

OCCUPATIONAL LUNG DISEASE

Clinical investigation of an outbreak of alveolitis and asthma in a car engine manufacturing plant

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Background: Exposure to metal working fluid (MWF) has been associated with outbreaks of extrinsic allergic alveolitis (EAA) in the USA, with bacterial contamination of MWF being a possible cause, but is uncommon in the UK. Twelve workers developed EAA in a car engine manufacturing plant in the UK, presenting clinically between December 2003 and May 2004. This paper reports the subsequent epidemiological investigation of the whole workforce. The study had three aims: (1) to measure the extent of the outbreak by identifying other workers who may have developed EAA or other work-related respiratory diseases; (2) to provide case detection so that those affected could be treated; and (3) to provide epidemiological data to identify the cause of the outbreak.

Methods: The outbreak was investigated in a three-phase cross-sectional survey of the workforce. In phase I a respiratory screening questionnaire was completed by 808/836 workers (96.7%) in May 2004. In phase II 481 employees with at least one respiratory symptom on screening and 50 asymptomatic controls were invited for investigation at the factory in June 2004. This included a questionnaire, spirometry and clinical opinion. 454/481 (94.4%) responded and 48/50 (96%) controls. Workers were identified who needed further investigation and serial measurements of peak expiratory flow (PEF). In phase III 162 employees were seen at the Birmingham Occupational Lung Disease clinic. 198 employees returned PEF records, including 141 of the 162 who attended for clinical investigation. Case definitions for diagnoses were agreed.

Results: 87 workers (10.4% of the workforce) met case definitions for occupational lung disease, comprising EAA (n=19), occupational asthma (n=74) and humidifier fever (n=7). 12 workers had more than one diagnosis. The peak onset of work-related breathlessness was Spring 2003. The proportion of workers affected was higher for those using MWF from a large sump (27.3%) than for those working all over the manufacturing area (7.9%) (OR=4.39, p<0.001). Two workers had positive specific provocation tests to the used but not the unused MWF solution.

Conclusions: Extensive investigation of the outbreak of EAA detected a large number of affected workers, not only with EAA but also occupational asthma. This is the largest reported outbreak in Europe. Mist from used MWF is the likely cause. In workplaces using MWF there is a need to carry out risk assessments, to monitor and maintain fluid quality, to control mist and to carry out respiratory health surveillance.

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Metal working fluids (MWF) have been recognised as causing work-related respiratory problems since the 1950s. Initial reports of respiratory effects due to the inhalation of oil mists were limited to lipoid pneumonia.^{1–3} Case reports of occupational asthma (OA) due to both clean and used MWF have been recorded.^{4–5} Subsequent surveys of workers exposed to MWF have found respiratory symptoms,^{6–9} often with associated bronchial hyper-responsiveness,^{7–9} cross-shift changes in lung function^{10–12} or reduced lung function.¹³ Many of these surveys have been done in the automotive industries.

The first cases of alveolitis due to MWF were reported in the mid 1990s by Bernstein *et al* in the USA who described six cases of hypersensitivity pneumonitis (extrinsic allergic alveolitis, EAA).¹⁴ Precipitating antibodies were found to a number of microbial isolates, the most common being *Pseudomonas fluorescens*. Further outbreaks in the USA have been reported,^{15–17} several in the automotive industry.^{14–16} Bacterial (particularly mycobacteria) or fungal contamination of MWF are thought to be the causes, but no specific agent has fulfilled the criteria for a specific cause.^{16–17}

MWF has been an uncommon cause of EAA in the UK with only one case being reported to SWORD, the UK national voluntary notification scheme, from 1995 to 2002. Twelve employees from a car engine manufacturing plant in England

who presented to us between December 2003 and May 2004 were diagnosed as having EAA. Dawkins *et al* have presented the findings from this case series of 12 workers, which showed heterogeneous clinical, radiological and pathological findings, but all met the case definition for EAA.¹⁸ The factory machined engine parts from aluminium alloys or cast iron and assembled car engines. The machining process used MWF (oil water emulsions with chemical additives including biocides). During use the MWF became contaminated by lubricating and hydraulic oil (tramp oil). Some machines had their own MWF sumps, but most used one of four common sumps, the largest with a capacity of >200 000 litres. Machined parts were washed with a mixture of water and detergent which was recirculated. Some washers produced inhalable aerosols.

In May 2004 we carried out an epidemiological investigation of the whole workforce which had three aims:

- To measure the extent of the outbreak by identifying other workers who may have developed EAA or other work-related respiratory diseases.

