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# Hypersensitivity Pneumonitis Due to Metalworking Fluid Aerosols

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**Abstract**
*Purpose of Review* This review summarises the clinical knowledge of hypersensitivity pneumonitis in workers exposed to aerosols of metalworking fluid, reviewing published outbreaks and clinical cases.
*Recent Findings* Metalworking fluid exposure has become the commonest recognised cause of occupational hypersensitivity pneumonitis, having been rare before 2000. There are many possible agents in the metalworking fluid which may be the cause of disease including bacteria, mycobacteria, fungae, biocides, emulsifiers, reodorants and dissolved chrome and cobalt. Causes are likely to be different in different outbreaks. Mycobacteria growing in the metalworking fluid have generated immune responses in some workers, but their role in disease causation is not yet established. Many outbreaks have been identified in large workplaces using common sumps.
*Summary* It is not possible to prevent microbial contamination of metalworking fluids in use. Disease prevention should focus on stopping inhalation of aerosols, particularly by re-engineering to remove recirculation.

**Keywords** Hypersensitivity pneumonitis · Metalworking fluid · Occupational asthma · Aerosol inhalation

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## Introduction

Metalworking fluids are needed to cool and lubricate metal being ground, drilled or otherwise worked on. The industry started by using neat mineral oils. These have largely been replaced by water-based emulsions using soluble mineral and semi-synthetic or synthetic oil. The addition of water encourages microbial growth so that biocides are added, together with corrosion inhibitors, detergents, high-temperature additives, reodorants and many others. Many products are sold based on their properties; their formulation can change without change of product. In addition, the metalworking fluid may become contaminated by hydraulic and sliding oils used on the same machines (tramp oil), as well as metals dissolved from the machine tools or the metals being worked on, resulting in a complicated mix that changes over time and between workplaces.

Hypersensitivity pneumonitis is only one of the many respiratory diseases caused by the inhalation of metalworking fluid aerosols. Outbreak investigations have identified workers with occupational asthma as well as a wide range of interstitial lung diseases. The first case of hypersensitivity pneumonitis due to metalworking fluid aerosols was published in full in 1996, although there is an abstract describing the microbiology of an outbreak in 1993 [1, 2]. Since then, metalworking fluid aerosols have become the commonest recognised cause of occupational hypersensitivity pneumonitis in the UK moving from 5 % before 2004 to 50 % since [3].

## Epidemiology

A comparison of European registries showed that hypersensitivity pneumonitis accounts for 4–15 % of all interstitial lung diseases [4]; in our service in Birmingham, UK, 9.4 % of

interstitial lung diseases are due to hypersensitivity pneumonitis [5]. The UK data since 2004 shows that metalworking fluid exposure accounts for half of all recognised causes of occupational hypersensitivity pneumonitis [3], most recognised cases occurring as part of outbreaks in individual workplaces.

## What Does Hypersensitivity Pneumonitis Incorporate?

There is no generally agreed definition of hypersensitivity pneumonitis nor on its classification into stages or subgroups. All agree that there needs to be 'immunologically induced inflammation of the lung parenchyma' [6] or 'pulmonary disease with symptoms resulting from the inhalation of an antigen to which the patient has previously been sensitised' [7••]. There is general agreement that a new classification of disease is required based on clinically relevant data. Lacasse proposed two clusters largely related to the presence or absence of pulmonary fibrosis. The presence of more restrictive spirometry, fibrosis on high-resolution CT (HRCT), hypoxia and clubbing identified cluster 2, features of cluster 1 included more recent systemic symptoms of fever, chills and body ache and a normal CXR. Non-discriminatory features included nodular features on the HRCT [7••]. There is little agreement as to whether cluster 1 develops into cluster 2 (or in old terminology whether acute hypersensitivity pneumonitis develops into chronic hypersensitivity pneumonitis), although there is some clinical evidence against this [8•]. Subacute hypersensitivity pneumonitis, part of the old classification, is inseparable from cluster 1. The fibrotic form of the disease often has the histological features (and prognosis) of non-specific interstitial pneumonitis or usual interstitial pneumonitis [9•].

