemical additives including biocides) but during use the MWF had became contaminated by lubricating and hydraulic oil (tramp oil). Transfer machines performing a number of sequential machining operations dominated the northern half of this building. Metal working fluids from large sumps of 210,000, 55,000 and 19,000 litres capacity lubricated these machines. Individual metalworking and transfer machines with their own sumps predominated the southern half of the factory. After machining the components were washed in twenty dedicated machines spread around the factory. The company employed 832 workers (33 subcontractors, 799 direct employees) and there were an additional four workers who were on sick leave because of EAA, making a total of 836. Employees were assigned to one of fifty-seven operational codes, which in most cases were closely linked to a specific workplace.

Methods and results

Hygiene data from previous HSE investigations at the plant included air samples for mist generation as well as bulk samples of used metal working fluids, sumps, tramp oil and machine wash solutions which were subjected to microbiological tests. Results of air monitoring between May 2002 and October 2003 showed that concentrations of metalworking fluid concentrate in air were generally below the then HSE guidance value of 1mg/m^3. In October 2003, levels were between 1 and 4 mg/m^3 with an average concentration of just above 1 mg/m^3. Personal samples

taken at the same time indicated exposures of between 1 – 1.7 mg/m^3, with an average exposure of 1.3 mg/m^3. Samples of MWF from the largest common sump showed no viable bacterial, mycobacterial or fungal growth, and no increase in endotoxin levels. *Acinetobacter spp* and *Ochrobactrum anthropi* were identified in the main common sump on the basis of DNA evidence and they were isolated as cultures from wash machine samples.

In addition, information collected by the stewardship company that managed the MWF sump supplies included data on changes to pH, MWF concentration, tramp oil contamination and microbial growth (monitored using dip slide tests). Factory records showed a steep rise in tramp oil contamination of MWF in the large communal sump around April 2003, just after the hydraulic oil used in machines was changed. The rise in tramp oil bore a temporal relationship with the onset of workers reporting breathlessness. The factory records also indicated that there was an oil leak in March 2003, which may have contributed to the outbreak of disease.

Twelve employees from the plant were clinically diagnosed as having EAA from 2003 to May 2004 and this led to the UK Health & Safety Executive starting an incident investigation in May 2004. Most of the twelve reported that their symptoms had started during the previous springtime. Staff from Birmingham Heartlands Trust hospital carried out the clinical investigation.

This investigation involved four phases:

- In the first phase 808 of the 836 (i.e., 96.7%) of the workers completed a 'self reporting' symptom questionnaire. The results of this phase demonstrated a prevalence of 9.3% for occupational bronchitis, 18.6% for work-related asthma and 2.1% for humidifier fever.
- In the second phase, 481 (60%) workers who had complained of at least one respiratory symptom and forty-eight out of fifty (i.e., 96%) asymptomatic employees agreed to participate in further investigations.
- In phase three, based on the results of the initial clinical assessment, one hundred and sixty one workers were seen for more detailed investigation at the Birmingham Chest Clinic. This included pulmonary lung functions, chest

x-rays, methacholine challenge tests (for bronchial hyperreactivity), skin prick tests for common environmental allergens, and high-resolution computer tomography (HRCT). Out of all the symptomatic workers one hundred and ninety eight returned peak flow records.

- In phase four, case definitions for extrinsic allergic alveolitis (EAA) and occupational asthma (OA) were applied to define cases that met predefined objective criteria with onset of disease after January 2003.

Based on clinical opinion, one hundred and two workers were diagnosed with probable or definite occupational lung disease including twenty-four with EAA, eighty-eight with OA and seven with humidifier fever (some with more than one diagnosis). Fifteen workers were diagnosed with occupational chronic bronchitis and three workers were diagnosed with other respiratory conditions.

Applying diagnostic criteria (based on that used by Fox et al. [1]), nineteen workers were finally diagnosed with EAA. Using criteria for the diagnosis of OA based on a peak flow records in 2003-05 (i.e., an OASYS score of at least 2.67 and/or a mean day interpreted difference between work and rest days of at least 16 l/min) seventy-four workers had serial peak flow recordings consistent with OA. Half of these experienced an onset of asthma like symptoms since January 2003. Eight of the seventy-four OA cases with a positive peak flow diary also met the diagnostic criteria for EAA. Considering the overlap of symptoms, 10.4% of the workforce met case definitions for at least one occupational respiratory disease.

Comparing the control group to the workers with EAA, or with OA, no difference in smoking history, demographic characteristics, or the length of employment was observed. When the cases of illness were mapped to the area of the factory (using operational codes) it was found that 97% of the workers with OA and 100% of the workers with EAA had worked in the manufacturing area compared to 61% of the control group.

Specific bronchial challenge tests were carried out on two individuals, with a positive challenge being defined as a fall in forced expiratory volume in 1 sec (FEV_1) of

>15%. One of the workers with EAA was challenged with 'used' and 'unused' MWF and demonstrated a positive response only to the used MWF.

A total of one hundred and ninety three staff consented to give a peripheral blood sample including those who were symptomatic, non-symptomatic but exposed; and a group of non-exposed staff. In addition another sixty-five blood samples from healthy non-exposed staff working at another organisation were included for comparison. Immunological tests were then carried out to provide evidence of sensitisation status as well as evidence of inflammatory reactions in those exposed to metal working fluids. Ouchterlony double diffusion gel precipitation tests were used to detect precipitating immunoglobulin G (IgG) antibodies to the prepared extracts of oils, washes and bacteria. The precipitin tests were carried out against *Ochrobactrum* spp and *Acinetobacter* spp derived from MWF, and which had been identified in the original sump oil sample from the Powertrain plant. In addition, species of mycobacteria (*Mycobacterium immunogenum, Mycobacterium chelonae* and *Mycobacterium fortuitum*) were included in the test panel to compare with the results of studies from the USA even though there was no evidence of their presence in MWF samples from Powertrain. Of the EAA cases, 59% had precipitating antibodies to at least one of the microbial species compared to only 10% of the workers with OA and 5% of the controls. No workers tested positive to mycobacteria.

Specific IgE levels to common environmental allergens (Phadiatop – atopy) and to 'mixed' fungi (*Penicillium notatum, Cladosporium herbarum, Aspergillus fumigatus* and *Alternaria alternata*) were determined for individuals participating in the study using the automated UniCAP system. It was concluded that the balance of evidence suggested that contaminated MWF, and the bacterial contaminants *Acinetobacter* spp and *Ochrobactrum* spp had a contributory role in the development of occupational EAA at the Powertrain factory. The presence of precipitating antibodies in most of the symptomatic workers was not taken as proof that bacterial agents caused the development of this condition. Since the tests were only carried out against two specific organisms it remained a possibility that untested organisms were also involved in the development of EAA. The role of other chemical constituents (including biocides) of the used MWF and wash solutions in the development of these cases of EAA and OA remained unresolved.

Conclusions

On completion of this investigation no further work was carried out because the plant subsequently ceased production in 2005

Fishwick, D. et al. 2005 [304]

Background

This investigation involved a small engineering plant where less than 50 workers were employed in machining small components. Twenty-one of the workers were exposed to water soluble MWFs. The investigation started after one worker was diagnosed with EAA.

Methods and results

All of the workers gave written consent to participate and eleven of the exposed workers were assessed. Six of the exposed workers completed a demographic and respiratory symptom questionnaire, as well as spirometry and three of them provided peripheral blood samples. Two of the group underwent more detailed clinical investigation. The mean age of the workers undergoing evaluation was 46 years.

Seventy-five percent of the workers completing the questionnaire complained of work-related respiratory symptoms, and fifty percent complained of ocular and nasal irritation as well as work-related cough, shortness of breath or chest tightness. Two individuals reported respiratory and flu like symptoms and six workers underwent spirometry but no abnormal patterns were recorded. Precipitating IgG antibodies to used MWF were detected in serum samples from three workers with work-related respiratory symptoms. Precipitating IgG to extracts of *Pseudomonas* spp were detected in four workers, two of who had work-related symptoms. No precipitating antibodies to used MWF or extracts of *Pseudomonas* spp were detected in the unexposed control subjects.

Samples of MWF were taken from the sump of each machine. On the initial visit to the site, biofilm was present on the MWF in the sump; this was sampled and grew *Fusarium* spp. On future visits, this biofilm had reduced. A total of fifteen samples of MWF were collected and whilst half yielded less than 100 CFU/ml bacteria, others

yielded as high as 8.2 x 10^6 CFU/ml. The samples contained up to 2200 CFU/ml of fungi and endotoxin levels ranged from 56 to 680 EU/ml. Air sampling identified *Pseudomonas fluorescens* but endotoxin levels were below the limit of detection.

This investigation was limited in its scope due to a clean-up operation that began before the workplace could be fully evaluated. Three of the eight staff interviewed spontaneously reported improvements in their symptoms following the changes in the working environment.

Conclusions

The authors recommend that physicians and public health professionals remain vigilant to the possible respiratory illness caused by the bio aerosol of contaminated MWF.

Outbreaks of ill health associated with MWF reported in mainland Europe

Despite cases of ill health being reported to surveillance schemes in Europe, few publications related to outbreak investigations were identified during the search of the literature.

Outbreaks in Croatia

Jaksic, S. 1998 [309]

Background

A paper was published referring to an automobile production plant in Croatia, where an increase in staff exposed to MWF who complained of ill health was reported. The first cases were observed in the spring and summer of 1992.

Methods and results

Eighteen workers were diagnosed with bronchitis and thirty-eight with skin infections of the hands and face. In total thirty-eight workers required medical care. The MWF was described as an emulsion. One hundred and fifty samples of the MWF were taken and examined for microbial growth. Several bacteria were isolated, most frequently *Pseudomonas spp, Escherichia Coli* and *Proteus spp*. The total bacterial

colony count in the tested samples was relatively high, and in most samples amounted to 3 x 10^5 CFU/ml. Moulds and yeasts were also isolated from all of these samples.

Conclusions

The conclusion of the paper was that the cause for the ill health associated with MWF was microbial infection.

Appendix 2

Powertrain questionnaire phase 2

Respiratory Survey June 2004

Thank you for taking part in this survey of [Company Name]. Please complete all of the questions. If you are not sure what a question means then please ask one of the survey team. If you are not sure whether you have had a symptom or not, please answer "no"
Thank you for your help.

First Names……Last Name……

Date of Birth…… Payroll Number……

Address……

……..