Abbreviations: EAA, extrinsic allergic alveolitis; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; HF, humidifier fever; MWF, metal working fluid; OA, occupational asthma; PEF, peak expiratory flow

Table 1 Case definitions for work-related respiratory disease

Disease	Criteria for case definitions
Extrinsic allergic alveolitis (at least 4 of the 7 criteria must be met) ¹⁶	Onset of disease after December 2002 and: (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% predicted and FEV ₁ /FVC >70%; (5) pulmonary carbon monoxide transfer factor <80% predicted; (6) chest radiograph 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) ^{21, 22}
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

EAA, extrinsic allergic alveolitis; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

- To provide case detection so that those affected could be treated.
- To provide epidemiological data to identify the cause of the outbreak so that appropriate remedial action could be taken; specifically, to examine the association of MWF quality and MWF usage with work-related respiratory disease.

This paper reports the results of the epidemiological investigation. A brief summary of the environmental investigation is given.

METHODS

Clinical investigation

A three-phase cross-sectional survey of the entire workforce was carried out to identify cases of respiratory disease. The payroll list from the Human Resources Department was used as the sample frame, which identified 832 current employees (33 subcontractors, 799 direct employees) and four index cases of alveolitis who were on sick leave, totalling 836 employees. Employees were assigned by the workplace to one of 57 operational codes which, in most cases, were closely linked to a specific work area.

Phase I: Screening questionnaire

A short respiratory screening questionnaire (11 questions on respiratory and nasal symptoms) was distributed to the 836 employees in May 2004. Workers were asked to report symptoms present in the previous 18 months. Non-responders were contacted twice more.

Phase II: Factory-based assessment

In June 2004 those workers with one or more respiratory symptoms and/or weight loss on the screening questionnaire were invited for further assessment. A control group of 50 asymptomatic workers was selected randomly from the 180 employees who declared no symptoms on the respiratory screening questionnaire. The selection of the controls was done

with a random number table using the last three digits of their payroll number.

The assessment consisted of:

Questionnaire

A detailed self-completed questionnaire asked about demographic information, job history and clinical information (available on www.occupationalasthma.com/resources/outbreak_respiratory_survey.doc). The questionnaire inquired whether symptoms were "better", the "same" or "worse" on "days away from work" and "holidays". Symptoms were classified as work-related if they improved on days off or on holiday. The month and year of first onset of each symptom was recorded.

Spirometry

Spirometry was measured on a wedge bellows spirometer (Vitalograph) according to ATS/ERS standards using ECCS predicted values.¹⁹

Clinical opinion

Participants were seen by an experienced occupational respiratory physician; those with possible OA were asked to record serial measurements of peak expiratory flow (PEF), with subsequent clinical investigation depending on the result. Those with possible alveolitis or humidifier fever (HF) were offered full clinical investigation (phase III).

Phlebotomy

20 ml blood was taken into two plain bottles with the serum frozen for later analysis for precipitins at the Health and Safety Laboratory (HSL), Sheffield, UK. The results are reported separately by the HSL.²⁰

Phase III: Full clinical assessment

Peak flow records

Standard instructions for PEF records included 2-hourly measurements from waking to bedtime on days at work and days away from work for a total of 4 weeks.²¹ Records were analysed using Oasys-2 computing program which plots and analyses serial measurements of PEF for occupational effect. Oasys-2 works by discriminant analysis, scoring "complexes" that are comprised of a work-rest-work pattern or a rest-work-rest pattern. Validation studies show that Oasys-2 has a sensitivity of 75% and a specificity of 94% for detecting OA.²² An Oasys score of ≥ 2.67 and/or a mean day interpreted difference between work and rest days of ≥ 16 l/min were defined as showing OA.^{21, 22}

Clinical investigation

Workers selected in the previous phase were seen between November 2004 and March 2005 by two occupational respiratory physicians. Investigations included lung function tests, including transfer factor (single breath Jaeger Masterscreen system 2), chest radiograph and methacholine challenge (Yan method) for bronchial hyper-reactivity. Skin prick tests were performed for common environmental allergens with saline negative control, histamine positive control plus allergens – house dust, house dust mite, feathers, horse hair, cat dander, dog dander, mixed grasses, mixed tree pollens, plantain pollen, egg, milk, fish, wheat pollen, *Cladosporium*, *Alternaria alternaria*, *Aspergillus fumigatus*, *Penicillium* sp and *Merulius lacrymans*. Atopy was defined as at least one positive weal (≥ 3 mm above saline control) to a common inhalable allergen. Lung volumes (helium dilution), high-resolution CT (HRCT) scans and bronchoscopy were performed if indicated. A clinical diagnosis was made on the results of investigations and history.