Clinicians have problems in identifying hypersensitivity pneumonitis in the first place, and an even bigger problem in identifying its cause. In many outbreaks, there are more workers with occupational asthma than hypersensitivity pneumonitis from the same work environment, and an increased incidence of other interstitial lung diseases including usual interstitial pneumonitis, desquamative interstitial pneumonitis, non-specific interstitial pneumonitis, lipoid pneumonia, sarcoidosis and Langerhans cell granulomatosis, all of which may have a common cause [10••, 11].

## The Diagnosis of Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis (previously called extrinsic allergic alveolitis in the English literature) is commonly misdiagnosed, both by primary care and hospital physicians. Cases may occur during outbreaks from a single source, or sporadically. In one outbreak, none of 12 patients admitted to hospital with acute symptoms during the outbreak had a diagnosis of hypersensitivity pneumonitis; diagnoses ranged from 'not heart' in two initially suspected of myocardial infarction to pneumonia, asthma, COPD or idiopathic pulmonary fibrosis [12]. Similarly in patients undergoing lung biopsy for interstitial lung diseases where the pre-biopsy diagnosis was unclear, only 2/8 with a multi-disciplinary consensus diagnosis of hypersensitivity pneumonitis had this in the pre-biopsy differential diagnosis [13]. Features which should alert the physician following an acute presentation include the length of history (usually weeks or more making pneumonia unlikely), the presence of bilateral crackles on lung auscultation (unlikely in asthma or COPD), weight loss, which is often prominent (making tuberculosis in the differential diagnosis) and restrictive spirometry (separating it from asthma and COPD). Confusion may arise because the chest X-ray is often normal, crackles may be absent and lung function has not been carried out during an acute admission. Thin-section HRCTs and bronchoalveolar lavage differential cell counts often provide sufficient evidence for and Interstitial Lung Disease Multi-Disciplinary Team (MDT) diagnosis of hypersensitivity pneumonitis. Thin-section HRCT of the lungs showing ground class opacification with sparing of some pulmonary lobules (mosaic attenuation) is very characteristic, even on inspiratory scans. The CT was only normal in 4/116 in the largest series of hypersensitivity pneumonitis from a mixture of causes [7••]. If there is any doubt as to the diagnosis, a bronchoalveolar lavage showing >20 % lymphocytes supports the diagnosis [14•]. Exposure to a known cause of hypersensitivity pneumonitis, such as metalworking fluid, has a higher predictive value than the presence of precipitating (IgG) antibodies, particularly when exposure-related symptoms are present [7••].

In clinical practice, hypersensitivity pneumonitis is often a firm diagnosis from an interstitial lung disease MDT on the basis of lung CT, physiology and bronchoalveolar lavage (BAL) lymphocytosis, when the causative agent is unrecognised. The cause may be at work, at home, from the environment or undetermined (perhaps idiopathic hypersensitivity pneumonitis). Serial 2-h measurements of peak expiratory flow over 4 weeks with periods at and away from work analysed with the Oasys plotter have identified occupation as the cause in 75 % of those with hypersensitivity pneumonitis in one outbreak [15]. It may seem illogical to use peak expiratory flow as the marker of hypersensitivity pneumonitis, as it cannot differentiate between obstructive and restrictive lung diseases, but is easier to measure reproducibly unsupervised in the workplace than FVC. However, PEF declines in parallel with FVC in restrictive lung disease (Fig. 1).