……

Cost Centre…….. Area of Work……..

General Practitioner……..

Address……

……

……

Sex(Please circle) Male / Female

Date……/…../…….

Job History

1) Current employer

[Company Name 1] ☐ [Company Name 4] ☐

[Company Name 2] ☐ [Company Name 5] ☐

[Company Name 3] ☐ [Company Name 6] ☐

Other ☐…..(specify)…….

2) When did you first start working in [Problem Area]

Month ☐ Year ☐

3) On average, how many hours do you work in a week? ☐☐Hrs

4) Where were you working in [Problem Area]

in January 2003?.....

5) Do you mostly work in the manufacturing areas? Yes ☐ No ☐

6) Have you ever worked on a machine that uses coolant oils?

Yes ☐ No ☐

If "No" Go To Question 11

7) When did you start working on a machine that uses coolant oils?

Month ☐ Year ☐

8) Do you currently work on a machine(s) that uses coolant oils?

Yes ☐ No ☐

10) If NO when did you last work on a machine that uses coolant oils

Month ☐ Year ☐

Cigarette Smoking

11) Do you smoke? Yes ☐ No ☐

If **YES** go to Ques 14

12) Have you ever smoked as much as one cigarette a day, or one cigar a week, or one ounce of tobacco a month for as long as a year?

Yes ☐ No☐

If NO go to Question 19

13) How long ago did you give up smoking all together? Years☐Months☐

14) How old were you when you started smoking? Years☐Months☐

15) Do (did) you smoke manufactured cigarettes? Yes ☐ No ☐

If NO go to Ques 17

If YES 16) How many per day? ☐ How many years?... ☐.....

17) Did you smoke something else? Yes ☐ No ☐

If YES 18) How much per week? ☐ How many years?... ☐.....

Symptom – Shortness of Breath.

19) Are you are disabled from walking by a disease **other than** heart or lung disease Yes ☐ No ☐

If "YES" Go To Question 35

If "No" - On your worst day in the last 12 months;-

20) Were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill ? Yes ☐ No ☐

If "No" Go To Question 35

If Yes 21) Did you get short of breath walking with other people of your own age and sex on level ground? Yes ☐ No ☐

If "No" Go To Question 24

If "Yes" 22) Did you have to stop for breath when walking at your own pace on level ground? Yes ☐ No ☐

If "No" Go To Question 24

If "Yes" 23) Were you short of breath when washing or dressing? Yes☐ No ☐

24) On how many days do you have breathlessness? (Tick one only)

Never ☐
Less than monthly ☐
At Least monthly ☐
At least once a week ☐
At least once a day ☐
More frequently ☐

25) Are you breathless on waking? Yes ☐ No ☐
26) Are you breathless during the day? Yes ☐ No ☐
27) Are you woken from sleep by your breathlessness? Yes ☐ No ☐

Is your breathlessness worse ;

28) At the beginning of the working week? Yes ☐ No ☐

29) At the end of the working week? Yes ☐ No ☐

30) No difference? Yes ☐ No ☐

31) On days away from work is your breathlessness (Tick one only)

Better ☐
The same ☐ than days at work
Worse ☐

32) On holidays is your breathlessness (Tick one only)

Better ☐
The same ☐ than days at work
Worse ☐

33) When did you first develop breathlessness? Month ☐ Year ☐

34) Do you suffer from breathlessness at present? Yes ☐ No ☐

Symptom – Cough.

35) Do you cough? Yes☐ No ☐
If "No" Go To Question 46

36) When did you first develop a cough? Month ☐Year ☐

37) On how many days do you cough (Tick one only)

Never	☐
Less than monthly	☐
At Least monthly	☐
At least once a week	☐
At least once a day	☐
More frequently	☐

38) Do you cough on waking? Yes ☐ No ☐
39) Do you cough during the day? Yes ☐ No ☐
40) Are you woken from sleep by your cough? Yes ☐ No ☐

Is your cough worse ;

41) At the beginning of the working week? Yes ☐ No ☐
42) At the end of the working week? Yes ☐ No ☐
43) No difference? Yes ☐ No ☐

44) On days away from work is your cough (Tick one only)

Better	☐	
The same	☐	than days at work
Worse	☐	

45) On holidays is your cough (Tick one only)

Better	☐	
The same	☐	than days at work
Worse	☐	

Symptom – Phlegm (Sputum)

46) Do you cough up phlegm (sputum) from your chest? Yes☐ No ☐

If "No" Go To Question 58

47) Do you do this for at least 3 months each year? Yes☐ No ☐

48) Have you been doing this for the last 2 years or more? Yes☐ No ☐

49) On how many days do you cough up phlegm from your chest

(Tick one only)

Never	☐
Less than monthly	☐
At Least monthly	☐
At least once a week	☐
At least once a day	☐
More frequently	☐

50) Do you cough up phlegm on waking ? Yes ☐ No ☐

51) Do you cough up phlegm during the day? Yes ☐ No ☐

Is your phlegm production worse ;

52) At the beginning of the working week? Yes ☐ No ☐

53) At the end of the working week? Yes ☐ No ☐

54) No difference? Yes ☐ No ☐

55) On days away from work is your phlegm (Tick one only)

Better	☐	
The same	☐	than days at work
Worse	☐	

56) On holidays is your phlegm (Tick one only)

Better	☐	
The same	☐	than days at work
Worse	☐	

57) When did you first develop phlegm? Month ☐ Year ☐

Symptom – Eyes

58) In the past twelve months have you had more than two episodes of irritation or watering of the eyes? Yes☐ No ☐

If "No" Go To Question 62

59) On how many days do you have this?

(Tick one only)

Never	☐
Less than monthly	☐
At Least monthly	☐
At least once a week	☐
At least once a day	☐
More frequently	☐

60) On days away from work is this (Tick one only)

Better	☐	
The same	☐	than days at work
Worse	☐	

61) On holidays is this (Tick one only)

Better	☐	
The same	☐	than days at work
Worse	☐	

Symptom – Nasal

62) In the past twelve months have you had more than two episodes of blocked or stuffy nose? Yes☐ No ☐

If "No" Go To Question 66

63) On how many days have you had this?

(Tick one only)

Never	☐
Less than monthly	☐
At Least monthly	☐
At least once a week	☐
At least once a day	☐
More frequently	☐

64) On days away from work is this (Tick one only)

Better	☐	
The same	☐	than days at work
Worse	☐	

65) On holidays is this (Tick one only)

Better	☐	
The same	☐	than days at work
Worse	☐	

Symptom –Throat

66) In the past twelve months have you had more than two episodes of a dry or sore throat? Yes☐ No ☐

If "No" Go To Question 70

67) On how many days do you have this?

(Tick one only)

Never	☐
Less than monthly	☐
At Least monthly	☐
At least once a week	☐
At least once a day	☐
More frequently	☐

68) On days away from work is this (Tick one only)

Better	☐	
The same	☐	than days at work
Worse	☐	

69) On holidays is this (Tick one only)

Better	☐	
The same	☐	than days at work
Worse	☐	

70) How many days off work have you had in the last 12 months due to chest illness? Days ☐☐☐

Past Illnessess

71) Have you ever had any chest illnesses? Yes ☐ No ☐
Specify…….

72) Are you taking any treatment for your chest? Yes ☐ No ☐
Specify.....

73) Have you ever had a lymphoma? Yes ☐ No ☐

74) Have you lost weight since [Likely Start of Outbreak] Yes ☐ No ☐

Symptom – Asthma

75) Has any doctor told you that you have asthma? Yes ☐ No ☐

76) In the last 12 months has your chest ever felt tight or your breathing become difficult? Yes☐ No ☐

If "No" Go To Question 87

77) When did you first develop this? Year ☐ Month ☐

78) On how many days do you had this (Tick one only)

Never	☐
Less than monthly	☐
At Least monthly	☐
At least once a week	☐
At least once a day	☐
More frequently	☐

79) Do you have this on waking? Yes ☐ No ☐

80) Do you have this during the day? Yes ☐ No ☐

81) Are you woken from sleep by this? Yes ☐ No ☐

Is this worse ;

82) At the beginning of the working week? Yes ☐ No ☐

83) At the end of the working week? Yes ☐ No ☐

84) No difference? Yes ☐ No ☐

85) On days away from work is this (Tick one only)

Better ☐
The same ☐ than days at work
Worse ☐

86) On holidays is your this (Tick one only)

Better ☐
The same ☐ than days at work
Worse ☐

87) In the past 12 months have you had wheezing or whistling in your chest?
Yes☐ No ☐
If "No" Go To Question 98

88) When did you first develop this? Year ☐..Month ☐

89) On how many days do you have this? (Tick one only)

Never ☐
Less than monthly ☐
At Least monthly ☐
At least once a week ☐
At least once a day ☐
More frequently ☐

90) Do you have this on waking? Yes ☐ No ☐
91) Do you have this during the day? Yes ☐ No ☐
92) Are you woken from sleep by this? Yes ☐ No ☐

Is this worse ;

93)At the beginning of the working week? Yes ☐ No ☐
94) At the end of the working week? Yes ☐ No ☐
95) No difference? Yes ☐ No ☐

96) On days away from work is this (Tick one only)

Better	☐	
The same	☐	than days at work
Worse	☐	

97) On holidays is this (Tick one only)

Better	☐	
The same	☐	than days at work
Worse	☐	

Symptom –'Flu

98) In the past twelve months have you suffered recurrent flu like symptoms?

Yes☐ No ☐

If "No" you have now completed the questionnaire.

If yes please specify the symptoms below;

99) Fever Yes☐ No ☐
100) Shivering Yes☐ No ☐
101) Tiredness Yes☐ No ☐
102) Weakness Yes☐ No ☐
103) Joint/ muscle pains Yes☐ No ☐

104) How many episodes have you experienced in the last year? Number☐

105) How long did these symptoms last

Less than 72 hours Yes☐ No ☐
More than 72 hours Yes☐ No ☐

106) Do these symptoms occur more frequently after doing a particular job?

Yes☐ No ☐

If Yes specify…….