Case definitions

Case definitions for work-related respiratory diseases were agreed (table 1) and applied to workers that had undergone further clinical investigations. Case definitions for EAA were adapted from Fox *et al.*¹⁶ OA required a diagnostic PEF record^{21 22} and HF was based on history (table 1). We defined January 2003 as the onset date for the outbreak based on the presentation of the 12 index cases of EAA.

Specific challenge tests

Two individuals, one with a pre-test diagnosis of EAA and one with OA and resolved HF, had occupational-type bronchial provocation testing 6 months after removal from exposure. Challenges to unused MWF used at the factory (a mixture of two products and water containing a number of chemicals including tolytriazole, ethanolamines, tall oil and boric acid) and used MWF taken from the largest common sump were performed on separate days. Initially, exposures were by a Pari Pot nebuliser with the aerosol directed generally into the challenge chamber for sequential periods of 10, 20 then 40 min (total exposure 70 min). Rest breaks occurred between challenges and any significant response would have terminated the challenge. Further challenges were made with the aerosol inhaled directly from the nebuliser using a mouthpiece for up to 17 min (2, 5 and 10 min with breaks). Spirometric parameters were measured pre-challenge and regularly for at least 11 h

post-challenge. A fall in forced expiratory volume in 1 s (FEV₁) of >15% from baseline was taken as a positive test.

Environmental investigation

Over the period of the outbreak, area and personal measurements of MWF in air were conducted using Health and Safety Executive (HSE) standard methodology, estimating total aerosol by extrapolating from the boron content of MWF.²³ Personal sampling was done over a 4–5-h period. Common sumps were monitored for pH, concentration, tramp oil, bacteria and fungi. Smaller sumps were monitored for concentration and pH. From November 2003, sump samples were analysed for bacteria and fungi.

Ethical approval

Ethical approval was not obtained as this report is the result of surveillance and the investigation of surveillance failures required by a legally binding improvement notice from the Health and Safety Executive. The surveillance was approved by both worker and management representatives.

Analysis of data

The onset (month and year) of work-related breathlessness reported in the phase II questionnaire was plotted and related to the concentration of tramp oil in MWF. Gender, ethnicity, smoking and use of MWF were then compared for the affected and non-affected populations using a χ^2 test (with Yates