There are several scoring systems to identify workers with hypersensitivity pneumonitis during epidemiological investigations of epidemics, weighting work-related respiratory symptoms, weight loss, restrictive spirometry, CT changes,

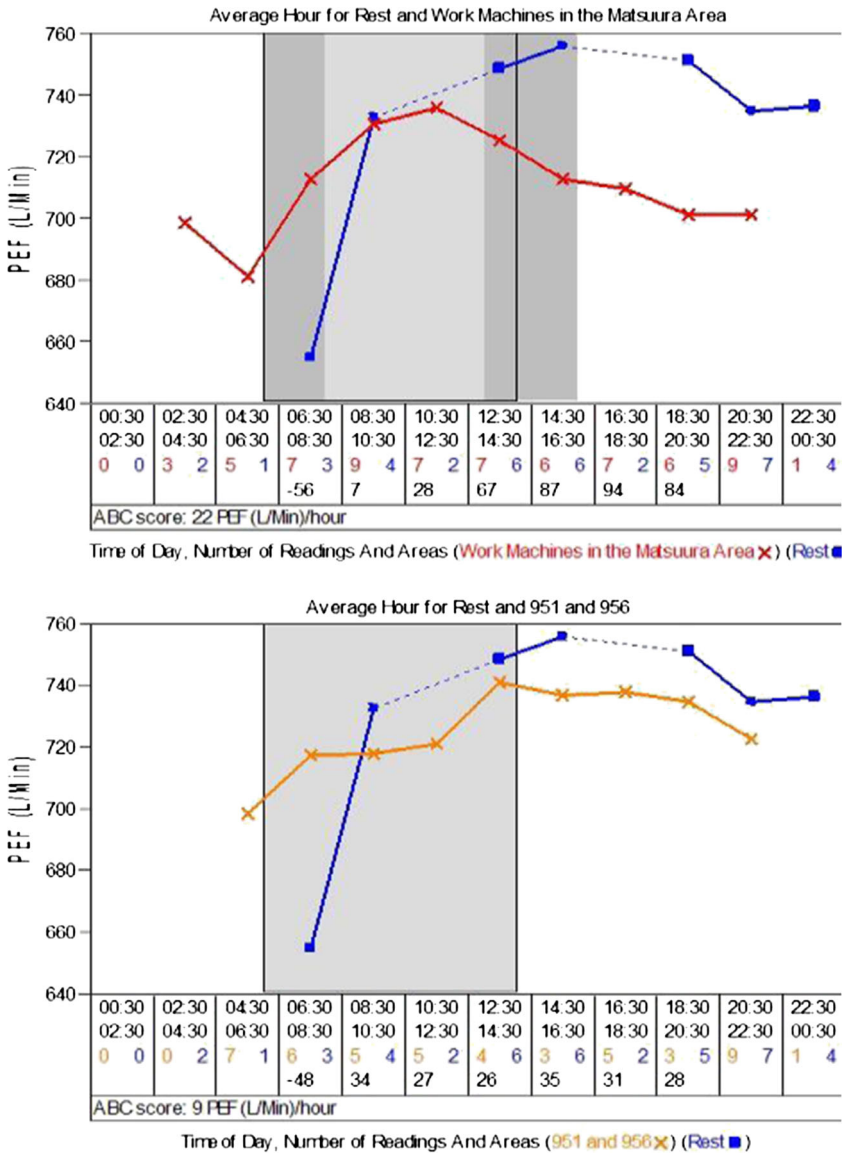


**Fig. 1** Area between curves (ABC) plots of serial peak expiratory flow measurements in a CNC operator with hypersensitivity pneumonitis from used metalworking fluid, using the Oasys analysis system. The plot shows mean PEF on the *y*-axis divided into 2-h time intervals from waking to sleeping on the *x*-axis. The working period is *shaded*. The mean values for all days away from work are in *blue*, showing a rise from waking to peak in the early afternoon. The *top panel* shows the mean PEF on days working on one set of machines (Matsuura) declining 8–14 h after starting work, with an ABC score of 22 l/min/h (positive >15). The *lower panel* shows in *orange* the PEF on days working on different machines (951 and 956) showing a negative ABC score of 9 l/min/h, suggesting that the cause was associated with the Matsuura machine. At the foot of each panel is the time and the number of days contributing to each point, with the difference between work and no-work for each time point below this (a minus value showing higher values on work days)

and BAL lymphocytosis or lung histology (Table 1) [14•]. This is a development of the scoring system developed by Fox in 1999 [16].

