

Systematic review of respiratory case definitions in metalworking fluid outbreaks

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Background	Since the mid-1990s, outbreaks of asthma and extrinsic allergic alveolitis (EAA) have been identified in workers exposed to metalworking fluids (MWFs). The cause of these outbreaks remains to be determined.
Aims	To identify and review all previously published occupational lung disease case definitions and diagnostic criteria that have been utilized during MWF outbreak investigations.
Methods	Respiratory outbreaks due to MWFs were identified by a systematic literature search for articles published between 1990 and October 2011. Investigations reporting the usage of disease case definitions or diagnostic criteria for respiratory disease were reviewed and summarized.
Results	The literature search identified 35 papers relating to 27 outbreaks of respiratory disease in MWF-exposed workers. Fourteen case definitions for MWF-related respiratory disease were identified: seven for EAA, five for occupational asthma and one each for humidifier fever and industrial bronchitis. A single paper was identified where any comparison of different disease case definitions (for EAA) had been performed.
Conclusions	A range of case definitions and diagnostic criteria for MWF respiratory disease have been utilized in outbreak investigations, but the majority have been produced for individual outbreak investigations without previous validation. It may be difficult to compare the findings of future workplace studies without a more standardized approach to case identification and diagnosis.
Key words	Case definitions; extrinsic allergic alveolitis; hypersensitivity pneumonitis; metalworking fluids; occupational asthma; outbreak.

Introduction

Cases of occupational asthma due to exposure to water-containing metalworking fluid (MWF) began to be recognized in the UK in the mid- to late 1980s [1,2], shortly after the first outbreaks of extrinsic allergic alveolitis due to MWFs (MWF-EAA) were reported in the USA [3–5]. Outbreaks have also been identified in the UK [6–8] and France [9]. Despite detailed health and hygiene investigations, the exact aetiology has been difficult to establish [10], in part due to the complexity of possible exposures [11].

Where outbreaks of respiratory disease have occurred in large workplaces, often with several hundred MWF-exposed employees, a number of investigators have proposed disease case definitions. Accurate recognition of workers with allergic occupational lung disease

is of great importance during outbreaks to improve prognosis for the individual and to assist in identifying the cause. The aim of this study was to identify all previously published outbreaks of MWF respiratory disease in order to compare and summarize previously utilized case definitions.

Methods

A multidisciplinary research team, comprising two clinical staff, two microbiologists and an immunologist, agreed appropriate search terms for a systematic literature review, in consultation with the Health & Safety Executive library information search team. The literature review was designed to identify all previously published health outbreaks due to exposure to MWFs, published

between 1990 and October 2011. Further details can be found elsewhere [11], but briefly searches were conducted in OSHROM (HSELINE, NIOSHTIC, CISDOC, RILOSH and OSHLINE) databases, Embase, Medline, HEALSAFE and Web of Science. A total of 1681 titles were identified by the literature search, and following review by the multidisciplinary team, 384 abstracts were reviewed. From these, 35 papers relating to 27 outbreaks of respiratory disease in MWF-exposed workers were identified, and the references of selected articles were checked for other relevant articles. Eleven articles relating to outbreaks where case definitions or diagnostic criteria for MWF respiratory disease had been utilized were selected for inclusion in the review. Case definitions for MWF-EAA and asthma were summarized in standardized summary tables.

Results

The first case definitions for MWF-related respiratory ill-health identified by the review were utilized in an outbreak in a Wisconsin automobile manufacturing plant that employed nearly 1600 workers [12]. Thirty workers presented to the Asthma and Allergy Centre at the Medical College of Wisconsin between March 1996 and May 1997. Assessments included history, examination, pulmonary function testing (spirometry, lung volumes, diffusing capacity, methacholine challenge and pre- to post-exercise blood gases as appropriate), chest X-rays (CXR), serum precipitins (to used and neat MWFs, and isolated bacteria) and in one case transbronchial biopsy. The case definitions used for this outbreak were based on required and supportive features, and included EAA, occupational asthma and industrial bronchitis. No specific detail was provided in the paper as to how these case definitions had been developed or selected, but seven cases of MWF-EAA, 12 cases of occupational asthma and six cases of industrial bronchitis were identified. Of the seven cases of hypersensitivity pneumonitis, four workers were able to return to work off medication with respiratory protective equipment, one worker was not able to tolerate the workplace due to recurrent symptoms, and two workers remained off work due to persistent symptoms.