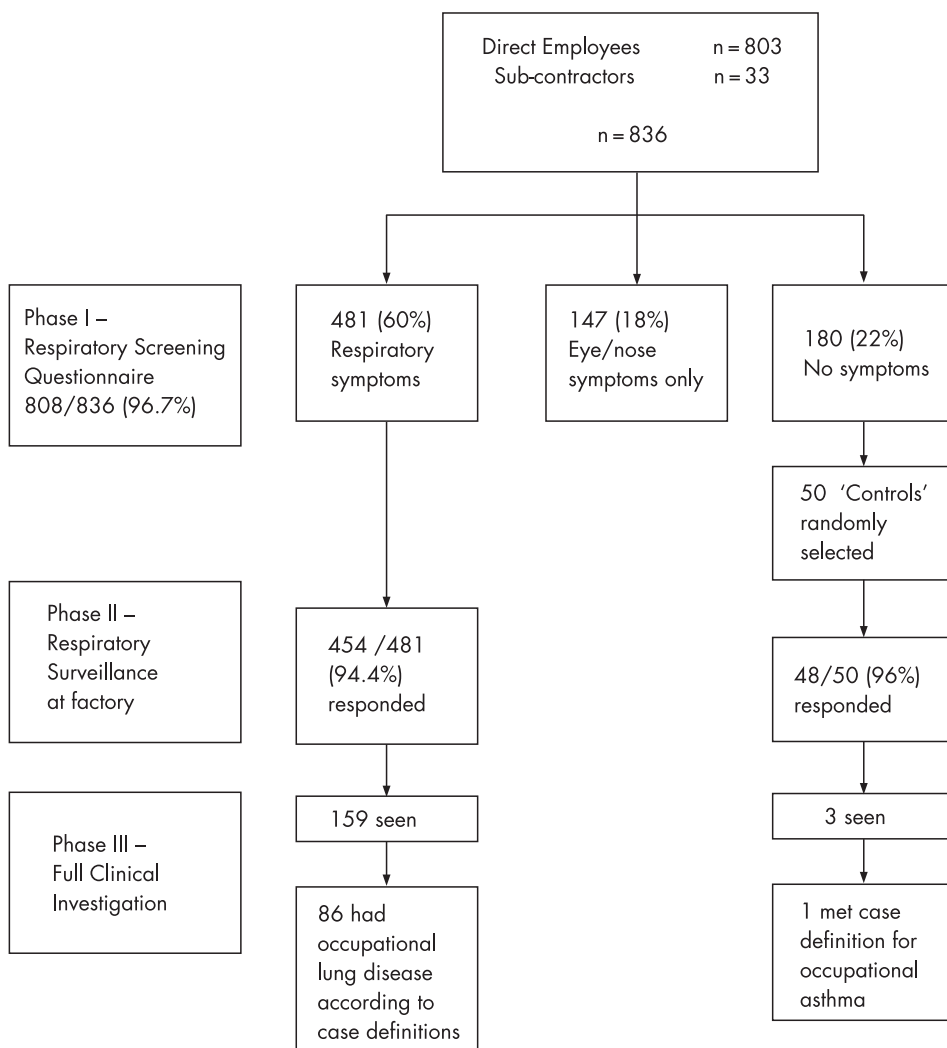


Figure 1 Diagram showing participation in the three phases of the investigation and diagnoses following the clinical investigations.

Table 2 Characteristics of employees with respiratory symptoms, the asymptomatic control group who completed phase II and those meeting the case definitions for extrinsic allergic alveolitis (EAA) and occupational asthma (OA) in phase III

		(1) Respiratory symptoms on screening questionnaire (n = 454)	(2) Met case definition for EAA (n = 19)*	(3) Met case definition for OA (n = 66)†	(4) Controls (n = 47)	Statistical difference (1 vs 4)‡	Statistical difference (2 vs 3 vs 4)§
Age (years)	Mean (SD)	44.7 (8.6)	47.5 (7.9)	43.4 (7.6)	43.6 (10.5)	p = 0.417	p = 0.176
Gender							
Men	n (%)	419 (92.2%)	17 (89.5%)	59 (89.4%)	43 (91.5%)	p = 1.000	Not done
Women		35 (7.8%)	2 (10.5%)	7 (10.6%)	4 (8.5%)		
Ethnicity							
Caucasian	n (%)	396 (87.2%)	18 (94.7%)	53 (80.3%)	44 (93.6%)	p = 0.298	p = 0.064
Non-Caucasian		58 (12.8%)	1 (5.3%)	13 (19.7%)	3 (6.4%)		
Smoking							
Current	n (%)	125 (28%)	3 (15.8%)	15 (22.7%)	6 (14.3%)	p = 0.086 (current vs others)	p = 0.513 (current vs others)
Ex							
Never		127 (28%)	7 (36.8%)	18 (27.3%)	13 (31.0%)		
Ever		197 (44%)	9 (47.4%)	33 (50%)	23 (54.7%)		
FEV ₁ (l)	Mean (SD)	3.52 (0.76)	2.90 (0.66)	3.45 (0.69)	3.91 (0.76)		
FEV ₁ (% predicted)	Mean (SD)	96.8 (15.8)	83.4 (15.9)	94.9 (14.9)	102.8 (14.9)	p = 0.012	p < 0.001
FVC (l)	Mean (SD)	4.50 (0.93)	3.58 (0.74)	4.40 (0.86)	4.99 (0.98)		
FVC (% predicted)	Mean (SD)	103.5 (15.7)	85.1 (15.9)	101.4 (14.9)	110.0 (17.1)	p = 0.008	p < 0.001
Works mostly in manufacturing							
Yes	n (%)	368 (81%)	19 (100%)	64 (97%)	28 (60.9%)	p = 0.002	p < 0.001
No	n (%)	86 (19%)	0 (0%)	2 (3%)	18 (39.1%)		
Ever worked on machine with MWF							
Yes	n (%)	270 (60%)	14 (73.7%)	43 (65.2%)	22 (46.8%)	p = 0.111	p = 0.06
No	n (%)	180 (40%)	5 (26.3%)	23 (34.8%)	25 (53.2%)		
Duration of employment at factory (years)	Median (IQR)	10.5 (5–15)	9 (4–12)	12 (6–15)	9 (4–15)	p = 0.403	p = 0.306

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; MWF, metal working fluid.

