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Systematic Review of Respiratory Outbreaks Associated with Exposure to Water-Based Metalworking Fluids

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Introduction: Potential demographic risk factors for outbreaks of respiratory disease due to water-based metalworking fluids (MWFs) were investigated through systematic review of published outbreak investigations.

Methods: Search terms were selected by a multidisciplinary team, assisted by an experienced library information service. Several computerized literature databases were searched for articles published between January 1990 and October 2011, relating to ill health outbreaks due to MWFs. Papers meeting the search criteria were reviewed in detail, and their references checked for additional articles. Study design and demographic details of the outbreak were extracted from the selected articles and entered into standardized evidence tables.

Results: Thirty-five articles relating to investigations of 27 outbreaks of respiratory ill health attributed to MWF exposure were identified. The majority of reports were case series of disease or observational cross-sectional studies of symptoms and hygiene measurements. Eight of the outbreak investigations included an element of case–control analysis. Most outbreaks were from the USA, had occurred in large car- or aeronautical-manufacturing plants, and were associated with the use of central shared sumps. Hygiene studies have not demonstrated consistent risk factors for respiratory outbreaks, in terms of the type of MWF utilized, degree of microbial contamination, or levels of personal exposure. Six studies were identified that found workers with MWF exposure during outbreaks were more likely to report respiratory or systemic symptoms than unexposed control workers. Six case–control analyses were also identified that found workers with extrinsic allergic alveolitis (EAA) were more likely to demonstrate certain immune responses to microbial contaminants and/or used MWFs than workers without EAA.

Conclusion: Despite a number of detailed workplace and immunological studies of asthma and alveolitis outbreaks in MWF-exposed workforces, our understanding of their aetiology remains limited.

Keywords: demographics; disease outbreaks; extrinsic allergic alveolitis; metalworking fluids; systematic review

INTRODUCTION

Metalworking fluids (MWFs) are used as coolants and lubricants to facilitate the manufacture of metal components. Originally, neat mineral oils were used, but in the last 30 years the composition of MWFs has evolved, with many formulations being water-based emulsions of soluble mineral, semi-synthetic, or synthetic oil. MWFs also contain many other chemical constituents to enhance the performance of the product and during their recirculation these may become contaminated with dust, debris, metal swarf, metal

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fines, hydraulic oil, bacteria, and fungi (Gordon, 2004; Gilbert *et al.*, 2010).

Health problems related to working with traditional mineral oil MWFs have predominantly been from skin disease such as folliculitis, dermatitis, and skin cancer (Mirer, 2010). Respiratory problems occurred much less commonly and were largely restricted to rare cases of lipoid pneumonia (Cullen *et al.*, 1981). With the introduction of more complex water-based MWFs, a different pattern of health problems has emerged, particularly outbreaks of occupational asthma (OA) and extrinsic allergic alveolitis (EAA; also referred to as hypersensitivity pneumonitis) (Kreiss and Cox-Ganser, 1997).

Although it has been possible to confirm that certain MWF constituents (such as alkanolamines, pine oil reodorants, and colophony) may act as occupational asthmagens (Savonius *et al.*, 1994; Piipari *et al.*, 1998), the exact aetiology of MWF outbreaks has remained elusive (Rosenman, 2009).

The aim of this study was to investigate potential demographic risk factors for outbreaks of respiratory ill health due to water-based MWFs through systematic review of published outbreak investigations.

METHODS

A systematic literature review was performed based on previously published guidance for occupational health research (Nicholson, 2007). A multidisciplinary team was formed comprising two occupational lung disease specialists, two microbiologists, and an immunologist, all with previous experience of MWF ill health investigations. This team agreed appropriate search terms for the review, in consultation with the Health and Safety Executive (HSE) library information search team. The search terms selected were divided into two groups (Table 1), and searches were carried out combining each term in list 1 with each term in list 2. List 1 included search terms for skin and dermatitis in order to identify as wider range of MWF health outbreaks as possible, as some outbreaks reported a combination of skin and respiratory disease. In order to focus the searches, they were performed based on the terms in the two lists appearing in any order within the document abstract. The 'near' operator refers to the words being no more than five words apart.

The HSE library services independently completed the search on OSHROM (HSELINE, NIOSHTIC, CISDOC, RILOSH, and OSHLINE) database, Embase, Medline, HEALSAFE, and Web of Science for articles published between January 1990 (prior to the large-scale introduction of water-based MWF) and October 2011. The search was performed in two phases, initially for articles between January 1990 and October 2008, and then repeated for articles between October 2008 and October 2011. To be included in the study, articles had to clearly relate to investigations of respiratory outbreaks in workers exposed to water-soluble MWFs (Fig. 1). Study design was assessed for each of the outbreaks, and data relating to the demographics of each outbreak were summarized in a standardized format into three evidence tables.

Table 1. 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	

RESULTS

Literature review

The majority of papers were simple observational studies comprising either case series of disease or cross-sectional workplace surveys of exposed workers with workplace hygiene measurements. The main findings from each of the outbreaks are summarized in Tables 2 and 3. Seven papers were identified where symptom prevalence, demographic factors, and/or immune responses were compared between MWF-exposed and non-exposed workers.