Another case definition published around the same time for MWF-EAA was used in an investigation in workers from a large US engine manufacturing plant [13]. Between August 1995 and April 1996, 81 of 1592 workers had reported work-related respiratory symptoms. The Wisconsin Division of Health carried out an investigation, and employees who had previously reported respiratory symptoms were offered a comprehensive evaluation comprising a self-administered respiratory questionnaire; a structured interview to assess medical history, work history and occupational exposures; spirometry and diffusion capacity; phlebotomy for precipitin analysis; and

a review of medical and employment records. Of the 81 workers reporting respiratory symptoms, 71 were evaluated by pulmonologists or allergists. Of these workers, 22 were diagnosed with EAA, 12 with occupational bronchitis/possible EAA, 15 with occupational bronchitis and three with occupational asthma. An epidemiological case definition for MWF-EAA was then developed to facilitate a case-control study in order to identify risk factors for disease. This was based on seven criteria, with a definite case having six or seven positive criteria, a probable case having five criteria and a possible case having four criteria. Of the 22 workers who had previously been clinically diagnosed with MWF-EAA, 20 met the epidemiological case definition, with 10 definite cases, five probable cases and five possible cases. In their discussion, the authors acknowledged that the case definitions had been developed by themselves for the purpose of their case-control study and had not been previously validated.

A further US outbreak of EAA in MWF-exposed workers was reported in 2001, in a Connecticut factory that produced precision parts for the aerospace industry. This outbreak began in 1996 and was recognized following the identification of a cluster of EAA cases [14]. All workers from the plant were then invited to be examined at the University of Connecticut Occupational and Environmental Medicine Unit, where they underwent a standard clinical assessment of history, examination, spirometry before and after work, CXR, thin-section computed tomography of the chest, gallium scan and full lung function tests. Workers suspected of having EAA after these tests were then offered invasive tests in the form of transbronchial or thoracoscopic lung biopsies for confirmation. Diagnosis of EAA required symptoms consistent with the disease (including at least one systemic symptom and one respiratory complaint) in association with a positive biopsy. The workplace was also screened with a cross-sectional survey using a combination of three previously developed questionnaires. Questionnaire-based case definitions were then developed for EAA and occupational asthma, which required all features to be present.

In contrast to other previously published MWF-EAA case definitions [12,13], these did not require respiratory or systemic symptoms to be work related. The authors stated two main reasons for this, the first relating to work pattern, with workers spending 6 or 7 days a week in the plant and not having sufficient time away to recover. The second reason cited was that MWF-EAA may present in a chronic form, where improvement away from work may not be evident. Although the sensitivity and specificity of these criteria were not documented, an attempt to examine the validity of the questionnaire case definitions was made by comparison with the definite biopsy-proven cases of MWF-EAA. This demonstrated that 7 of 10 biopsy-proven cases did fulfil the above case definition,

but that a much looser case definition would have been needed to identify all 10 cases. The authors also noted a significant overlap of the questionnaire case definitions, with 60% of the MWF-EAA clinical cases also fulfilling their looser definition for occupational asthma.

The investigation of this outbreak led to the development of an evidence-based case definition for MWF-EAA, in part to avoid the cost and morbidity of lung biopsies [15]. Using regression models, a non-invasive hypersensitivity pneumonitis diagnostic index (HPDI) was developed based on significant clinical differences between 16 biopsy-proven MWF-EAA cases and 14 workers from the same workplace who were thought least likely to have MWF-EAA. The HPDI criteria were similar in concept to the case definitions published by Fox *et al.* [13], resulting in definite (HPDI 6 or more), probable (HPDI 4–5) or possible (HPDI 3) cases. In the HPDI, the seven criteria allowed a maximum score of 9, as two of the seven criteria (gas transfer and erythrocyte sedimentation rate) were weighted and could be scored as 0, 1 or 2 depending on the severity of abnormality.

The authors went on to attempt to validate the HPDI by applying it to the other 31 workers from the outbreak (i.e. not biopsy-proven MWF-EAA and not the group thought originally to be the least likely to have MWF-EAA), identifying a further 20 cases and 11 non-cases. They also compared the performance of their HPDI with the criteria published by Fox *et al.* [13] for all 61 workers. This demonstrated a good level of agreement between the two sets of case definitions ($\kappa = 0.766 \pm 0.093$), although four patients who met the case definition by the HPDI did not meet the Fox *et al.* criteria, and the reverse was true for two other patients.

After three machinists had been hospitalized with EAA, the National Institute of Occupational Safety and Health (NIOSH) performed a health hazard evaluation (HHE) in a US automobile brake manufacturing facility in Ohio [16,17]. Review of employment records found that 107 of the 400 workers in the factory had been placed on work restriction due to respiratory problems in the preceding 11 months. Review of health records for 32 of the 37 workers on medical leave at the time of the investigation found that 14 met their case definition for occupational asthma and 12 met their case definition for MWF-EAA. No reference is made in the report as to how these criteria were developed or selected.