Even if the diagnosis of hypersensitivity pneumonitis has been made correctly during an acute presentation, identifying the cause is difficult. The patients work is often not recorded in the medical records. In one study of electronic primary care records, the job was only recorded in 14 % of asthmatics of working age [17]. As hypersensitivity pneumonitis is not a notifiable disease in most administrations, linking cases to a common source is outside the scope of most clinicians. The occupational physician has a better chance, but only if the treating physician has made the correct diagnosis and that this is available to the occupational physician. Unfortunately in the UK, most workers do not have access to occupational physicians.

In the context of interstitial lung disease in workers exposed to metalwork fluids, hard metal disease must also be considered. This can occur from cobalt (the binder in sintered hard metal) from tools used in metalworking dissolving into the metalworking fluid, or from cobalt-containing alloys being worked. The histology is giant cell interstitial pneumonitis, distinct from hypersensitivity pneumonitis, but with many similar clinical features. Exposed workers would usually have elevated levels of cobalt in urine or blood. BAL lymphocytosis is not seen but multinucleated macrophages are characteristic [18, 19].

## Measurement of Metalworking Fluid in Air

Most measurements of metalworking fluid in air measure the mineral oil content. Using this, measurements have declined from a mean of 5.4 mg/m$^2$ prior to the 1970s to 2.5 mg/m$^2$ in the 1970s, 1.2 mg/m$^2$ in the 1980 and 0.50 mg/m$^2$ in the 1990s

**Table 1** Scoring system for the diagnosis of metalworking fluid hypersensitivity pneumonitis for use during outbreaks

| | Score |
|---|---|
| Respiratory symptoms | |
| Work-related cough, wheeze, chest tightness or breathlessness | +4 |
| Stopping for breath while walking at own pace on level ground | +6 |
| Previous time off work with chest illness | +7 |
| Constitutional symptoms | |
| Recurrent flu-like symptoms worse at the end of the working week | +5 |
| Unexplained weight loss | +7 |
| Lung function | |
| FVC <80 % predicted | +3 |
| FVC <70 % predicted and DLCO <80 % predicted | +5 |
| DLCO <60 % predicted | +10 |
| Radiology/clinical examination | |
| CXR diffuse ground glass nodules | +6 |
| CT ground glass nodules, mosaic attenuation or UIP pattern | +7 |
| Velcro crackles on auscultation | +7 |
| Evidence of inflammation | |
| Neutrophils $>7 \times 10^9$/l or CRP ≥10 mg/l | +5 |
| BAL lymphocytes ≥20 % | +8 |
| Lung biopsy typical of subacute HP or UIP | +10 |
| Total (maximum 41) | |

Only the highest score in each box is used. Definite hypersensitivity pneumonitis >26, possible 19–26, and definitely not hypersensitivity pneumonitis <19

and 2000s. This is taken from an important review of the measurement of metalworking fluid in air [20•]. This reduction seems largely due to the lower concentration of mineral oil in semi-synthetic and synthetic metalworking fluids, whose use has increased over this period. Grinding produces higher total levels than other types of machining, and the measurements from the automotive industry are generally higher than those from smaller workshops, which correlates with the larger number of reports from automotive than other areas of metal machining [21••].

There is a need for a more relevant measure of metalworking fluid in air, as nearly all the outbreaks have had exposure measurements within the exposure standards based on mineral oil in air. Boron was used as a corrosion inhibitor in water-based metalworking fluids and provided a useful measure of metalworking fluid in air. However, boron may be teratogenic and has been withdrawn from most synthetic oils leaving a current gap in our ability to have a relevant measure of metalworking fluid in air. There is a current consultation from the UK Health and Safety Executive proposing a measure of respirable particles as a standard [22].