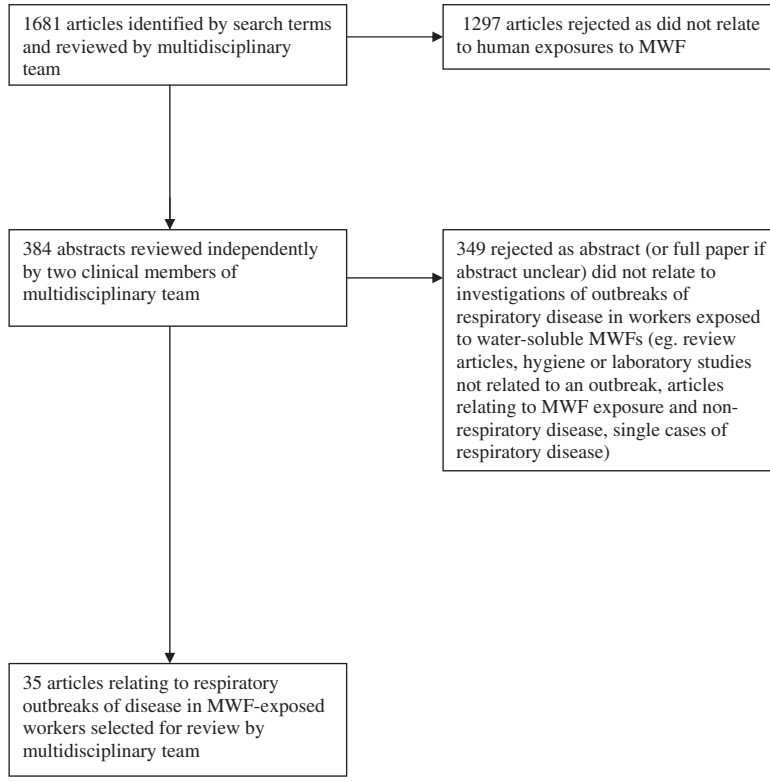

Fig. 1. Literature search.

Eight papers were identified containing some element of case–control analysis, and all comparisons identified are summarized in Table 4.

Outbreak demographics

Of the 27 outbreaks identified, 18 were related to respiratory disease, and 9 were outbreaks of a combination of respiratory and skin disease. The identified outbreak investigations dated back to the late 1980s and showed a peak incidence between 1996 and 2000 (Fig. 2). The date allocated is the date of diagnosis of the sentinel case, where it could be identified, and where this was not available, the date on which the outbreak was first recognized.

Workplace demographics

The majority (81%) of published MWF respiratory outbreak reports originated in the USA, with the remainder coming from the UK (11%), France (4%), and Croatia (4%). The most commonly affected workplaces were those manufacturing components for the automobile (63%) or the aeronautical/aerospace (15%) industry. The majority of outbreaks have been reported in large workplaces, with 73% of the workplaces (details only available for 17 outbreaks) having at least 100 MWF-exposed workers or alternatively at least 250 workers employed in total. For the 10 outbreaks where it was possible to calculate, the mean (range) proportion of exposed workers developing allergic respiratory disease was 5.6% (0.3–37.5%).

Respiratory outbreaks were identified in workplaces utilizing all types of water-based MWFs, and for the 25 outbreaks where this could be ascertained, 36% used soluble oil-/water-mixed MWFs, 32% used a range of different MWF types, 24% used semi-synthetic MWFs, and 8% used synthetic MWFs. For the 18 workplaces where information was provided, the majority operated shared central sumps (44%) or a combination of shared and stand-alone sumps (39%). Nineteen outbreaks were identified where some form of hygiene monitoring had been performed, with either personal and/or static sampling. The majority of these found mean exposure levels below the relevant national exposure limit, although in 12 of the outbreak investigations at least one reading exceeded it.

Table 2. Summary of MWF outbreak investigations in order of year of initial case.