*Eight also had OA.

†Excludes eight with EAA.

‡Analysis by *t* test for age, FEV₁ and FVC; Mann-Whitney U test for duration of employment.

§Analysis by one-way ANOVA for age, FEV₁ and FVC; Kruskal-Wallis test for duration of employment.

‡,§Categorical data analysed by χ^2 test.

continuity correction for 2×2 tables). Age and lung function were compared using a *t* test and one-way analysis of variance. Duration of employment was not normally distributed so differences were analysed by the Mann-Whitney U and Kruskal-Wallis tests.

The prevalence of work-related respiratory disease (EAA, OA and HF) was calculated for the 57 operational codes using the number working in each operational code as the denominator. Fisher's exact test was used to compare the proportion with disease in a specific work location with the proportion of disease in the rest of the workforce. Each code was also assigned to one of the following five groups: (1) machining using MWF from a large common sump; (2) machining using MWF from a single or local sump; (3) assembly and other manufacturing: working in the manufacturing area but not using MWF directly (predominantly assembly jobs); (4) working all over the plant in the manufacturing area; and (5) working outside the main plant or in the office block.

Logistic regression was used to see if the occurrence of disease differed across these five location groups and an odds ratio was obtained using the fourth group (working all over the plant) as the reference category. There was not enough disease in the fifth group (working outside the plant or in offices) for this to be used as the reference group. Statistical analysis was performed using SPSS Version 12.

RESULTS

The workers investigated in the three phases of the study and their diagnoses are shown in fig 1.

Phase I: Screening questionnaire

The screening questionnaire was completed by 808/836 (96.7%) workers; 481 (60%) had at least one respiratory symptom, 147

(18%) had eye or nasal symptoms only and 180 (22%) were asymptomatic.

Phase II: Factory-based assessment

Four hundred and fifty-four (94.4%) of the 481 workers with at least one respiratory symptom on the screening questionnaire and 48/50 (96%) asymptomatic "controls" attended phase II. Table 2 shows their demographic characteristics. Compared with asymptomatic controls, those with respiratory symptoms had lower lung function, more worked in manufacturing and more smoked.

The detailed questionnaire showed that 146 employees had at least grade 1 MRC breathlessness, which was better on days away from work and/or on holiday ("work-related") (table 3). Of these, 54/127 who gave a year when they first developed breathlessness had an onset in 2003 or later. Seventy workers defined the month when they first developed breathlessness, showing peaks in March and June 2003 (fig 2). The prevalence of symptoms was 9.3% consistent with occupational bronchitis, 18.6% with work-related asthma and 2.1% with HF (table 3).

Phase III: Full clinical assessment

One hundred and seventy-three employees were identified for full clinical investigation as a result of either the factory assessment or the results of their PEF chart. Of the 173, 162 attended, 7 declined and 4 failed to attend. In total, 198 workers completed PEF charts for analysis; this included 141 of the 162 who attended for clinical investigation and a further 57 employees who were not seen (as their results were negative). Four controls were among those who completed PEF records. Based on clinical opinion, 102 workers were diagnosed with probable or definite occupational lung disease including 24 with EAA, 88 with OA and 7 with HF (some with more than