NIOSH also reported the results of another HHE, following an index case of EAA in a toolmaker [18,19]. The company in Indiana manufactured automatic transmissions for automobiles, using semi-synthetic MWFs, and employed approximately 2000 workers. The investigators utilized the MWF-EAA case definition developed by Fox *et al.* [13] and compared cytokine responses to *Mycobacterium immunogenum* between cases and controls.

Further outbreaks of MWF-EAA were identified in 2003–04, following an investigation in Michigan by Michigan Occupational Safety and Health Administration of three separate plants manufacturing automobile parts [20]. This followed the identification of seven cases of MWF-EAA, 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. The investigation comprised a medical notes review, and cases were identified based on general (not specific for MWF exposure) diagnostic criteria previously developed for EAA [21]. Diagnosis of a case of MWF-EAA required the patient to fulfil four major and two minor criteria, in addition to other diseases with similar symptoms being ruled out. The criteria were originally designed for clinical diagnosis, including follow-up of individual cases, rather than an outbreak investigation, and are therefore quite stringent.

Of the seven cases of MWF-EAA described in this investigation, all fulfilled four of the major criteria, but only five fulfilled the requirement of two minor criteria. In this study, the investigators noted limitations of their diagnostic criteria and stated that they had confirmed definite MWF-EAA cases with three other diagnostic criteria [22–24], although no comparative data were presented. Only two of the workers with MWF-EAA from this outbreak returned to work with MWFs, both with modifications to their exposures and without recurrence of their symptoms.

In 2006–07, a report of a large outbreak of respiratory ill-health was published outside of the USA, relating to cases occurring between 2003 and 2004 in a UK car engine manufacturing plant [6,25]. This outbreak was investigated in detail using a phased approach. Initially, all (836) employees were provided with a self-completed 11-point screening questionnaire, with symptomatic workers being invited to undertake a detailed health questionnaire, spirometry and phlebotomy. Based on these results, workers with suspected occupational lung disease were invited to attend Birmingham Chest Clinic for detailed clinical assessments as appropriate, including allergy tests, radiology, airway responsiveness to methacholine, full lung function, serial peak flow measurements and bronchoscopy. In this study, the investigators agreed case definitions for MWF-EAA, occupational asthma and humidifier fever, although the rationale for their selection and/or modification was not reported.

The case definition for MWF-EAA was based on the criteria developed by Fox *et al.* [13] although five of the seven criteria were slightly modified. The case definition for occupational asthma was based on compatible symptoms with a positive work effect on computer analysis of peak flow charts (OASYS), and the humidifier fever case definition was based on compatible symptoms. This study also noted some overlap in that eight workers met the case definitions for both MWF-EAA and asthma.

Table 1. Summary of components of different case definitions for EAA due to MWF exposure

References	Respiratory symptoms	Systemic symptoms	Crackles/crepitations on chest auscultation	FVC	Gas transfer	Radiology	Histology or cytology	Blood test	Other
Zacharisen <i>et al.</i> [12]	Work related or progressive	Insidious	–	+	+	Chest X-ray	Biopsy	Ppn	–
Fox <i>et al.</i> [13]	2 recurrent	1 recurrent	–	+	+	Chest X-ray/ CT scan	Biopsy	–	Physician diagnosis
Hodgson <i>et al.</i> [14]	1 usually or sometimes	1 usually or sometimes	–	–	–	–	–	–	–
Dangman <i>et al.</i> [15]	2 work related	1 work related	+	+	+	Chest X-ray/ CT scan	–	ESR	Gallium
Weiss <i>et al.</i> [16]	1 work related	1 work related	–	+	–	Chest X-ray/ CT scan	–	–	–
Gupta and Rosenman [20]	Symptoms of EAA	Symptoms of EAA	+	–	+	Chest X-ray/ CT scan	BAL/biopsy	Ppn	Challenge, hypoxia
Robertson <i>et al.</i> [25]	2 work related	1 work related	–	+	+	Chest X-ray/ CT scan	BAL/biopsy	–	Physician diagnosis

BAL, bronchoalveolar lavage; CT, computed tomography; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; Ppn, serum precipitating antibody.

When presented in summary format (Table 1), it can be seen that all of the case definitions for MWF-EAA contain broadly similar elements but differ in the exact number and combination of required symptoms and abnormal test results. Similarly for occupational asthma (Table 2), the case definitions require work-related symptoms but vary in terms of the physiological test chosen to confirm asthma.

Discussion

This review identified 14 different case definitions for MWF-related respiratory disease: seven for EAA, five 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 [12–14,16,20,25]. Only one paper was identified where the performance of different disease case definitions was compared [15]. The systematic review failed to identify any accepted ‘gold standard’ respiratory case definitions for use in MWF outbreaks.