Outbreak references	Disease	Year of initial case	Country	Industry	Exposed/ total workers	Type of MWF used	Sump	MWF aerosol levels (mg m^{-3})	Design
Hendy *et al.* (1985), Robertson *et al.* (1988)	R	1983	UK	Aeronautical	NA/NA	Soluble, neat	NA	Single reading, oil mist 0.66	Case series
Daniels *et al.* (1988)	R + S	1988	USA	Automobile	152/NA	Soluble	Both	Oil mist 7, PBZ 0.14 to 1.08	Case series
Filios *et al.* (1994)	R + S	1990	USA	Aluminium ingots	150/NA	NA	NA	NT	Cross-sectional
Piacitelli and Washko (1999)	R + S	1990	USA	Roof bolts	55/66	Soluble	Stand alone	PBZ 0.07 to 0.88	Cross-sectional
Bernstein *et al.* (1995)	R	1992	USA	Automobile	16/NA	Synthetic	Central	NT	Case–control
Rose *et al.* (1996)	R	1994	USA	Automobile (three sites)	NA/NA	Soluble	NA	NT	Case series
Fox *et al.* (1999)	R	1995	USA	Automobile	NA/1592	Synthetic	NA	Oil mist mean 0.8 (0.0 to 2.7); total particulate mean 1.0 (0.0 to 3.6)	Case–control
Zacharisen *et al.* (1998)	R	1995	USA	Automobile	800/1600	Synthetic, soluble	Central	Total particulate <REL (no values given)	Case series
Trout *et al.* (1996)	R	1996	USA	Automobile	265/NA	Soluble, semi-synthetic	Central	PBZ total particulate 0.4 to 1.4	Cross-sectional and case–control
Kiefer and Trout (1998)	R	1997	USA	Aeronautical	80/1600	Soluble	Both	PBZ total particulate 0.09 to 0.62	Cross-sectional
Trout and Burton (1997)	R	1997	USA	Firearms	450/1100	Semi-synthetic	Central	Oil mist 0.18 to 2.1	Cross-sectional
Hodgson *et al.* (2001), Dangman *et al.* (2002), Bracker *et al.* (2003), Dangman *et al.* (2004)	R	1997	USA	Aeronautical	105/120	Neat, soluble, semi-synthetic, synthetic	Central	Total particulate 0.09 to 0.38	Cross-sectional and case–control
Trout and Decker (1998)	R	1997	USA	Automobile	338/1000	Soluble, semi-synthetic, neat	Both	Total particulate 0.33 to 1.29	Cross-sectional
Kiefer and Gittleman (1999)	R + S	1998	USA	Automobile	NA/850	Neat, semi-synthetic	Central	Thoracic particulate <0.002 to 0.74	Cross-sectional
Jaksic *et al.* (1998)	R + S	1998	Croatia	Automobile	NA/NA	Soluble	NA	NA	Case series

Table 2. *Continued*

Outbreak references	Disease	Year of initial case	Country	Industry	Exposed/ total workers	Type of MWF used	Sump	MWF aerosol levels (mg m^{-3})	Design
Roegner *et al.* (2001)	R + S	1999	USA	Aerospace	204/345	Soluble, synthetic	Both	Total particulate ND to 1.84	Cross-sectional
Shelton *et al.* (1999)	R	1999	USA	Automobile (three sites)	NA/700	NA	NA	NT	Case series
Trout *et al.* (2000)	R	1999	USA	Automobile	250/462	Semi-synthetic	Central	Total particulate 0.04 to 0.74	Cross-sectional
Weiss (2002), Trout and Harney (2002a), O'Brien (2003)	R	2000	USA	Automobile	150/400	Semi-synthetic	Both	Total particulate ND to 0.9	Case series and cross-sectional
Trout and Harney (2002b), Trout *et al.* (2003)	R	2000	USA	Automobile	NA/2000	Semi-synthetic	Central	All but one total particulate <REL	Cross-sectional and case–control
Gupta and Rosenman (2006)	R	2003	USA	Automobile (three sites)	NA/942 (mean)	Semi-synthetic	NA	Below PEL	Case series
Dawkins *et al.* (2006), Robertson *et al.* (2007)	R	2003	UK	Automobile	NA/836	Soluble	Both	PBZ oil mist 1 to 1.7	Case–control and cross-sectional
Achutan and Nemhauser (2003)	R + S	2003	USA	Steel bars and coils	50/NA	Neat, soluble	NA	Total particulate 0.57 to 2.6	Cross-sectional
Tillie-Leblond *et al.* (2011)	R	2004	France	Automobile engine	NA	Semi-synthetic	NA	NA	Case–control
Fishwick *et al.* (2005)	R	2005	UK	Small component	21/<50	Soluble	Stand alone	NT	Case series
Tapp and Ewers (2005)	R + S	2005	USA	Bicycle	30–40/520	Soluble	Stand alone	NT	Cross-sectional
Cummings *et al.* (2008)	R + S	2007	USA	Aluminium car wheels	100/NA	Soluble	Both	Oil mist <0.11 to 1.13	Cross-sectional

mg m^{-3}, milligrams per cubic metre of air; NA, information not available; ND, tested for but not detected; NT, not tested; R, respiratory; R + S, respiratory and skin.

Table 3. Microbiological findings in MWF outbreak investigations in order of year of initial case.