107) Do these symptoms occur;

At the beginning of the working week? Yes ☐ No ☐
At the end of the working week? Yes ☐ No ☐
No difference? Yes ☐ No ☐

108) Do these symptoms occur more frequently or are more severe on returning to work after a;

Weekend break from work Yes ☐ No ☐
Holiday break from work Yes ☐ No ☐

Doctor Diagnosis

200) Exposure category

High (Working with suds oil) ☐ Low (Visits area only) ☐
High (cleaning) ☐ None (Never in production area) ☐
Medium (In suds area – not directly working) ☐

201) Asthma No /Possible/ Probable/ Definite

202) Occupational Asthma No /Possible/ Probable/ Definite

203) Rhinitis No /Possible/ Probable/ Definite

204) Alveolitis No /Possible/ Probable/ Definite

205) Humidifier Fever No /Possible/ Probable/ Definite

206) Chronic Bronchitis No /Possible/ Probable/ Definite

Needs peak flows Yes ☐ No ☐

Would you like us to send your results to your General Practitioner
Yes ☐ No ☐
Would you like us to send your results to the Occupational Health Dept?
Yes ☐ No ☐

Signed……
Advised needs appointment at Chest Clinic? Yes ☐ No ☐
Known case Y?N

Currently being seen Yes ☐ No ☐
where?.....
.....
Permission to write? Yes ☐ No ☐Signed……
Physician ……

Spirometry

First Names……Last Name……..

Date of Birth…… Payroll Number……

Height……cms Sex(Please circle) Male / Female

Spiro Completed Yes ☐ No ☐

Quality check…….. Yes ☐ No ☐

Ethnic Race (Please tick box)

White ☐ Afro-caribbean ☐ Oriental.☐ Asian ☐

Other ……. ☐

Blood taken…… Yes ☐ declined ☐ too difficult ☐

Already done adequate peak flows Yes ☐ No ☐

Given peak flow cards Yes ☐ No ☐

Given peak flow meter Yes ☐ No ☐

Information Sheet

As you may know there have been several workers at [Company Name] who have a chest problem that may be caused by their work. We are trying to find out how common this is and what the cause is. We would like your help.

Many workers are exposed to coolant oils without problems. There have, however, been outbreaks of lung inflammation (alveolitis) in factories similar to [Company Name] in the USA, which have been caused by impurities in the used cooling oil. We are trying to find out if this is the cause at [Company Name]. The best method is to see if you are allergic to the oil from blood tests. Please would you complete the questionnaire and then have breathing and blood tests. Then you will be seen by a specialist who will tell you what we have found.

This is a confidential study, your personal results will not be shown to anybody without your permission. We will send the results to you personally. If you want your results sent to your GP and/ or Occupational Health we will do so. This is often the best way forward if you are ill.

Many thanks.

Prof Sherwood Burge

Dr Alastair Robertson

Birmingham Chest Clinic, Solihull and Birmingham Heartlands NHS Trust

Appendix 3

Phase 1 questionnaire calculations

Qu 1: In the past 18 months, have you had any episodes of wheeze or chest tightness?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	13	323	336
	No	1	466	467
	Total	14	789	803

Sensitivity = 13/14 x 100
Sensitivity = 93%

Specificity = 466/789 x 100
Specificity = 59%

Positive predictive value = 13/336 x100
Positive predictive value = 4%

Negative predictive value = 466/467 x 100
Negative predictive value = 100%

Qu 2: In the past 18 months, have you taken any treatment for your chest?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	14	151	165
	No	0	639	639
	Total	14	790	804

Sensitivity = 14/14 x 100
Sensitivity = 100%

Specificity = 639/790 x 100
Specificity = 81%

Positive predictive value = 14/165 x100
Positive predictive value = 8%

Negative predictive value = 639/639 x 100
Negative predictive value = 100%

Qu 3: In the past 18 months, have you woken at night with a cough or chest tightness?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	14	251	265
	No	0	538	538
	Total	14	789	803

Sensitivity = 14/14 x 100
Sensitivity = 100%

Specificity = 538/789 x 100
Specificity = 68%

Positive predictive value = 14/265 x 100
Positive predictive value = 5%

Negative predictive value = 538/538 x 100
Negative predictive value = 100%

Qu 4: In the past 18 months, have you had any episodes of breathlessness?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	13	235	248
	No	1	552	553
	Total	14	787	801

Sensitivity = 13/14 x 100
Sensitivity = 93%

Specificity = 235/787 x 100
Specificity = 30%

Positive predictive value = 13/248 x100
Positive predictive value = 5%

Negative predictive value = 552/553 x 100
Negative predictive value = 100%

Qu 5: In the past 18 months, have you had any time off with a chest illness?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	14	92	106
	No	0	698	698
	Total	14	790	804

Sensitivity = 14/14 x 100
Sensitivity = 100%

Specificity = 698/790 x 100
Specificity = 88%

Positive predictive value = 14/106 x100
Positive predictive value = 13%

Negative predictive value = 698/698 x 100
Negative predictive value = 100%

Qu 6: In the past 18 months, have you developed chest tightness or breathlessness after exercise?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	13	293	306
	No	1	493	494
	Total	14	786	800

Sensitivity = 13/14 x 100
Sensitivity = 93%

Specificity = 493/786 x 100
Specificity = 63%

Positive predictive value = 13/306 x100
Positive predictive value = 4%

Negative predictive value = 493/494 x 100
Negative predictive value = 100%

Qu 7: In the past 18 months, have you developed difficulty with breathing?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	13	162	175
	No	1	620	621
	Total	14	782	796

Sensitivity = 13/14 x 100
Sensitivity = 93%

Specificity = 620/782 x 100
Specificity = 79%

Positive predictive value = 13/175 x100
Positive predictive value = 7%

Negative predictive value = 620/621 x 100
Negative predictive value = 100%

Qu 8: In the past 18 months, have you had irritation or watering of the eyes?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	9	317	326
	No	5	469	474
	Total	14	786	800

Sensitivity = 9/14 x 100
Sensitivity = 64%

Specificity = 469/786 x 100
Specificity = 60%

Positive predictive value = 9/326 x100
Positive predictive value = 3%

Negative predictive value = 469/474 x 100
Negative predictive value = 99%

Qu 9: In the past 18 months, have you had a stuffy nose?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	9	480	489
	No	5	303	308
	Total	14	783	797

Sensitivity = 9/14 x 100
Sensitivity = 64%

Specificity = 303/783 x 100
Specificity = 39%

Positive predictive value = 9/489 x100
Positive predictive value = 2%

Negative predictive value = 303/308 x 100
Negative predictive value = 98%

Qu 10: In the past 18 months, have you had any soreness of the nose lips or mouth?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	6	223	229
	No	8	561	569
	Total	14	784	798

Sensitivity = 6/14 x 100
Sensitivity = 43%

Specificity = 561/784 x 100
Specificity = 72%

Positive predictive value = 6/229 x100
Positive predictive value = 3%

Negative predictive value = 561/569 x 100
Negative predictive value = 99%

Qu 11: In the past 18 months, have you had any unexplained weight loss?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	11	33	44
	No	3	753	756
	Total	14	786	800

Sensitivity = 11/14 x 100
Sensitivity = 79%

Specificity = 753/786 x 100
Specificity = 96%

Positive predictive value = 11/44 x100
Positive predictive value = 25%

Negative predictive value = 753/756 x 100
Negative predictive value = 100%

Phase 2 questionnaire calculations

Shortness of breath

Questions 24 and 33 are not included as the responses are in the style of continuous data and therefore the sensitivity, specificity, positive predictive value and negative predictive value cannot be calculated.

Qu 20: On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	14	212	226
	No	0	275	275
	Total	14	487	501

Sensitivity =14/14 x 100

Sensitivity = 100%

Specificity = 275/487 x 100

Specificity = 56%

Positive predictive value = 14/226 x100

Positive predictive value = 6%

Negative predictive value = 275/275 x 100

Negative predictive value = 100%

Qu 21: On your worst day in the last 12 months, did you get short of breath walking with other people of your own age and sex on level ground?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	14	117	131
	No	0	366	366
	Total	14	483	497

It is presumed that the 275 workers who answered no to the previous question, ‘On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity =14/14 x 100
Sensitivity = 100%

Specificity = 366/483 x 100
Specificity = 76%

Positive predictive value = 14/131x100
Positive predictive value = 11%

Negative predictive value = 366/366 x 100
Negative predictive value = 100%

Qu 22: On your worst day in the last 12 months, did you have to stop for breath walking at your own pace on level ground?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	13	45	58
	No	1	440	441
	Total	14	485	499

It is presumed that the 366 workers who answered no to either the previous question, ‘On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?’ or On your worst day in the last 12 months, did you get short of breath walking with other people of your own age and sex on level ground? would answer no to this question. In reality they did not answer this question as they were requested to bypass to a different question.

Sensitivity =13/14 x 100
Sensitivity = 93%

Specificity = 440/485 x 100

Specificity = 91%

Positive predictive value = 13/58 x100

Positive predictive value = 22%

Negative predictive value = 440/441 x 100

Negative predictive value = 100%

Qu 23: On your worst day in the last 12 months, were you short of breath washing or dressing?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	9	14	23
	No	5	474	478
	Total	14	488	501

It is presumed that the 440 who had not been diagnosed with EAA the expert panel, and the 1 worker who had has been diagnosed with EAA, who answered no to either the previous question, ‘On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?’ or On your worst day in the last 12 months, did you get short of breath walking with other people of your own age and sex on level ground?’ or On your worst day in the last 12 months, did you have to stop for breath walking at your own pace on level ground? would answer no to this question. In reality they did not answer this question as they were requested to bypass to a different question.