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.

Table 2. Summary of components of different case definitions for occupational asthma due to MWF exposure

References	Respiratory symptoms	Systemic symptoms	Pulmonary function test	Bronchial hyperresponsiveness	Total lung capacity	Radiology
Zacharisen <i>et al.</i> [12]	Work related	–	Obstruction with reversibility	+	Normal	Hyperinflation or atelectasis
Hodgson <i>et al.</i> [14] ^a	1 work related	–	–	–	–	–
Hodgson <i>et al.</i> [14] ^b	3 work related	–	–	–	–	–
Weiss <i>et al.</i> [16]	1 work related	Absent	Obstruction with reversibility	–	–	No infiltrate on chest X-ray/ computed tomography
Robertson <i>et al.</i> [25]	Suggestive of OA	–	Diagnostic peak expiratory flow record	–	–	–

OA, occupational asthma.

^aLoose case definition.

^bTight case definition.

The range of case definitions identified reflects the different formats of outbreak investigations that have been utilized, which in part may be determined by the nature of the outbreak. By definition, the outbreaks are usually unexpected and have to be investigated quickly in order to minimize further harmful exposures. Case definitions need to identify workers with occupational lung disease while excluding workers with identical symptoms due to irritant bronchitis, humidifier fever, unrelated viral infections or chronic obstructive pulmonary disease. The value of utilizing a positive biopsy as a gold standard test for EAA during outbreaks [4,14] is limited by a number of factors, including interpretation of histopathology, false-negative rates, cost and patient acceptability [15].

For MWF-EAA, the most common case definitions utilized in outbreaks have been those published by Fox *et al.* [13], which were used in their original or modified format in four outbreaks [13,15,19,25]. In their original paper, the authors acknowledged that a major limitation to their study was that their 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 cases.

One set of MWF-EAA criteria (the HPDI) has been developed by statistical analysis of outbreak data, with some attempt at validation and comparison with another MWF-EAA case definition [15]. Despite this, since their publication in 2002, they have not been utilized in subsequent US, UK or French outbreaks [9,20,25]. The HPDI includes a criterion based on the results of a gallium scan, a test that is not routinely performed in the assessment of EAA [26].

In one further outbreak, the MWF-EAA case definition chosen was an existing general EAA diagnostic criterion that had previously been developed for EAA of any cause [21]. The level of clinical certainty required to diagnose a single isolated case of EAA is clearly different from that required when a number of similar cases have been diagnosed from the same workplace. These criteria were not developed from MWF outbreak data, are comparatively stringent and may be limited in usefulness for MWF-EAA unless a standardized serum or bronchoalveolar lavage antibody can be established. The authors acknowledged the limitations of these criteria in MWF outbreaks and therefore checked their cases by applying three other general EAA diagnostic criteria. 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 utilized in this study [21,22,24] have not been previously validated [26]. This study did also utilize an evidence-based EAA prediction rule developed by an international study group, based on clinical differences between patients with suspected EAA, who did or did not have EAA as their final diagnosis [23].

The significant predictive factors for EAA in this study included exposure to a known cause of EAA, positive serum precipitins, recurrent episodes of symptoms, lung crackles, symptoms 4–8 h after exposure, and weight loss. These factors were then combined into a model to allow a calculation of how likely EAA was to be the underlying cause for any patient presenting with possible EAA. Further studies are required to see whether this type of prediction rule is also of value in MWF outbreaks, where all workers are exposed, and no standard precipitin test has been established.

For occupational asthma, case definitions used have also varied, with no published comparative data or validation against specific challenge.

Although the majority of health investigations have originated in the USA, MWF outbreaks have also been reported from Europe [6–9,25]. In addition to this, cross-sectional studies have reported an excess of respiratory symptoms in German [27], Belgian [28], Swedish [29] and Finnish [30] MWF-exposed workers. Given the large number of MWF-exposed workers (estimated at over 1 million US workers) [10] and the largely unexplained nature of these outbreaks, it is likely that future health investigations will be required. At present, the Fox criteria offer the case definition for MWF-EAA that investigators have most experience with. Further research is required, however, to examine whether more valid and evidence-based case definitions can be developed to facilitate comparison between study findings and better understand the aetiology of these complex diseases.

Key points

- Workers exposed to metalworking fluids are at risk of developing occupational lung disease, particularly asthma and alveolitis.
- A number of outbreaks of these diseases have been reported in large workplaces, where different case definitions have been utilized to identify workers with occupational lung disease.
- Very little comparative or validation data currently exist to inform the choice of case definitions for occupational lung disease in future outbreak investigations.

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Conflicts of interest

None declared.

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