Outbreak references	Bacteria in MWF (CFU ml^{-1})	Mycobacteria in MWF (CFU ml^{-1})	Fungi in MWF (CFU ml^{-1})	Endotoxin in MWF (EU ml^{-1})	Endotoxin in air (EU m^{-3})
Hendy *et al.* (1985), Robertson *et al.* (1988)	Heavy growth	NA	NA	NT	NT
Daniels *et al.* (1988)	NT	NT	NT	NT	NT
Filios *et al.* (1994)	Number of organisms very low	NA	NA	NT	NT
Piacitelli and Washko (1999)	ND to 2.5×10^8	NA	NA	<0.05 to 5.37×10^5	0.52 to 11.56
Bernstein *et al.* (1995)	1.1×10^6 to 1.3×10^6	NA	<10	0.4 to 1.7×10^3	NT
Rose *et al.* (1996)	NT	NT	NT	NT	NT
Fox *et al.* (1999)	Present but not quantified	Present but not quantified	Present but not quantified	NT	NT
Zacharisen *et al.* (1998)	Present but not quantified	Present but not quantified	Present but not quantified	NT	NT
Trout *et al.* (1996)	1.4×10^3 to 3.9×10^8	Predominant microorganism	0 to 40	ND to 4.4×10^4	NT
Kiefer and Trout (1998)	ND	ND	NT	ND to 7.5×10^4	2.6 to 1.3×10^2
Trout and Burton (1997)	ND to $>3 \times 10^7$	ND to $>3 \times 10^3$	$<1 \times 10^1$ to 4.4×10^4	NT	NT
Hodgson *et al.* (2001), Dangman *et al.* (2002), Bracker *et al.* (2003), Dangman *et al.* (2004)	10^5 to 10^8	Present but not quantified	Low concentration	7.2×10^3 to 2.0×10^5	1.3 to 58.1
Trout and Decker (1998)	ND to 1.2×10^7	ND to $>6.0 \times 10^3$	ND to 3.5×10^2	NT	NT
Kiefer and Gittleman (1999)	NT	NT	NT	NT	NT
Jaksic *et al.* (1998)	Up to 3×10^5	NA	Present in all samples	NT	NT
Roegner *et al.* (2001)	ND to 4.7×10^5	NA	ND	8.4 to 6.9×10^3	NT
Shelton *et al.* (1999)	ND to 1.7×10^6	ND to 10^7	<10 to 6.0×10^3	NT	NT
Trout *et al.* (2000)	6.3×10^5 to 2.5×10^8	NA	8 to 23	ND to 4.8×10^5	NT
Weiss (2001), Trout and Harney (2002a), O'Brien (2003)	ND to 1.4×10^5	ND to $>3.6 \times 10^6$	ND to 4×10^3	ND to 1.05×10^5	NT
Trout and Harney (2002b), Trout *et al.* (2003)	NA	Present but not quantified	Present but not quantified	NT	NT
Gupta and Rosenman (2006)	NA	Present but not quantified	NA	NT	NT

Table 3. *Continued*

Outbreak references	Bacteria in MWF (CFU ml^{-1})	Mycobacteria in MWF (CFU ml^{-1})	Fungi in MWF (CFU ml^{-1})	Endotoxin in MWF (EU ml^{-1})	Endotoxin in air (EU m^{-3})
Dawkins *et al.* (2006), Robertson *et al.* (2007)	Identified by DNA extraction	ND	ND	Not increased	NT
Achutan and Nemhauser (2003)	Present but not quantified	ND	NA	1.1×10^3 to 4.2×10^5	NT
Tillie-Leblond *et al.* (2011)	Present but not quantified	ND to >4000	Present but not quantified	NT	NT
Fishwick *et al.* (2005)	<100 to 8.2×10^6	NA	<100 to 2.2×10^3	5.6×10^1 to 6.5×10^4	ND
Tapp and Ewers (2005)	NT	NT	NT	NT	NT
Cummings *et al.* (2008)	200 to 2700	DNA present	Glucans present	52 to 150	NT

CFU, colony-forming unit; EU, endotoxin unit; ml m^{-3}, milligrams per cubic metre of air; NA, information not available; ND, tested for but not detected; NT, not tested; PBZ, personal breathing zone; PEL, permissible exposure limit; REL, recommended exposure limit set by NIOSH[a].
[a]NIOSH recommends an 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 concentration for up to 10 h per day during a 40-h week. Measurement of total particulate is an acceptable substitute for measuring thoracic particulate and the NIOSH REL is 0.5 mg m^{-3}.

The results of microbial and endotoxin measurements from the workplaces with outbreaks are summarized in Table 3. Microbial contamination of MWF samples was variable, with some samples showing no detectable microbial growth and others with high levels of bacteria, opportunistic mycobacteria, or fungi. Although certain types of microorganisms could not be cultured in some studies, their presence was detectable by DNA studies or inferred by the presence of endotoxin or glucans. Endotoxin contamination of MWF samples was very variable, ranging from non-detectable to 5.4×10^5 endotoxin unit (EU) ml^{-1} and measured airborne levels ranging from non-detectable to 126 EU m^{-3}.

One study did not find any significant differences in exposure levels to microbial organisms, endotoxin, or total particulate when comparing plants with and without a history of an outbreak.

Worker demographics

Six analyses (in workplaces with outbreaks) found an increased prevalence of certain respiratory or constitutional symptoms in workers exposed to MWFs, as compared to non-exposed controls. Eight case–control analyses were found comparing cases with and without EAA. No significant demographic risk factors for EAA were found in terms of age, gender, or smoking status. One case–control study found no link between EAA and working with MWF (Trout and Harney, 2002a), whereas another study found an increased risk of disease associated with working in a particular manufacturing department and with using machines linked to a large central sump (Robertson *et al.*, 2007). Six case–control analyses found cases of EAA had an increased prevalence of serum precipitins or antibodies to microbial organisms and/or used MWFs, when compared with non-cases.