Sensitivity = 9/14 x 100

Sensitivity = 64%

Specificity = 474/488 x 100

Specificity = 97%

Positive predictive value = 9/23 x100

Positive predictive value = 39%

Negative predictive value = 474/478 x 100

Negative predictive value = 99%

Qu 25: Are you breathless on waking?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	7	46	53
	No	7	433	440
	Total	14	479	493

It is presumed that the 275 workers who answered no to the previous question, ‘On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 7/14x 100

Sensitivity = 50%

Specificity = 433/479 x 100

Specificity = 90%

Positive predictive value = 7/53 x100

Positive predictive value = 13%

Negative predictive value = 433/440 x 100

Negative predictive value = 98%

Qu 26: Are you breathless during the day?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	14	118	132
	No	0	364	364
	Total	14	482	496

It is presumed that the 275 workers who answered no to the previous question, ‘On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 14/14 x 100

Sensitivity = 100%

Specificity = 364/482 x 100

Specificity = 76%

Positive predictive value = 14/132 x100

Positive predictive value = 11%

Negative predictive value = 364/364 x 100

Negative predictive value = 100%

Qu 27: Are you woken from sleep by your breathlessness?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	10	45	55
	No	4	437	441
	Total	14	482	496

It is presumed that the 275 workers who answered no to the previous question, ‘On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 10/14 x 100
Sensitivity = 71%

Specificity = 437/482 x 100
Specificity = 91%

Positive predictive value = 10/55 x100
Positive predictive value = 18%

Negative predictive value = 437/441 x 100
Negative predictive value = 99%

Qu 28: Is your breathlessness worse at the beginning of the week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	1	14	15
	No	12	452	464
	Total	13	466	479

It is presumed that the 275 workers who answered no to the previous question, ‘On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 1/13 x 100
Sensitivity = 8%

Specificity = 452/466 x 100

Specificity = 97%

Positive predictive value = 1/15 x100

Positive predictive value = 7%

Negative predictive value = 452/464 x 100

Negative predictive value = 97%

Qu 29: Is your breathlessness worse at the end of the working week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	11	56	67
	No	3	409	412
	Total	14	465	479

It is presumed that the 275 workers who answered no to the previous question, 'On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 11/14 x 100

Sensitivity = 79%

Specificity = 409/465 x 100

Specificity = 88%

Positive predictive value = 11/67 x100

Positive predictive value = 16%

Negative predictive value = 409/412 x 100

Negative predictive value = 99%

Qu 30: Is your breathlessness no different at the beginning or end of the week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	3	125	128
	No	9	352	361
	Total	12	477	489

It is presumed that the 275 workers who answered no to the previous question, 'On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 3/12 x 100
Sensitivity = 25%

Specificity = 352/477 x 100
Specificity = 74%

Positive predictive value = 3/128 x100
Positive predictive value = 2%

Negative predictive value = 352/361 x 100
Negative predictive value = 98%

Qu 31a: On days away from work is your breathlessness better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	11	108	119
	No	2	377	379
	Total	13	485	498

It is presumed that the 275 workers who answered no to the previous question, ‘On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 11/13 x 100
Sensitivity = 85%

Specificity = 377/485 x 100
Specificity = 78%

Positive predictive value = 11/119 x100
Positive predictive value = 9%

Negative predictive value = 377/379 x 100
Negative predictive value = 99%

Qu 31b: On days away from work is your breathlessness the same than days at work?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	2	101	103
	No	11	384	395
	Total	13	485	498

It is presumed that the 275 workers who answered no to the previous question, ‘On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 2/13x 100
Sensitivity = 15%

Specificity = 384/485 x 100

Specificity = 79%

Positive predictive value = 2/103 x100

Positive predictive value = 2%

Negative predictive value = 384/395 x 100

Negative predictive value = 97%

Qu 31c: On days away from work is your breathlessness worse than days at work?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	1	1
	No	13	484	497
	Total	13	485	498

It is presumed that the 275 workers who answered no to the previous question, 'On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 0/13 x 100

Sensitivity = 0%

Specificity = 484/485 x 100

Specificity = 100%

Positive predictive value = 0/1 x100

Positive predictive value = 0%

Negative predictive value = 484/497 x 100

Negative predictive value = 97%

Qu 32a: On holiday is your breathlessness better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	11	137	148
	No	2	348	350
	Total	13	485	498

It is presumed that the 275 workers who answered no to the previous question, 'On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 11/13 x 100
Sensitivity = 85%

Specificity = 348/485 x 100
Specificity = 72%

Positive predictive value = 11/148 x100
Positive predictive value = 7%

Negative predictive value = 348/350 x 100
Negative predictive value = 99%

Qu 32b: On holiday is your breathlessness the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	2	72	74
	No	11	413	424
	Total	13	485	498

It is presumed that the 275 workers who answered no to the previous question, ‘On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 2/13 x 100
Sensitivity = 15%

Specificity = 413/485 x 100
Specificity = 85%

Positive predictive value = 2/74 x100
Positive predictive value = 3%

Negative predictive value = 413/424 x 100
Negative predictive value = 97%

Qu 32c: On holiday is your breathlessness worse?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	1	1
	No	13	484	497
	Total	13	485	498

It is presumed that the 275 workers who answered no to the previous question, ‘On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 0/13 x 100
Sensitivity = 0%

Specificity = 484/485 x 100

Specificity = 100%

Positive predictive value =0/1 x100

Positive predictive value = 0%

Negative predictive value = 484/497 x 100

Negative predictive value = 97%

Qu 34: Do you suffer from breathlessness at present?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	12	132	144
	No	2	352	354
	Total	14	484	498

It is presumed that the 275 workers who answered no to the previous question, 'On your worst day in the last 12 months, were you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 12/14 x 100

Sensitivity = 86%

Specificity = 352/484 x 100

Specificity = 73%

Positive predictive value = 12/144 x100

Positive predictive value = 8%

Negative predictive value = 352/354 x 100

Negative predictive value = 99%

Cough

Questions 36, 37 and 49 are not included as the responses as the answers are not in an appropriate style, for example continuous data, therefore the sensitivity and positive predictive value cannot be calculated.

		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
Qu 35: Do you cough?	Yes	13	280	293
	No	1	216	217
	Total	14	496	510

Sensitivity = 13/14 x 100

Sensitivity = 93%

Specificity = 216/496 x 100

Specificity = 44%

Positive predictive value = 13/293 x100

Positive predictive value = 4%

Negative predictive value = 216/217 x 100

Negative predictive value = 100%

		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
Qu 38: Do you cough on waking?	Yes	8	111	119
	No	5	367	372
	Total	13	478	491

It is presumed that the 1 expert panel definite EAA case and the 216 workers not diagnosed with definite EAA, who answered no to question 35, ‘Do you cough?’

would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 8/13 x 100
Sensitivity = 62%

Specificity = 367/478 x 100
Specificity = 77%

Positive predictive value = 8/119 x100
Positive predictive value = 7%

Negative predictive value = 367/372 x 100
Negative predictive value = 99%

Qu 39: Do you cough during the day?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	12	250	262
	No	1	239	240
	Total	13	489	502

It is presumed that the 1 expert panel definite EAA case and the 216 workers not diagnosed with definite EAA, who answered no to question 35, ‘Do you cough?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 12/13 x 100
Sensitivity = 92%

Specificity = 239/489 x 100
Specificity = 49%

Positive predictive value = 12/262 x100

Positive predictive value = 5%

Negative predictive value = 239/240 x 100

Negative predictive value = 100%

Qu 40: Are you woken from sleep by your cough?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	6	74	80
	No	8	412	420
	Total	14	486	500

It is presumed that the 1 expert panel definite EAA case and the 216 workers not diagnosed with definite EAA, who answered no to question 35, 'Do you cough?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 6/14 x 100

Sensitivity = 43%

Specificity = 412/486 x 100

Specificity = 85%

Positive predictive value = 6/80 x100

Positive predictive value = 8%

Negative predictive value = 412/420 x 100

Negative predictive value = 98%

Qu 41: Is your cough worse at the beginning of the working week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	1	15	16
	No	13	464	477
	Total	14	479	493

It is presumed that the 1 expert panel definite EAA case and the 216 workers not diagnosed with definite EAA, who answered no to question 35, 'Do you cough?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 1/14 x 100

Sensitivity = 7%

Specificity = 464/479 x 100

Specificity = 97%

Positive predictive value = 1/16 x100

Positive predictive value = 6%

Negative predictive value = 464/477 x 100

Negative predictive value = 97%

Qu 42: Is your cough worse at the end of a working week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	7	71	78
	No	7	407	413
	Total	14	478	491

It is presumed that the 1 expert panel definite EAA case and the 216 workers not diagnosed with definite EAA, who answered no to question 35, 'Do you cough?'

would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 7/14 x 100
Sensitivity = 50%

Specificity = 407/478 x 100
Specificity = 85%

Positive predictive value = 7/78 x100
Positive predictive value = 9%

Negative predictive value = 407/413 x 100
Negative predictive value = 99%

Qu 43: Is your cough no different at the beginning and end of the week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	6	186	192
	No	8	304	312
	Total	14	490	504

It is presumed that the 1 expert panel definite EAA case and the 216 workers not diagnosed with definite EAA, who answered no to question 35, ‘Do you cough?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 6/14 x 100
Sensitivity = 43%

Specificity = 304/490 x 100
Specificity = 62%

Positive predictive value = 6/192 x100

Positive predictive value = 3%

Negative predictive value = 304/312 x 100

Negative predictive value = 97%

Qu 44a: On days away from work, is your cough better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	9	127	136
	No	4	368	372
	Total	13	495	508

It is presumed that the 1 expert panel definite EAA case and the 216 workers not diagnosed with definite EAA, who answered no to question 35, 'Do you cough?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 9/13 x 100

Sensitivity = 69%

Specificity = 368/495 x 100

Specificity = 74%

Positive predictive value = 9/136 x100

Positive predictive value = 7%

Negative predictive value = 368/372 x 100

Negative predictive value = 99%

Qu 44b: On days away from work, is your cough the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	3	152	155
	No	10	343	353
	Total	13	495	508

It is presumed that the 1 expert panel definite EAA case and the 216 workers not diagnosed with definite EAA, who answered no to question 35, 'Do you cough?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 3/13 x 100

Sensitivity = 23%

Specificity = 343/495 x 100

Specificity = 69%

Positive predictive value = 3/155 x100

Positive predictive value = 2%

Negative predictive value = 342/353 x 100

Negative predictive value = 97%

Qu 45: On holiday is your cough better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	9	163	172
	No	4	332	336
	Total	13	495	508

It is presumed that the 1 expert panel definite EAA case and the 216 workers not diagnosed with definite EAA, who answered no to question 35, 'Do you cough?'

would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 9/13 x 100
Sensitivity = 69%

Specificity = 332/495 x 100
Specificity = 67%

Positive predictive value = 9/172 x100
Positive predictive value = 5%

Negative predictive value = 332/336 x 100
Negative predictive value = 99%

Qu 45b: On holidays is your cough the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	3	115	118
	No	10	380	390
	Total	13	495	508

It is presumed that the 1 expert panel definite EAA case and the 216 workers not diagnosed with definite EAA, who answered no to question 35, 'Do you cough?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 3/13 x 100
Sensitivity = 23%

Specificity = 380/495 x 100
Specificity = 77%

Positive predictive value = 3/118 x100

Positive predictive value = 3%

Negative predictive value = 380/390 x 100

Negative predictive value = 97%

Qu 45c: On holidays is your cough worse?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	1	1
	No	12	494	507
	Total	13	495	508