## Causes of Hypersensitivity Pneumonitis Due to Metalworking Fluid

An excellent systematic review identified all 27 published outbreak reports of occupational asthma or occupational hypersensitivity pneumonitis due to metalworking fluid aerosols from 1990 up to October 2011. It included many reports from regulatory agencies outside the usual sources of references [21••]. The review did not separate outbreaks with occupational asthma alone from those with hypersensitivity pneumonitis, but nearly all are likely to have contained workers with hypersensitivity pneumonitis. Automobile manufacturers comprised 63 % of the outbreaks and aerospace 15 %. Smaller users were uncommon, which could be due to lower exposures or a reduced likelihood of identification of cases. The average risk of developing an allergic respiratory disease was 5.6 % (0.3–37.5) in the workplaces studied. All types of metalworking fluid were in use in the outbreak workplaces, with 36 % using soluble oil, 24 % semi-synthetic and 8 % synthetic metalworking fluids. Many used a combination. Most workplaces (83 %) had at least some machines using a common sump.

Microbial contamination of the metalworking fluids was very variable, ranging from no detectable growth to those with high levels of bacteria, mycobacteria, and fungae. High levels of microbial growth have been found in workplaces without disease showing that contaminated metalworking fluid alone is insufficient to cause disease [11, 23]. In some samples where no organisms could be grown, their presence could be inferred by finding increased levels of endotoxin or glucans, or detected by identification of microbial DNA. Endotoxin levels in metalworking fluid varied from undetectable to

$5.4 \times 10^5$ endotoxin units/ml. Airborne endotoxin varied from undetectable to 126 endotoxin units/ml. Again, there is no clear relationship between measurements of endotoxin and the presence or absence of disease [11]. Reports since this systematic review have not altered the conclusions or identified new causes in this group [24–27].

An interesting study from France showed that there were significant differences between samples taken from automotive and non-automotive workplaces. Gram-negative rods were common in screw and metal cutting workplaces, where hypersensitivity pneumonitis was uncommon. In contrast, samples taken from factories with cases of hypersensitivity pneumonitis manufacturing parts for the automotive industry showed predominantly Gram-positive rods. *Mycobacterium immunogenum* was found in both situations, but more so (up to 38 % of samples) in those from the automotive industry. Working with chrome, nickel or iron encouraged Gram-negative rods; conversely, the growth of Gram-positive rods was associated with the absence of these metals. The type of metalworking fluid also influenced microbial growth, with a prominence of Gram-positive rods in samples based on vegetable oils, while mineral oils encouraged Gram-negative rods. Synthetic oils showed the least microbial growth [28•]. These findings support the results from the epidemiological studies of outbreaks [21••, 29].

## Role of IgG Antibodies or Precipitins

The role of type 3 IgG-related hypersensitivity in the aetiology of hypersensitivity pneumonitis is unclear. The timing of reaction post-exposure, with most starting within 8 h of exposure, fits with a type 3 reaction, but the presence of granulomas and most of the pathology is more characteristic of a type 4 reaction. IgG antibodies to used metalworking fluid or some cultured bacteria have shown a good relationship with exposure, but a less clear distinction between those with hypersensitivity pneumonitis and exposed workers without hypersensitivity pneumonitis, and are not sufficient to identify the cause of the hypersensitivity pneumonitis alone [1, 10••, 16, 30–32]. There are few studies of type 4 reactions in metalworking fluid hypersensitivity pneumonitis. One study of 6 cases and 48 exposed controls confirmed that IgG antibody levels against *M. immunogenum* were increased in both exposed workers and workers with hypersensitivity pneumonitis. Tests for lymphocyte proliferation using *M. immunogenum*-induced interleukin-8 secretion showed indistinguishable increases in both workers with hypersensitivity pneumonitis and exposed controls. There were trends for increased *M. immunogenum*-induced secretion of interferon-$\gamma$ by peripheral blood mononuclear cells from both exposed workers and diseased workers. Perhaps surprisingly, tests of cell-mediated immunity were not more informative than measurement of serum antibodies. An alternative explanation is that *M. immunogenum* was not responsible for the disease [33]. This interpretation is supported by finding tests for lymphocyte proliferation using avian antigens to be correlated with specific challenge tests to birds in a wide range of interstitial lung diseases caused by avian antigens [9•].