DISCUSSION

Principal findings

This study has identified and summarized the findings of 35 published articles relating to 27 respiratory outbreaks in workers exposed to water-soluble MWFs. The majority of these were case series and cross-sectional studies from the USA, relating to respiratory disease, with or without skin disease. The most commonly affected workplaces were large car-manufacturing plants, and outbreaks were identified with exposures to all types of water-based MWFs. Microbial contamination with bacteria, opportunistic mycobacteria, and fungi was commonly

Table 4. Summary of MWF outbreak investigations with comparative analyses, showing cross-sectional and case–control studies.

References	Exposed or cases	Controls	Summary findings
Kiefer and Trout (1998)	77 MWF exposed	84 unexposed (different department)	Exposed workers had significantly elevated ORs (range 1.8–2.2) for tightness in chest, sore throat, and ache all over
Roegner *et al.* (2001)	188 MWF exposed	92 unexposed (same workplace)	Exposed workers had significantly elevated ORs (range 1.4–3.4) for two upper airway, six respiratory, one constitutional, and one skin symptom
Trout and Burton (1997)	515 MWF exposed	435 unexposed (different department)	Exposed workers had significantly elevated ORs (range 1.4–2.6) for two upper airway, five respiratory, three constitutional, and one skin symptom
Trout and Harney (2002a)	137 MWF exposed; 53 with higher MWF exposure	158 unexposed (same workplace); 21 with lower MWF exposure	Exposed workers had significantly elevated ORs (range 1.2–2.2) for four respiratory, four constitutional, and one skin symptom (not work related); exposed workers had significantly elevated ORs for EAA (8.1) but not OA (2.0); no significantly increased ORs for EAA; OA; or eight respiratory, constitutional, and skin symptoms
Trout and Harney (2002b)	43 MWF exposed	11 unexposed (same workplace)	Exposed workers had significantly greater median antibody levels to *Mycobacterium immunogenum* and higher IL-8 secretion in response to *M. immunogenum*.
Trout *et al.* (1996)	163 MWF exposed	84 unexposed (different department)	Exposed workers had significantly elevated ORs (range 1.7–3.5) for six respiratory and two constitutional symptoms
Hodgson *et al.* (2001)	73 workers from plant with outbreak of EAA	61 exposed; 51 non-exposed (different plant)	Case plant employees younger, male, current smokers, with less years in industry; significantly increased symptoms in exposed versus non-exposed workers; exposed workers from case and control plants had similar mean exposure levels to bacteria, endotoxin, and total particulate
Bernstein *et al.* (1995)	6 EAA	9 non-exposed lab workers	All EAA cases and no controls had positive IgG precipitins to *Pseudomonas fluorescens* cultured from MWF
Trout *et al.* (1996)	6 EAA	171 exposed; 60 unexposed (same workplace)	EAA cases more likely to have positive ELISA to *Mycobacterium chelonae* and IgG precipitins to *Aspergillus fumigatus/Micropolyspora faeni*; MWF exposed more likely to have positive ELISA to *M. chelonae* and positive IgG precipitins to *Aureobasidium pullulans/Thermophilic actinomycetes*

Table 4. *Continued*

References	Exposed or cases	Controls	Summary findings
Fox *et al.* (1999)	18 EAA	51 randomly selected without symptoms (same workplace)	No significantly elevated ORs for 34 demographic risk factors, including age, gender, smoking, and working directly with MWF; EAA cases had significantly elevated ORs (range 4.8–10.5) for positive IgG precipitins to three of seven used MWFs (two synthetic and one oil soluble)
Dangman *et al.* (2004)	36 EAA	25 without EAA (same workplace)	No significant difference in smoking status, other than EAA smokers had smoked for longer
Trout and Harney (2002b)	6 EAA	48 without EAA (same workplace)	EAA cases had significantly greater median antibody levels to *M. immunogenum* and *Fusarium* sp. No difference in cytokine secretion of IFN-g, TNF-a, and IL-8 in response to *M. immunogenum*.
Dawkins *et al.* (2006), Robertson *et al.* (2007)	12 index EAA; 19 EAA; 66 OA	11 exposed and 65 non-exposed (different workplace); 47 randomly selected without respiratory symptoms (same workplace)	Proportion of EAA cases and exposed controls had positive precipitins to *Acinetobacter* or *Ochrobactrum* (unexposed controls had none); no positive precipitins to *Mycobacterium* sp. in any group; no significant differences between groups for age, gender, smoking status, or duration of employment; cases more likely than controls to work mostly in manufacturing and use machines supplied by largest sump
Tillie-Leblond *et al.* (2011)	13 EAA	12 exposed non-EAA (same workplace)	EAA cases had a significantly greater number of electrosyneresis precipitin arcs to *M. immunogenum* than exposed controls but no difference seen for *Bacillus* or *Fusarium*.

ELISA, enzyme-linked immunosorbant assay; IFN-g, interferon gamma; IL-8, interleukin 8; OR, odds ratio; TNF-a, tumour necrosis factor-alpha.