It is presumed that the 1 expert panel definite EAA case and the 216 workers not diagnosed with definite EAA, who answered no to question 35, 'Do you cough?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 0/13 x 100

Sensitivity = 0%

Specificity = 494/495 x 100

Specificity = 100%

Positive predictive value = 0/1 x100

Positive predictive value = 0%

Negative predictive value = 494/508 x 100

Negative predictive value = 97%

Qu 46: Do you cough up phlegm (sputum) from your chest?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	12	231	243
	No	2	265	267
	Total	14	496	510

Sensitivity = 12/14 x 100

Sensitivity = 86%

Specificity = 265/496 x 100

Specificity = 10%

Positive predictive value = 12/243 x100

Positive predictive value = 5%

Negative predictive value = 265/267 x 100

Negative predictive value = 99%

Qu 47: On holidays is your cough worse?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	10	156	166
	No	3	340	343
	Total	13	496	509

It is presumed that the 2 expert panel definite EAA case and the 265 workers not diagnosed with definite EAA, who answered no to question 46, Do you cough up phlegm (sputum) from your chest? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 10/13 x 100

Sensitivity =77%

Specificity = 340/496 x 100

Specificity = 69%

Positive predictive value = 10/166 x100

Positive predictive value = 6%

Negative predictive value = 340/343 x 100

Negative predictive value = 99%

Qu 48: Have you been doing this for the last 2 years?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	5	167	172
	No	8	330	338
	Total	13	497	510

It is presumed that the 2 expert panel definite EAA case and the 265 workers not diagnosed with definite EAA, who answered no to question 46, Do you cough up phlegm (sputum) from your chest? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 5/13 x 100

Sensitivity = 34%

Specificity = 330/497 x 100

Specificity = 66%

Positive predictive value = 5/172 x100

Positive predictive value = 3%

Negative predictive value = 330/338 x 100

Negative predictive value = 98%

Qu 50: Do you cough up phlegm on waking?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	8	115	123
	No	5	375	380
	Total	13	490	503

It is presumed that the 2 expert panel definite EAA case and the 265 workers not diagnosed with definite EAA, who answered no to question 46, Do you cough up phlegm (sputum) from your chest? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 8/13 x 100
Sensitivity = 62%

Specificity = 375/490 x 100
Specificity = 77%

Positive predictive value = 8/123 x100
Positive predictive value = 7%

Negative predictive value = 375/380 x 100
Negative predictive value = 99%

Qu 51: Do you cough up phlegm during the day?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	10	168	178
	No	4	322	326
	Total	14	490	504

It is presumed that the 2 expert panel definite EAA case and the 265 workers not diagnosed with definite EAA, who answered no to question 46, Do you cough up

phlegm (sputum) from your chest? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 10/14 x 100
Sensitivity =71%

Specificity = 322/490 x 100
Specificity = 66%

Positive predictive value = 10/178 x100
Positive predictive value = 6%

Negative predictive value = 322/326 x 100
Negative predictive value = 99%

Qu 52: Is your phlegm production worse at the beginning of the working week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	12	12
	No	14	469	483
	Total	14	481	495

It is presumed that the 2 expert panel definite EAA case and the 265 workers not diagnosed with definite EAA, who answered no to question 46, Do you cough up phlegm (sputum) from your chest? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 0/14 x 100
Sensitivity = 0%

Specificity = 469/481 x 100
Specificity = 98%

Positive predictive value = 0/12 x100

Positive predictive value = 0%

Negative predictive value = 469/483 x 100

Negative predictive value = 97%

Qu 53: Is your phlegm production worse at the end of the working week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	6	65	71
	No	8	416	424
	Total	14	481	495

It is presumed that the 2 expert panel definite EAA case and the 265 workers not diagnosed with definite EAA, who answered no to question 46, Do you cough up phlegm (sputum) from your chest? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 6/14x 100

Sensitivity =43%

Specificity = 416/481 x 100

Specificity = 86%

Positive predictive value = 6/71 x100

Positive predictive value = 8%

Negative predictive value = 416/424 x 100

Negative predictive value = 98%

Qu 54: Is your phlegm production the same at the beginning and end of the working week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	6	142	148
	No	8	352	360
	Total	14	494	508

It is presumed that the 2 expert panel definite EAA case and the 265 workers not diagnosed with definite EAA, who answered no to question 46, Do you cough up phlegm (sputum) from your chest? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 6/14 x 100

Sensitivity =43%

Specificity = 352/494 x 100

Specificity = 71%

Positive predictive value = 6/148 x100

Positive predictive value = 4%

Negative predictive value = 352/360 x 100

Negative predictive value = 98%

Qu 55a: On days away from work is your phlegm better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	6	108	114
	No	7	388	395
	Total	13	496	509

It is presumed that the 2 expert panel definite EAA case and the 265 workers not diagnosed with definite EAA, who answered no to question 46, Do you cough up

phlegm (sputum) from your chest? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 6/13 x 100
Sensitivity =46%

Specificity = 388/496 x 100
Specificity = 78%

Positive predictive value = 6/114 x100
Positive predictive value = 5%

Negative predictive value = 388/395 x 100
Negative predictive value = 98%

Qu 55b: On days away from work is your phlegm the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	5	123	128
	No	8	373	381
	Total	13	496	509

It is presumed that the 2 expert panel definite EAA case and the 265 workers not diagnosed with definite EAA, who answered no to question 46, Do you cough up phlegm (sputum) from your chest? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 5/13 x 100
Sensitivity = 38%

Specificity = 373/496 x 100
Specificity = 75%

Positive predictive value = 5/128 x100

Positive predictive value = 4%

Negative predictive value = 373/381 x 100

Negative predictive value = 98%

Qu 56: On holidays is your phlegm better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	8	131	139
	No	5	365	370
	Total	13	496	509

It is presumed that the 2 expert panel definite EAA case and the 265 workers not diagnosed with definite EAA, who answered no to question 46, Do you cough up phlegm (sputum) from your chest? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 8/13 x 100

Sensitivity = 62%

Specificity = 365/370 x 100

Specificity = 99%

Positive predictive value = 8/139 x100

Positive predictive value = 6%

Negative predictive value = 365/370 x 100

Negative predictive value = 99%

Qu 56: On holidays is your phlegm the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	3	100	103
	No	10	396	406
	Total	13	496	509

It is presumed that the 2 expert panel definite EAA case and the 265 workers not diagnosed with definite EAA, who answered no to question 46, Do you cough up phlegm (sputum) from your chest? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 3/13 x 100
Sensitivity = 23%

Specificity = 396/496 x 100
Specificity = 80%

Positive predictive value = 3/103 x100
Positive predictive value = 3%

Negative predictive value = 396/406 x 100
Negative predictive value = 98%

Eyes

Question 59 is not included as the answers are not in an appropriate style.

Qu 58: In the past twelve months have you had more than two episodes of irritation or watering of the eyes?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	9	247	256
	No	5	249	254
	Total	14	496	510

Sensitivity = 9/14 x 100
Sensitivity = 64%

Specificity = 249/496 x 100
Specificity = 50%

Positive predictive value = 9/256 x100
Positive predictive value = 4%

Negative predictive value = 249/254 x 100
Negative predictive value = 98%

Qu 60a: On days away from work is this better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	5	142	147
	No	9	353	362
	Total	14	495	509

It is presumed that the 5 expert panel definite EAA case and the 249 workers not diagnosed with definite EAA, who answered no to question 58, In the past twelve months have you had more than two episodes of irritation or watering of the eyes?

would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 5/14 x 100
Sensitivity = 36%

Specificity = 353/495 x 100
Specificity = 71%

Positive predictive value = 5/147 x100
Positive predictive value = 3%

Negative predictive value = 353/362 x 100
Negative predictive value = 98%

Qu 60b: On days away from work is this the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	4	98	102
	No	10	397	407
	Total	14	495	509

It is presumed that the 5 expert panel definite EAA case and the 249 workers not diagnosed with definite EAA, who answered no to question 58, In the past twelve months have you had more than two episodes of irritation or watering of the eyes? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 4/14 x 100
Sensitivity = 29%

Specificity = 397/495 x 100
Specificity = 80%

Positive predictive value = 4/102 x100

Positive predictive value = 4%

Negative predictive value = 397/407 x 100

Negative predictive value = 98%

Qu 60c: On days away from work is this worse?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	6	6
	No	14	489	503
	Total	14	495	509

It is presumed that the 5 expert panel definite EAA case and the 249 workers not diagnosed with definite EAA, who answered no to question 58, In the past twelve months have you had more than two episodes of irritation or watering of the eyes? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 0/14 x 100

Sensitivity = 0%

Specificity = 489/495 x 100

Specificity = 99%

Positive predictive value = 0/6 x100

Positive predictive value = 0%

Negative predictive value = 489/503 x 100

Negative predictive value = 97%

Qu 61a: On holidays is this better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	6	157	163
	No	8	337	345
	Total	14	494	508

It is presumed that the 5 expert panel definite EAA case and the 249 workers not diagnosed with definite EAA, who answered no to question 58, In the past twelve months have you had more than two episodes of irritation or watering of the eyes? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 6/14 x 100
Sensitivity = 43%

Specificity = 337/494 x 100
Specificity = 68%

Positive predictive value = 6/163 x100
Positive predictive value = 4%

Negative predictive value = 337/345 x 100
Negative predictive value = 98%

Qu 61b: On holidays is this the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	3	85	88
	No	11	409	420
	Total	14	494	508

It is presumed that the 5 expert panel definite EAA case and the 249 workers not diagnosed with definite EAA, who answered no to question 58, In the past twelve

months have you had more than two episodes of irritation or watering of the eyes? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 3/14 x 100
Sensitivity = 21%

Specificity = 409/494 x 100
Specificity = 83%

Positive predictive value = 3/88 x100
Positive predictive value = 3%

Negative predictive value = 409/508 x 100
Negative predictive value = 81%

Qu 61c: On holidays is this worse?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	3	3
	No	14	491	505
	Total	14	494	508

It is presumed that the 5 expert panel definite EAA case and the 249 workers not diagnosed with definite EAA, who answered no to question 58, In the past twelve months have you had more than two episodes of irritation or watering of the eyes? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 0/14 x 100
Sensitivity = 0%

Specificity = 491/494 x 100

Specificity = 99%

Positive predictive value = 0/3 x100

Positive predictive value = 0%

Negative predictive value = 491/505 x 100

Negative predictive value = 97%

Nasal

Question 63 is not included as the answers are not in an appropriate style.