## Specific Bronchial Provocation Tests

Specific inhalation challenge testing is the only way to clearly establish that a particular agent or antigen is the cause of hypersensitivity pneumonitis. These tests are most commonly done for patients with asthma or rhinitis; however, their use in hypersensitivity pneumonitis is well established [34•]. To my knowledge, the only positive test in a worker with hypersensitivity pneumonitis was provoked by used exposure to metalworking fluid. The metalworking fluid had no identifiable mycobacterial antigens and had a low microbial content. The exposure caused a delayed reaction with no increase in non-specific reactivity, not present after exposure to the unused metalworking fluid from his workplace [35]. There are several reports of specific bronchial provocation testing with metalworking fluid in patients with occupational asthma. Most react to used metalworking fluid, but a few have reacted to unused metalworking fluid, or have reacted to constituents of unused metalworking fluid colophony and pine oil used as reodorants [36, 37], biocides [38] or detergents [39, 40]. Dissolved metal, particularly cobalt and chrome, may also give positive reactions [41, 42]. Whether any of these agents are responsible for hypersensitivity pneumonitis in workers exposed to metalworking fluid is unknown, but at least colophony in the reodorant has provoked hypersensitivity pneumonitis following specific challenge [43], and cobalt can cause hard metal disease, whose presentation is very similar to hypersensitivity pneumonitis [18]. Attributing a specific organism as the cause of hypersensitivity pneumonitis is more difficult, as the antigens produced when grown in optimal conditions in the laboratory are often different from those produced under the stress conditions in the workplace. Using carefully validated recombinant antigens could provide the answer [27, 44, 45].

## Control

It is probably impossible to stop microbial growth in water-based metalworking fluids. The use of biocides selects resistant organism which can flourish in areas of the coolant circuit [46]. Cleaning and replacement of the metalworking fluid work in the short term, but microbial growth soon re-establishes itself [47•]. This was born out in our study where serial PEF monitoring showed initial control of physiological work-related

changes in workers with a mix of hypersensitivity pneumonitis and occupational asthma in 6/10 keeping records before and after cleaning. However, 3 months later, there had been at least one new case of occupational asthma and PEF records had become positive in 16 workers, only controlled satisfactorily in 4 after the stringent use of air-fed RPE in all [48].

Methods are being developed to replace recirculated metalworking fluid with nebulised coolant (minimum quantity lubricant technology). This should remove the need for biocides but still leaves the possibility of inhalation of the coolant [49]. Dry machining can also work with some alloys, but does not seem to have become at all common [50].

## Conclusions

Metalworking fluid aerosols have become a common cause of hypersensitivity pneumonitis, both when there is heavy microbial growth and when microbes cannot be identified. It is very unlikely that microbial growth can be eliminated from recycled metalworking fluids. Extensive use of biocides results in the proliferation of resistant organisms and contributes to the inhalable aerosol, at least sometimes causing occupational asthma. It seems very difficult to contain recirculated metalworking fluid aerosols using conventional enclosure, even with fully extracted CNC machines, delayed door opening and robot loading. The future is in new technology which eliminates recirculated metalworking fluid. This will prevent microbial growth and eliminate the need for biocides. There will still be a problem in capturing and removing the residual aerosol.

#### Compliance with Ethics Guidelines

**Conflict of Interest** Dr. Burge declares no conflicts of interest relevant to this manuscript.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance


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