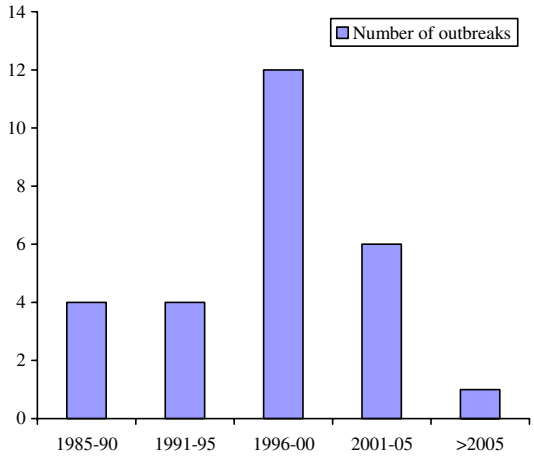

Fig. 2. Year of onset of MWF ill health outbreak.

demonstrated during hygiene investigations. A number of studies have established that during outbreak investigations, workers exposed to MWFs report more symptoms and are more likely to demonstrate immunoglobulin G (IgG) antibodies to workplace microbial agents and/or used MWFs, than unexposed workers. Limited data from case–control studies have shown that workers with MWF-EAA were also more likely to demonstrate this type of immune response than workers without disease. No consistent demographic risk factors have otherwise been identified for respiratory outbreaks in MWF-exposed workforces.

General limitations of the review

Given the comprehensive nature of the search terms and the search strategy employed, it seems unlikely that reports from outbreak investigations would have been missed. The 1990 start date for the search was chosen in an attempt to avoid articles relating to straight mineral oil (not containing water) exposure, and significant papers prior to this date were only included if identified from checking of references of the articles found from the search period. Due to the types of studies summarized in this review, the evidence is mostly observational and reflects the constraints placed on reactive health investigations as opposed to planned research studies. The findings from this literature review are predominantly from cross-sectional surveys of workplaces and case series of workers with disease, with little data from case–control studies. It is possible therefore that some of the cross-sectional outbreak studies may have underestimated the size of the problem, by studying a survivor population. Some of the outbreak investigations have, however, attempted to minimize this by collecting longitudinal data and by reviewing previous sickness absence records (Trout and Harney, 2002a). Conclusions of hygiene investigations during outbreaks may also be limited in usefulness, if improvements to limit the outbreak have already commenced during the investigation (Fishwick *et al.*, 2005). Again, some investigations have attempted to allow for this, by studying historical hygiene records of oil and MWF mist levels, sump contamination, and biocide usage (Fox *et al.*, 1999; Gupta and Rosenman, 2006).

Geographical distribution of MWF outbreaks

The majority of outbreaks of MWF-related ill health have been reported from USA, with the other outbreaks identified originating in the UK, France, and Croatia. It is not possible to tell from the literature review whether the high number of outbreaks from the USA is representative of a wider problem in that country or relates to other factors such as differences in occupational health provision, healthcare system, work culture, or simply reporting bias. One possible explanation to consider for such geographical differences in the incidence of reported MWF outbreaks is differences in socio-economics—i.e. 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 each country's annual consumption of MWFs. In 2007, the USA used ~420 000 metric tons of MWF, compared with 305 000 metric tons in Western Europe and 815 000 metric tons in the Asia/Pacific region (Freedonia group research; http://www.freedoniagroup.com/DocumentDetails.aspx?ReferrerId=FG-01#studyid=2454, last accessed 28 February 2011). While it is not possible to ascertain why there have been so few published outbreaks from mainland Europe and none from Asia, there is likely to have been some publication bias from the USA as National Institute for Occupational Safety and Health (NIOSH) was responsible for the majority of the US outbreak reports. This organization is well resourced, has a low threshold for investigating workplaces (this only requires three staff members to formally express concern regarding health in the workplace), and routinely publishes its findings as NIOSH technical reports. This approach is likely to vary considerably from that in other countries, which may in part explain a lack of published outbreaks. Evidence to support this comes from the UK, where a separate respiratory outbreak was identified in the literature review, due to a prosecution of the employer, without any details of an outbreak investigation being presented (Health and Safety Executive, 2009). In

addition, a number of other European papers were identified by the review that did not report outbreak investigations but either identified a single case of MWF-EAA (Merget, 2010) or reported respiratory symptoms in cross-sectional studies of Swedish (Lillienberg *et al.*, 2008), Finnish (Jaakkola *et al.*, 2009), Belgian (Godderis *et al.*, 2008), or German (Baumeister *et al.*, 2010) MWF-exposed workers. It is clear therefore that ill health from MWF exposure is not solely a problem in the USA and that the lack of a standardized approach to outbreak investigation and publication makes international comparisons difficult.

Industries affected by MWF outbreaks

The industry most commonly affected by MWF outbreaks has been that of car manufacturing accounting for >60% of all published outbreaks. Data for global car production in 2002 listed the top five car manufacturers as Japan (8.6 million), followed by Germany (5.1 million), the USA (5.0 million), France (3.3 million), and South Korea (2.7 million) (http://www.nationmaster.com/graph/ind_car_pro_percap-industry-car-production-per-capita, last accessed 05 January 2010). The lack of published outbreaks from Japan and Germany do not suggest a straightforward link between this industry *per se* and MWF outbreaks. A recent hygiene literature review has, however, demonstrated higher MWF exposure levels in automobile- and automobile component-manufacturing industries than for small-job machine shops (Park *et al.*, 2009). Whether there are other workplace factors in the automobile production industry that differ from other industries where MWF is utilized requires further research.