Qu 62: In the past twelve months have you had more than two episodes of blocked or stuffy nose?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	11	341	352
	No	3	154	157
	Total	14	495	509

Sensitivity = 11/14 x 100

Sensitivity = 79%

Specificity = 154/495 x 100

Specificity = 31%

Positive predictive value = 11/352 x100

Positive predictive value = 3%

Negative predictive value = 154/157 x 100

Negative predictive value = 98%

Qu 64a: On days away from work is this better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	5	159	164
	No	9	335	344
	Total	14	494	508

It is presumed that the 3 expert panel definite EAA cases and the 154 workers not diagnosed with definite EAA, who answered no to question 62, In the past twelve months have you had more than two episodes of blocked or stuffy nose? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 5/14 x 100
Sensitivity = 36%

Specificity = 335/494 x 100
Specificity = 68%

Positive predictive value = 5/164 x100
Positive predictive value = 3%

Negative predictive value = 335/344 x 100
Negative predictive value = 97%

Qu 64b: On days away from work is this the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	6	180	186
	No	8	314	322
	Total	14	494	508

It is presumed that the 3 expert panel definite EAA cases and the 154 workers not diagnosed with definite EAA, who answered no to question 62, In the past twelve

months have you had more than two episodes of blocked or stuffy nose? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 6/14 x 100
Sensitivity = 43%

Specificity = 314/494 x 100
Specificity = 64%

Positive predictive value = 6/186 x100
Positive predictive value = 3%

Negative predictive value = 314/322 x 100
Negative predictive value = 98%

Qu 64c: On days away from work is this worse?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	1	1
	No	14	493	507
	Total	14	494	508

It is presumed that the 3 expert panel definite EAA cases and the 154 workers not diagnosed with definite EAA, who answered no to question 62, In the past twelve months have you had more than two episodes of blocked or stuffy nose? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 0/14 x 100
Sensitivity = 0%

Specificity = 493/494 x 100
Specificity = 100%

Positive predictive value = 0/1 x100

Positive predictive value = 3%

Negative predictive value = 493/507 x 100

Negative predictive value = 97%

Qu 65a: On holidays is this better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	9	192	201
	No	5	301	306
	Total	14	493	507

It is presumed that the 3 expert panel definite EAA cases and the 154 workers not diagnosed with definite EAA, who answered no to question 62, In the past twelve months have you had more than two episodes of blocked or stuffy nose? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 9/14 x 100

Sensitivity = 64%

Specificity = 301/493 x 100

Specificity = 61%

Positive predictive value = 9/201 x100

Positive predictive value = 5%

Negative predictive value = 301/306 x 100

Negative predictive value = 98%

Qu 65b: On holidays is this the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	2	101	103
	No	12	392	404
	Total	14	493	507

It is presumed that the 3 expert panel definite EAA cases and the 154 workers not diagnosed with definite EAA, who answered no to question 62, In the past twelve months have you had more than two episodes of blocked or stuffy nose? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 2/14 x 100
Sensitivity = 14%

Specificity = 392/493 x 100
Specificity = 80%

Positive predictive value = 2/103 x100
Positive predictive value = 2%

Negative predictive value = 392/404 x 100
Negative predictive value = 97%

Qu 65c: On holidays is this worse?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	1	1
	No	14	492	506
	Total	14	493	507

It is presumed that the 3 expert panel definite EAA cases and the 154 workers not diagnosed with definite EAA, who answered no to question 62, In the past twelve months have you had more than two episodes of blocked or stuffy nose? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 0/14 x 100
Sensitivity = 0%

Specificity = 492/493 x 100
Specificity = 100%

Positive predictive value = 0/1 x100
Positive predictive value = 0%

Negative predictive value = 492/506 x 100
Negative predictive value = 97%

Throat

Question 67 is not included as the answers are not in an appropriate style

Qu 66: In the past twelve months have you had more than two episodes of a dry or sore throat?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	10	305	315
	No	4	191	195
	Total	14	496	510

Sensitivity = 10/14 x 100
Sensitivity = 71%

Specificity = 191/496 x 100
Specificity = 39%

Positive predictive value = 10/315 x100

Positive predictive value = 3%

Negative predictive value = 191/195 x 100

Negative predictive value = 98%

Qu 68a: On days away from work is this better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	7	183	190
	No	7	313	320
	Total	14	496	510

It is presumed that the 4 expert panel definite EAA cases and the 191 workers not diagnosed with definite EAA, who answered no to question 66, In the past twelve months have you had more than two episodes of a dry or sore throat? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 7/14 x 100

Sensitivity = 50%

Specificity = 313/496 x 100

Specificity = 63%

Positive predictive value = 7/190 x100

Positive predictive value = 4%

Negative predictive value = 313/320 x 100

Negative predictive value = 98%

Qu 68b: On days away from work is this the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	3	121	124
	No	11	375	386
	Total	14	496	510

It is presumed that the 4 expert panel definite EAA cases and the 191 workers not diagnosed with definite EAA, who answered no to question 66, In the past twelve months have you had more than two episodes of a dry or sore throat? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 3/14 x 100
Sensitivity = 21%

Specificity = 375/496 x 100
Specificity = 76%

Positive predictive value = 3/124 x100
Positive predictive value = 2%

Negative predictive value = 375/386 x 100
Negative predictive value = 97%

Qu 68c: On days away from work is this worse?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	1	1
	No	14	495	509
	Total	14	496	510

It is presumed that the 4 expert panel definite EAA cases and the 191 workers not diagnosed with definite EAA, who answered no to question 66, In the past twelve

months have you had more than two episodes of a dry or sore throat? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 0/14 x 100
Sensitivity = 0%

Specificity = 495/496 x 100
Specificity = 100%

Positive predictive value = 0/1 x100
Positive predictive value = 0%

Negative predictive value = 495/509 x 100
Negative predictive value = 97%

Qu 69a: On holidays is this better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	8	203	211
	No	6	293	299
	Total	14	496	510

It is presumed that the 4 expert panel definite EAA cases and the 191 workers not diagnosed with definite EAA, who answered no to question 66, In the past twelve months have you had more than two episodes of a dry or sore throat? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 8/14 x 100
Sensitivity = 57%

Specificity = 293/496 x 100
Specificity = 59%

Positive predictive value = 8/211 x100

Positive predictive value = 4%

Negative predictive value = 293/299 x 100

Negative predictive value = 98%

Qu 69b: On holidays is this the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	2	101	103
	No	12	395	407
	Total	14	496	510

It is presumed that the 4 expert panel definite EAA cases and the 191 workers not diagnosed with definite EAA, who answered no to question 66, In the past twelve months have you had more than two episodes of a dry or sore throat? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 2/14 x 100

Sensitivity = 14%

Specificity = 395/496 x 100

Specificity = 80%

Positive predictive value = 2/103 x100

Positive predictive value = 2%

Negative predictive value = 395/407 x 100

Negative predictive value = 97%

Qu 69c: On holidays is this worse?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	1	1
	No	14	495	509
	Total	14	496	510

It is presumed that the 4 expert panel definite EAA cases and the 191 workers not diagnosed with definite EAA, who answered no to question 66, In the past twelve months have you had more than two episodes of a dry or sore throat? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 0/14 x 100
Sensitivity = 0%

Specificity = 495/496 x 100
Specificity = 100%

Positive predictive value = 0/1 x100
Positive predictive value = 0%

Negative predictive value = 495/509 x 100
Negative predictive value = 97%

Past illnesses

Qu 71: Have you ever had any chest illnesses?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	7	179	186
	No	7	316	323
	Total	14	495	509

Sensitivity = 7/14 x 100

Sensitivity = 50%

Specificity = 316/495 x 100

Specificity = 64%

Positive predictive value = 7/186 x100

Positive predictive value = 4%

Negative predictive value = 316/323 x 100

Negative predictive value = 98%

Qu 72: Are you taking any treatment for your chest?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	11	62	73
	No	3	432	435
	Total	14	494	508

Sensitivity = 11/14 x 100

Sensitivity = 79%

Specificity = 432/494 x 100

Specificity = 87%

Positive predictive value = 11/73 x100

Positive predictive value = 15%

Negative predictive value = 432/435 x 100

Negative predictive value = 99%

Qu 73: Have you had a lymphoma?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	2	2
	No	14	485	499
	Total	14	487	501

Sensitivity = 0/14 x 100

Sensitivity = 0%

Specificity = 485/487 x 100

Specificity = 100%

Positive predictive value = 0/2 x100

Positive predictive value = 0%

Negative predictive value = 485/499 x 100

Negative predictive value = 97%

Qu 74: Have you lost weight since January 2003?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	9	92	101
	No	5	401	406
	Total	14	493	507

Sensitivity = 9/14 x 100

Sensitivity = 64%

Specificity = 401/493 x 100

Specificity = 81%

Positive predictive value = 9/101 x100

Positive predictive value = 9%

Negative predictive value = 401/406 x 100

Negative predictive value = 99%

Asthma

Question 77, 78, 88, and 89 is not included as the answers are not in an appropriate style.