Workplace risk factors for MWF outbreaks

Another aetiological 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 for the development of airway responsiveness (a feature of asthma), whereas this was not the case for mineral oil-based soluble MWFs (Kennedy *et al.*, 1999). Among cases of EAA, Fox *et al.* (1999) also found increased odds ratios for exposure to certain MWFs, two of which were synthetic. Our results, however, identified respiratory outbreaks associated with all types of modern MWFs, including soluble mineral oil, synthetic, and semi-synthetic fluids. Robertson *et al.* (2007) identified working with machines served by a large central sump as a significant risk factor for EAA, and few outbreaks have been reported in workplaces without common sumps (Piacitelli and Washko, 1999; Fishwick *et al.*, 2005; Tapp and Ewers, 2005). Despite this, it is difficult to interpret the relevance of sump type without knowing whether this simply reflects the normal pattern of usage of MWF by large industry (where the majority of reported outbreaks have occurred). Further data of interest come from a German cross-sectional study of 799 metalworkers (without any history of outbreaks), where differences were found in symptom prevalence depending on whether they were employed in small- or medium-sized enterprises, where central sump usage was twice as common in the latter (22.0 versus 43.4%). This demonstrated that skin symptoms were more common in small enterprises (20.2 versus 13.8%), whereas breathing problems were more common in medium enterprises (0.9 versus 4.2%) (Baumeister *et al.*, 2010). It is likely that contamination of MWF within a large common sump will expose more workers than a single contaminated stand-alone sump and may therefore be more likely to lead to an outbreak as opposed to a single case of disease. Again, more research is required in this area, particularly in looking for hygiene differences in workplaces of different sizes, with different types of MWF supply and management.

Microbial contamination in MWF outbreaks

For OA, specific inhalation challenge testing has confirmed that particular MWF components, e.g., alkanolamines, pine oil reodorants, and colophony, are asthmagens (Hendy *et al.*, 1985; Robertson *et al.*, 1988; Savonius *et al.*, 1994; Piipari *et al.*, 1998). Despite this, the exact aetiology of OA and EAA outbreaks has been difficult to establish, and the limited data relating to specific challenge have only found positive responses to used rather than pristine MWF, making a chemical aetiology less likely (Robertson *et al.*, 2007). Outbreak investigations have clearly demonstrated that microbial contamination of MWF is common, most frequently with bacteria (usually Gram negative), opportunistic mycobacteria, and fungi. In some outbreak investigations, it has been possible to culture these organisms from MWF samples, whereas in others their presence has only been confirmed with DNA testing or measures of substances such as endotoxin and glucans. Despite this, a clear relationship between outbreaks and any particular microbial contaminant remains elusive. It is possible that this may in part reflect biocide usage and hygiene improvements that have already occurred prior to outbreak investigations, but given that high levels of microbial contamination are also commonly

found in workplaces without outbreaks, this area is clearly complex (Hodgson *et al.*, 2001; Gilbert *et al.*, 2010). Specific serum IgG precipitating antibodies to workplace microorganisms or used MWFs have been demonstrated in workers exposed to MWFs and in some workers developing EAA (Trout *et al.*, 1996; Fox *et al.*, 1999; Trout and Harney, 2002b; Dawkins *et al.*, 2006; Tillie-Leblond *et al.*, 2011). Inhalation of microbial contaminants has commonly been implicated in causing EAA in farmer's lung, humidifier lung (Matar *et al.*, 2000), hot tub lung, and lifeguard lung (Rose *et al.*, 1998; Sood *et al.*, 2007), but establishing microbial causation in MWF outbreaks has been less straightforward. Detailed immunological investigation of workers with MWF-EAA has failed to demonstrate a clear causative link with any specific type of organism as workers with EAA may have specific IgG to a range of organisms including bacteria, fungi, and mycobacteria (Barber *et al.*, 2011). In addition, no clear differences between the exposure levels of inhaled bacteria and endotoxin have been demonstrated in workplaces with and without outbreaks (Hodgson *et al.*, 2001). Much attention has been focused on opportunistic mycobacteria as a cause for MWF-EAA (Shelton *et al.*, 1999; Weiss, 2002; Veillette *et al.*, 2008), but outbreaks have occurred in the absence of these organisms. In the large UK outbreak (Dawkins *et al.*, 2006; Robertson *et al.*, 2007), none of the 129 workers tested had IgG to mycobacteria, and no detectable DNA from opportunistic mycobacteria was found in 125 samples of MWF (Barber *et al.*, 2011). Detailed immunological studies, based on the presence of specific antibodies, or *in vitro* cytokine stimulation has also failed to establish a clear link between EAA and opportunistic mycobacteria (Trout *et al.*, 2003). Further work in this area has recently been published in a French outbreak, where workers with MWF-EAA were found to have more precipitin arcs (as measured by electrosyneresis) to *Mycobacterium immunogenum* than exposed asymptomatic controls (Tillie-Leblond *et al.*, 2011). This study, however, further highlights the difficulties of distinguishing immunological causation from exposure as 8 of 13 of the MWF-EAA cases also had positive arcs to a bacterium and 4 of 13 had positive arcs to a fungus. In addition, one of the asymptomatic exposed controls had 12 arcs to *M. immunogenum*, which was as strong a response as seen in any of the EAA cases.

Worker demographics

Given the uncertainty of causation of respiratory outbreaks, attention has been focused on attempting to identify individual risk factors for these diseases. A number of respiratory outbreak investigations have compared demographic data for affected and unaffected workers, but no consistent risk factors for MWF-related ill health have been established. Fox *et al.* (1999) compared 34 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. Similarly in the Powertrain outbreak, no differences in smoking history, demographic characteristics, or the length of employment were observed between cases and controls (Robertson *et al.*, 2007). Dangman *et al.* (2004) also found no differences in age between workers with and without EAA but did find that the smokers with EAA had smoked for longer.

Some outbreak investigations have reported a cessation of new cases following workplace hygiene measures aimed at reducing exposure levels, such as the installation of local exhaust ventilation and the usage of respiratory protective equipment during cleaning operations (Filios *et al.*, 1994; Fox *et al.*, 1999). Personal exposures to MWF mist are therefore likely to be important and may vary widely between workers depending on a wide range of factors including work tasks, usage of enclosed systems, availability of exhaust ventilation, usage of compressed air (Lillienberg *et al.*, 2008; Park *et al.*, 2009), and individual behavioural factors. Comparisons of personal MWF exposure are hampered by a lack of standardized methodology for measuring MWFs and variation in recommended exposure limits (Cohen and White, 2006; Park *et al.*, 2009). In the USA, NIOSH recommended exposure limits (RELs) for MWFs are 0.5 mg m^{-3} for total MWF particulates as a time-weighted average concentration for up to 10 h per day during a 40-h working week (Rosenman, 2009). Although exposure monitoring in US outbreaks has shown variable results, outbreaks have still been described where all measured exposure levels have been below the NIOSH REL (Hodgson *et al.*, 2001; Gupta and Rosenman, 2006). More recent cross-sectional studies of MWF-exposed workers from Scandinavia have confirmed an excess of respiratory symptoms even at relatively low average exposure levels of ~0.12–0.40 mg m^{-3} (Lillienberg *et al.*, 2008; Jaakkola *et al.*, 2009).

The relationship between exposure and respiratory disease has not been easy to establish, and findings have varied between different studies. Trout and Harney (2002a) 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. In a Finnish cross-sectional survey, Jaakkola *et al.* (2009) also found that throat symptoms, cough, and chronic bronchitis were more common among machine workers with at least 15 years exposure and that exposure to aerosol levels above the median ($\geq$0.17 mg m^{-3}) was also related to an increased risk of a range of respiratory symptoms. In contrast to this, Hodgson *et al.* (2001) found no clear association between qualitative exposure measurements and EAA using logistic regression models, and no clear hygiene differences were seen between plants with and without outbreaks. Fox *et al.* (1999) also did not find significant difference in oil mist exposure levels between EAA cases and controls, and Trout and Harney (2002a) found no difference in symptom prevalence between departments with higher and lower exposure to total particulate. In addition to this, Park *et al.* (2007) found that cross-shift peak flow decrements were not related to exposure category.

CONCLUSIONS

Outbreaks of allergic respiratory disease continue to occur in workers exposed to MWFs, and despite numerous investigations, significant knowledge gaps remain regarding the aetiology, natural history, and risk factors for these diseases. The available evidence supports the hypothesis that microbial contamination is important in the aetiology of occupational lung disease in this group of workers, and improvements in workplace hygiene have generally been associated with a cessation of new cases. While most published investigations of respiratory ill health attributed to work with MWFs have been published in the USA, the small number of European outbreaks linked with the results of cross-sectional studies of exposed workers confirm that these diseases are not unique to one country or region.

At present, the available evidence suggests that a preventative approach is required, minimizing inhaled MWF mist levels and microbial contamination as far as possible, in addition to carrying out regular health surveillance aimed at the early identification of symptomatic workers.

SUMMARY STATEMENTS

1. Twenty-seven outbreaks of allergic respiratory disease have been reported in workers exposed to water-containing MWFs.
2. The majority of outbreak reports have originated from Health Hazard Evaluations performed by NIOSH in the USA.
3. The industry most commonly affected by MWF respiratory outbreaks has been the automobile component-manufacturing industry.
4. Respiratory outbreaks have most commonly been reported from large workplaces with common shared MWF sumps or a combination of stand-alone and shared sumps.
5. Respiratory outbreaks have been reported in workforces with exposures to synthetic, semi-synthetic and soluble mineral oil and those exposed to a combination of MWF types.
6. Microbial contamination of MWFs with bacteria, fungi, and opportunistic mycobacteria has commonly been demonstrated in workplaces with and without ill health outbreaks.
7. Exposed workers and cases of MWF-EAA may demonstrate serum precipitating antibodies to used MWFs or to specific microbial contaminants within the MWFs.
8. The exact aetiology of respiratory outbreaks has been difficult to establish based on published workplace hygiene measurements and immune studies of affected workers.

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