Qu 75: Has a doctor told you that you have asthma?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	6	69	75
	No	8	426	434
	Total	14	495	509

Sensitivity = 6/14 x 100

Sensitivity = 43%

Specificity = 426/495 x 100

Specificity = 86%

Positive predictive value = 6/75 x100

Positive predictive value = 8%

Negative predictive value = 426/434 x 100

Negative predictive value = 98%

Qu 76: In the last 12 months has your chest ever felt tight or your breathing become difficult?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	14	244	258
	No	0	251	251
	Total	14	495	509

Sensitivity = 14/14 x 100

Sensitivity = 100%

Specificity = 251/495 x 100

Specificity = 51%

Positive predictive value = 14/258 x100

Positive predictive value = 5%

Negative predictive value = 251/251 x 100

Negative predictive value = 100%

Qu 79: Do you have this on waking?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	6	67	73
	No	6	410	416
	Total	12	477	489

It is presumed that the 251 workers not diagnosed with definite EAA, who answered no to question 76, In the last 12 months has your chest ever felt tight or your breathing become difficult? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 6/12 x 100

Sensitivity = 50%

Specificity = 410/477 x 100

Specificity = 86%

Positive predictive value = 6/73 x100

Positive predictive value = 8%

Negative predictive value = 410/416 x 100

Negative predictive value = 99%

Qu 80: Do you have this during the day?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	13	196	209
	No	1	286	287
	Total	14	482	496

It is presumed that the 251 workers not diagnosed with definite EAA, who answered no to question 76, In the last 12 months has your chest ever felt tight or your breathing become difficult? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 13/14 x 100

Sensitivity = 93%

Specificity = 286/482 x 100

Specificity = 59%

Positive predictive value = 13/209 x100

Positive predictive value = 6%

Negative predictive value = 286/287 x 100

Negative predictive value = 100%

Qu 81: Are you woken from sleep by this?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	6	56	62
	No	6	420	426
	Total	12	476	488

It is presumed that the 251 workers not diagnosed with definite EAA, who answered no to question 76, In the last 12 months has your chest ever felt tight or your breathing become difficult? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 6/12 x 100
Sensitivity = 50%

Specificity = 420/476 x 100
Specificity = 88%

Positive predictive value = 6/62 x100
Positive predictive value = 10%

Negative predictive value = 420/426 x 100
Negative predictive value = 99%

Qu 82: Is this worse at the beginning of the week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	11	11
	No	12	472	484
	Total	12	483	495

It is presumed that the 251 workers not diagnosed with definite EAA, who answered no to question 76, In the last 12 months has your chest ever felt tight or your

breathing become difficult? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 0/12 x 100
Sensitivity = 0%

Specificity = 472/483 x 100
Specificity = 98%

Positive predictive value = 0/11 x100
Positive predictive value = 0%

Negative predictive value = 472/484 x 100
Negative predictive value = 98%

Qu 83: Is this worse at the end of the working week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	9	57	66
	No	3	425	428
	Total	12	482	494

It is presumed that the 251 workers not diagnosed with definite EAA, who answered no to question 76, In the last 12 months has your chest ever felt tight or your breathing become difficult? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 9/12 x 100
Sensitivity = 75%

Specificity = 425/482 x 100
Specificity = 88%

Positive predictive value = 9/66 x100

Positive predictive value = 14%

Negative predictive value = 425/428 x 100

Negative predictive value = 99%

Qu 84: Is this no different at the beginning or end of the week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	3	162	165
	No	9	328	337
	Total	12	490	502

It is presumed that the 251 workers not diagnosed with definite EAA, who answered no to question 76, In the last 12 months has your chest ever felt tight or your breathing become difficult? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 3/12 x 100

Sensitivity = 25%

Specificity = 328/490 x 100

Specificity = 67%

Positive predictive value = 3/162 x100

Positive predictive value = 2%

Negative predictive value = 328/337 x 100

Negative predictive value = 97%

Qu 85a: On days away from work is this better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	10	116	126
	No	3	376	379
	Total	13	492	505

It is presumed that the 251 workers not diagnosed with definite EAA, who answered no to question 76, In the last 12 months has your chest ever felt tight or your breathing become difficult? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 10/13 x 100

Sensitivity = 77%

Specificity = 376/492 x 100

Specificity = 76%

Positive predictive value = 10/126 x100

Positive predictive value = 8%

Negative predictive value = 376/379 x 100

Negative predictive value = 99%

Qu 85b: On days away from work is this the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	3	121	124
	No	10	371	381
	Total	13	492	505

It is presumed that the 251 workers not diagnosed with definite EAA, who answered no to question 76, In the last 12 months has your chest ever felt tight or your

breathing become difficult? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 3/13 x 100
Sensitivity = 23%

Specificity = 371/492 x 100
Specificity = 75%

Positive predictive value = 3/124 x100
Positive predictive value = 2%

Negative predictive value = 371/381 x 100
Negative predictive value = 97%

Qu 85c: On days away from work is this worse?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	4	4
	No	10	488	501
	Total	13	492	505

It is presumed that the 251 workers not diagnosed with definite EAA, who answered no to question 76, In the last 12 months has your chest ever felt tight or your breathing become difficult? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 0/13 x 100
Sensitivity = 0%

Specificity = 488/492 x 100
Specificity = 99%

Positive predictive value = 0/4 x100

Positive predictive value = 0%

Negative predictive value = 488/501 x 100

Negative predictive value = 97%

Qu 86a: On holidays are you better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	12	142	154
	No	1	349	350
	Total	13	491	504

It is presumed that the 251 workers not diagnosed with definite EAA, who answered no to question 76, In the last 12 months has your chest ever felt tight or your breathing become difficult? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 12/13 x 100

Sensitivity = 92%

Specificity = 349/491 x 100

Specificity = 71%

Positive predictive value = 12/154 x100

Positive predictive value = 8%

Negative predictive value = 349/350 x 100

Negative predictive value = 100%

Qu 86b: On holidays are you the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	1	96	97
	No	12	395	407
	Total	13	491	504

It is presumed that the 251 workers not diagnosed with definite EAA, who answered no to question 76, In the last 12 months has your chest ever felt tight or your breathing become difficult? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 1/13 x 100

Sensitivity = 8%

Specificity = 395/491 x 100

Specificity = 80%

Positive predictive value = 1/97 x100

Positive predictive value = 1%

Negative predictive value = 395/407 x 100

Negative predictive value = 97%

Qu 86c: On holidays are you worse?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	2	2
	No	13	488	502
	Total	13	491	504

It is presumed that the 251 workers not diagnosed with definite EAA, who answered no to question 76, In the last 12 months has your chest ever felt tight or your

breathing become difficult? would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 0/13 x 100

Sensitivity = 0%

Specificity = 488/491 x 100

Specificity = 99%

Positive predictive value = 0/2 x100

Positive predictive value = 0%

Negative predictive value = 488/502 x 100

Negative predictive value = 97%

Qu 87: In the past 12 months have you had wheezing or whistling in your chest?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	12	217	229
	No	2	279	281
	Total	14	496	510

Sensitivity = 12/14 x 100

Sensitivity = 86%

Specificity = 279/496 x 100

Specificity = 56%

Positive predictive value = 12/229 x100

Positive predictive value = 5%

Negative predictive value = 279/281 x 100

Negative predictive value = 99%

Qu 90: Do you have this on waking?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	7	76	83
	No	6	411	417
	Total	13	487	500

It is presumed that the 2 expert panel definite EAA case and the 279 workers not diagnosed with definite EAA, who answered no to question 87, 'In the past 12 months have you had wheezing or whistling in your chest?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 7/13 x 100

Sensitivity = 54%

Specificity = 411/487 x 100

Specificity = 84%

Positive predictive value = 7/83 x100

Positive predictive value = 8%

Negative predictive value = 411/417 x 100

Negative predictive value = 99%

Qu 91: Do you have this during the day?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	12	150	162
	No	2	338	340
	Total	14	488	502

It is presumed that the 2 expert panel definite EAA case and the 279 workers not diagnosed with definite EAA, who answered no to question 87, ‘In the past 12 months have you had wheezing or whistling in your chest?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 12/14 x 100
Sensitivity = 86%

Specificity = 338/488 x 100
Specificity = 69%

Positive predictive value = 12/162 x100
Positive predictive value = 7%

Negative predictive value = 338/340 x 100
Negative predictive value = 99%

Qu 92: Are you woken from sleep by this?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	7	49	56
	No	6	439	445
	Total	13	488	501

It is presumed that the 2 expert panel definite EAA case and the 279 workers not diagnosed with definite EAA, who answered no to question 87, ‘In the past 12 months have you had wheezing or whistling in your chest?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 7/13 x 100
Sensitivity = 54%

Specificity = 439/488 x 100

Specificity = 90%

Positive predictive value = 7/56 x100

Positive predictive value = 13%

Negative predictive value = 439/445 x 100

Negative predictive value = 99%

Qu 93a: Is this worse at the beginning of the week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	1	9	10
	No	13	470	483
	Total	14	479	493

It is presumed that the 2 expert panel definite EAA case and the 279 workers not diagnosed with definite EAA, who answered no to question 87, ‘In the past 12 months have you had wheezing or whistling in your chest?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 1/14 x 100

Sensitivity = 7%

Specificity = 470/479 x 100

Specificity = 98%

Positive predictive value = 1/10 x100

Positive predictive value = 10%

Negative predictive value = 470/483 x 100

Negative predictive value = 97%

Qu 94: Is this worse at the end of the working week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	8	56	64
	No	6	423	429
	Total	14	479	493

It is presumed that the 2 expert panel definite EAA case and the 279 workers not diagnosed with definite EAA, who answered no to question 87, 'In the past 12 months have you had wheezing or whistling in your chest?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 8/14 x 100
Sensitivity = 57%

Specificity = 423/479 x 100
Specificity = 88%

Positive predictive value = 8/64 x100
Positive predictive value = 13%

Negative predictive value = 423/429 x 100
Negative predictive value = 99%

Qu 95: Is there no difference at the beginning or end of the working week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	3	143	146
	No	10	350	360
	Total	13	493	506

It is presumed that the 2 expert panel definite EAA case and the 279 workers not diagnosed with definite EAA, who answered no to question 87, ‘In the past 12 months have you had wheezing or whistling in your chest?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 3/13 x 100
Sensitivity = 23%

Specificity = 350/493 x 100
Specificity = 71%

Positive predictive value = 3/146 x100
Positive predictive value = 2%

Negative predictive value = 350/360 x 100
Negative predictive value = 97%

Qu 96a: On days away from work is this better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	8	90	98
	No	5	404	409
	Total	13	494	507

It is presumed that the 2 expert panel definite EAA case and the 279 workers not diagnosed with definite EAA, who answered no to question 87, ‘In the past 12 months have you had wheezing or whistling in your chest?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 8/13 x 100
Sensitivity = 62%

Specificity = 404/494 x 100

Specificity = 82%

Positive predictive value = 8/98 x100

Positive predictive value = 8%

Negative predictive value = 404/409 x 100

Negative predictive value = 99%

Qu 96b: On days away from work is this the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	3	123	126
	No	10	371	381
	Total	13	494	507

It is presumed that the 2 expert panel definite EAA case and the 279 workers not diagnosed with definite EAA, who answered no to question 87, ‘In the past 12 months have you had wheezing or whistling in your chest?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 3/13 x 100

Sensitivity = 23%

Specificity = 371/494 x 100

Specificity = 75%

Positive predictive value = 3/126 x100

Positive predictive value = 2%

Negative predictive value = 371/381 x 100

Negative predictive value = 97%

Qu 96c: On days away from work is this worse?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	0	2	2
	No	13	492	505
	Total	13	494	507

It is presumed that the 2 expert panel definite EAA case and the 279 workers not diagnosed with definite EAA, who answered no to question 87, 'In the past 12 months have you had wheezing or whistling in your chest?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 0/13 x 100
Sensitivity = 0%

Specificity = 492/494 x 100
Specificity = 100%

Positive predictive value = 0/2 x100
Positive predictive value = 0%

Negative predictive value = 402/505 x 100
Negative predictive value = 99%

Qu 97a: On holidays is this better?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	10	112	122
	No	3	381	384
	Total	13	493	506

It is presumed that the 2 expert panel definite EAA case and the 279 workers not diagnosed with definite EAA, who answered no to question 87, ‘In the past 12 months have you had wheezing or whistling in your chest?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 10/13 x 100
Sensitivity = 77%

Specificity = 381/493 x 100
Specificity = 77%

Positive predictive value = 10/122 x100
Positive predictive value = 8%

Negative predictive value = 381/384 x 100
Negative predictive value = 99%

Qu 97b: On holidays is this the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	1	102	103
	No	12	391	403
	Total	13	493	506

It is presumed that the 2 expert panel definite EAA case and the 279 workers not diagnosed with definite EAA, who answered no to question 87, ‘In the past 12 months have you had wheezing or whistling in your chest?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 1/13 x 100
Sensitivity = 8%

Specificity = 391/493 x 100

Specificity = 80%

Positive predictive value = 1/103 x100

Positive predictive value = 1%

Negative predictive value = 391/403 x 100

Negative predictive value = 97%

Qu 97c: On holidays is this the same?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	1	102	103
	No	12	391	403
	Total	13	493	506

It is presumed that the 2 expert panel definite EAA case and the 279 workers not diagnosed with definite EAA, who answered no to question 87, 'In the past 12 months have you had wheezing or whistling in your chest?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 1/13 x 100

Sensitivity = 8%

Specificity = 391/493 x 100

Specificity = 80%

Positive predictive value = 1/103 x100

Positive predictive value = 1%

Negative predictive value = 391/403 x 100

Negative predictive value = 97%

Flu

Questions 104 and 105 are not included due to the style of answer not been appropriate for these statistical analysis.

Qu 98: In the past twelve months have you suffered recurrent flu like symptoms?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	8	202	210
	No	5	292	297
	Total	13	494	507

Sensitivity = 8/13 x 100

Sensitivity = 62%

Specificity = 292/494 x 100

Specificity = 59%

Positive predictive value = 8/210 x100

Positive predictive value = 4%

Negative predictive value = 292/297 x 100

Negative predictive value = 98%

Qu 99: In the past twelve months have you suffered from fever?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	5	106	111
	No	8	345	353
	Total	13	451	464

It is presumed that the 5 expert panel definite EAA case and the 292 workers not diagnosed with definite EAA, who answered no to question 98, ‘In the past twelve

months have you suffered recurrent flu like symptoms?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 5/13 x 100
Sensitivity = 38%

Specificity = 345/451 x 100
Specificity = 76%

Positive predictive value = 5/111 x100
Positive predictive value = 5%

Negative predictive value = 345/353 x 100
Negative predictive value = 98%

Qu 100: In the past twelve months have you suffered from shivering?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	5	94	99
	No	8	355	363
	Total	13	449	462

It is presumed that the 5 expert panel definite EAA case and the 292 workers not diagnosed with definite EAA, who answered no to question 98, 'In the past twelve months have you suffered recurrent flu like symptoms?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 5/13 x 100
Sensitivity = 38%

Specificity = 355/449 x 100
Specificity = 79%

Positive predictive value = 5/99 x100

Positive predictive value = 5%

Negative predictive value = 355/363 x 100

Negative predictive value = 98%

Qu 101: In the past twelve months have you suffered from tiredness?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	8	186	194
	No	5	299	304
	Total	13	485	498

It is presumed that the 5 expert panel definite EAA case and the 292 workers not diagnosed with definite EAA, who answered no to question 98, ‘In the past twelve months have you suffered recurrent flu like symptoms?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 8/13 x 100

Sensitivity = 62%

Specificity = 299/485 x 100

Specificity = 62%

Positive predictive value = 8/194 x100

Positive predictive value = 4%

Negative predictive value = 299/304 x 100

Negative predictive value = 98%

Qu 102: In the past twelve months have you suffered from weakness?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	8	167	175
	No	5	307	312
	Total	13	474	487

It is presumed that the 5 expert panel definite EAA case and the 292 workers not diagnosed with definite EAA, who answered no to question 98, 'In the past twelve months have you suffered recurrent flu like symptoms?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 8/13 x 100
Sensitivity = 62%

Specificity = 307/474 x 100
Specificity = 65%

Positive predictive value = 8/175 x100
Positive predictive value = 5%

Negative predictive value = 307/312 x 100
Negative predictive value = 98%

Qu 103: In the past twelve months have you suffered from joint or muscle pain?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	7	159	166
	No	6	317	323
	Total	13	476	488

It is presumed that the 5 expert panel definite EAA case and the 292 workers not diagnosed with definite EAA, who answered no to question 98, 'In the past twelve

months have you suffered recurrent flu like symptoms?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 7/13 x 100
Sensitivity = 54%

Specificity = 317/476 x 100
Specificity = 67%

Positive predictive value = 7/166 x100
Positive predictive value = 4%

Negative predictive value = 317/323 x 100
Negative predictive value = 98%

Qu 106: Do these symptoms occur more freq after doing a particular job?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	3	15	18
	No	9	476	485
	Total	12	491	503

It is presumed that the 5 expert panel definite EAA case and the 292 workers not diagnosed with definite EAA, who answered no to question 98, 'In the past twelve months have you suffered recurrent flu like symptoms?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 3/12 x 100
Sensitivity = 25%

Specificity = 476/491 x 100

Specificity = 97%

Positive predictive value = 3/18 x100
Positive predictive value = 17%

Negative predictive value = 476/485 x 100
Negative predictive value = 98%

Qu 107a: Do these symptoms occur at the beginning of the working week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	2	16	18
	No	11	455	466
	Total	13	471	484

It is presumed that the 5 expert panel definite EAA case and the 292 workers not diagnosed with definite EAA, who answered no to question 98, ‘In the past twelve months have you suffered recurrent flu like symptoms?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 2/13 x 100
Sensitivity = 15%

Specificity = 455/471 x 100
Specificity = 97%

Positive predictive value = 2/18 x100
Positive predictive value = 11%

Negative predictive value = 455/466 x 100
Negative predictive value = 98%

Qu 107b: Do these symptoms occur at the end of the working week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	4	35	39
	No	9	437	446
	Total	13	472	485

It is presumed that the 5 expert panel definite EAA case and the 292 workers not diagnosed with definite EAA, who answered no to question 98, 'In the past twelve months have you suffered recurrent flu like symptoms?' would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 4/13 x 100
Sensitivity = 31%

Specificity = 437/472 x 100
Specificity = 93%

Positive predictive value = 4/39 x100
Positive predictive value = 11%

Negative predictive value = 437/446 x 100
Negative predictive value = 98%

Qu 107c: Are these symptoms no different at the beginning or end of the working week?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	2	134	136
	No	10	352	362
	Total	12	486	498

It is presumed that the 5 expert panel definite EAA case and the 292 workers not diagnosed with definite EAA, who answered no to question 98, ‘In the past twelve months have you suffered recurrent flu like symptoms?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 2/12 x 100
Sensitivity = 17%

Specificity = 352/486 x 100
Specificity = 72%

Positive predictive value = 2/136 x100
Positive predictive value = 1%

Negative predictive value = 352/362 x 100
Negative predictive value = 97%

Qu 108a: Do these symptoms occur more frequently or are more severe on returning to work after a weekend break from work?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	6	42	48
	No	7	429	436
	Total	13	471	484

It is presumed that the 5 expert panel definite EAA case and the 292 workers not diagnosed with definite EAA, who answered no to question 98, ‘In the past twelve months have you suffered recurrent flu like symptoms?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 6/13 x 100
Sensitivity = 46%

Specificity = 429/471 x 100

Specificity = 91%

Positive predictive value = 6/48 x100

Positive predictive value = 13%

Negative predictive value = 429/436 x 100

Negative predictive value = 98%

Qu 108b: Do these symptoms occur more frequently or are more severe on returning to work after a holiday break from work?		Expert panel definite EAA cases	Respondents not diagnosed with definite EAA	Total
	Yes	6	50	56
	No	7	420	427
	Total	13	470	483

It is presumed that the 5 expert panel definite EAA case and the 292 workers not diagnosed with definite EAA, who answered no to question 98, ‘In the past twelve months have you suffered recurrent flu like symptoms?’ would answer no to this question. In reality they did not answer this question as they were requested to miss this question.

Sensitivity = 6/13 x 100

Sensitivity = 46%

Specificity = 420/470 x 100

Specificity = 89%

Positive predictive value = 6/56 x100

Positive predictive value = 11%

Negative predictive value = 420/427 x 100

Negative predictive value = 98%

Appendix 4
Published work

Systematic Review of Respiratory Outbreaks Associated with Exposure to Water-Based Metalworking Fluids

C. M. Burton, B. Crook, H. Scaife, G. S. Evans and C. M. Barber.

Ann. Occup. Hyg., Vol. 56, No. 4, pp. 374–388, 2012

Systematic review of respiratory case definitions in metalworking fluid outbreaks

C. M. Barber, C. M. Burton, H. Scaife, B. Crook and G. S. Evans

Occupational Medicine 2012;62:337–342 8 May 2012

Hypersensitivity Pneumonitis in Workers Exposed to Metalworking Fluids

C. M. Barber, C. M. Burton, D. J. Hendrick, A. C. Pickering, A. S. Robertson, W. Robertson, P. S. Burge.

Am J Ind Med. 2014 Jun 20. doi: 10.1002/ajim.22337.

Re: Hypersensitivity pneumonitis and metalworking fluids contaminated by mycobacteria.

C.M.Barber, C. M. Burton, E. Robinson, B. Crook, G. Evans, D. Fishwick.

Eur Respir J. 2011 Aug;38(2):486-7; author reply 487-8. doi: 10.1183/09031936.00027611.