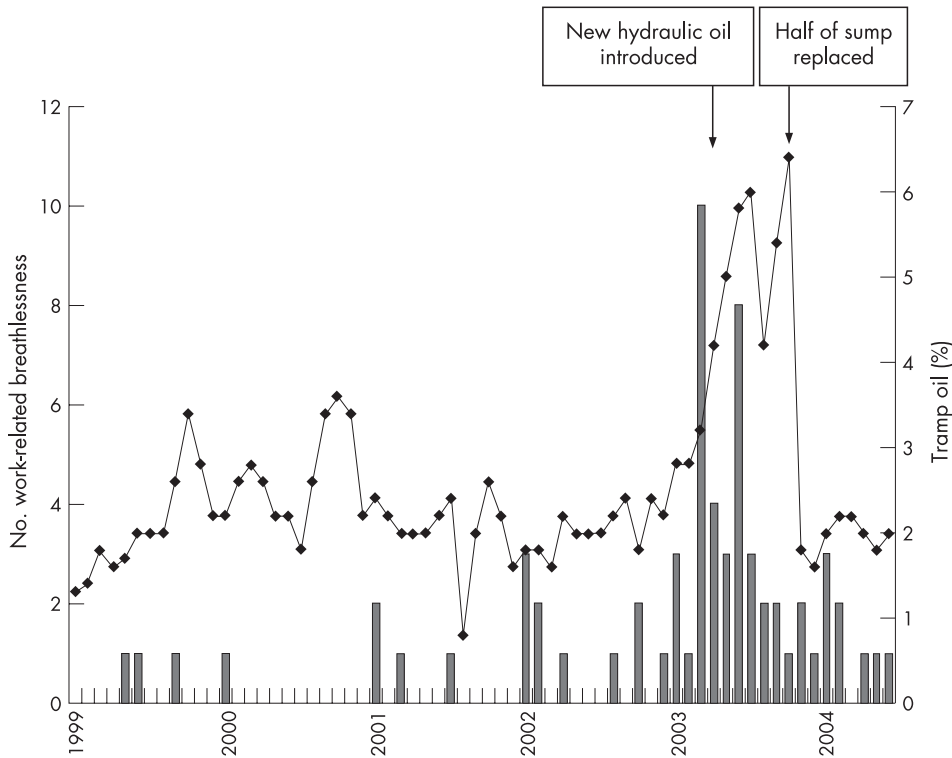


Figure 2 Onset of work-related breathlessness from phase II questionnaire (bars) in relation to the peak monthly tramp oil levels in metal working fluid (line).

one diagnosis). Additionally, 15 workers were diagnosed with occupational bronchitis (defined by cough productive of sputum which was better away from exposure). There were also single cases of bronchopulmonary aspergillosis (diagnosed immunologically), lipoid pneumonitis and Langerhans' cell histiocytosis (both diagnosed from histology).

Phase III: Numbers meeting the case definitions

Nineteen workers met the case definition for EAA (at least four of the seven criteria; table 4). Sixteen of these had the onset of symptoms after January 2003 (table 4). Seventy-four of the 198 employees who returned PEF records had a recording which met the case definition for OA (table 4). Half of these had first

Table 3 Self-reported work-related respiratory symptoms at the factory assessment (phase II)

	Respiratory symptoms on screening questionnaire (n = 454)*			Controls: asymptomatic on screening questionnaire (n = 48)		
	Work-related n (%)	Not work-related n (%)	Total n (%)	Work-related n (%)	Not work-related n (%)	Total n (%)
MRC Breathlessness						
MRC1: Troubled by shortness of breath when hurrying on level ground or walking up a slight hill	146 (17.5%)	77 (9.2%)	223 (26.7%)	2 (4%)	-	2 (4%)
MRC2: Short of breath walking with other people of own age and sex on level ground	89 (10.6%)	41 (4.9%)	130 (15.5%)	1 (2%)	-	1 (2%)
MRC3: Had to stop for breath when walking at own pace on level ground	41 (4.9%)	17 (2%)	58 (6.9%)	-	-	-
MRC4: Short of breath washing or dressing	16 (1.9%)	7 (0.8%)	23 (2.7%)	-	-	-
MRC Chronic Bronchitis						
MRC chronic bronchitis: sputum production for 3 months each year for 2 years or more	78 (9.3%)	53 (6.3%)	131 (15.6%)	-	-	-
Asthma type symptoms						
In last 12 months has your chest ever felt tight or your breathing become difficult?	156 (18.6%)	100 (12.0%)	256 (30.6%)	-	2 (4%)	2 (4%)
In the past 12 months have you had wheezing or whistling in your chest?	122 (14.6%)	105 (12.6%)	227 (27.2%)	-	2 (4%)	2 (4%)
Humidifier fever type symptoms						
In the past 12 months have you suffered recurrent flu-like symptoms on five or more occasions? (Work-relatedness was defined as symptoms at the beginning of the working week and/or being more frequent/severe on returning to work after a weekend or holiday)	18 (2.1%)	13 (1.6%)	31 (3.7%)	-	-	-

*Note that the total workforce of 836 used as denominator.

Table 4 Numbers with work-related respiratory disease according to case definitions for extrinsic allergic alveolitis (EAA), occupational asthma and humidifier fever with year of onset of symptoms from phase III

Disease	Met case definition		Total
	Symptoms before 2003	Symptoms 2003 and onwards	
Occupational asthma	37	37	74
Humidifier fever	1	6	7
EAA meeting at least 4 out of 7 Fox criteria	3	16	19
Numbers meeting each of the Fox criteria for EAA ¹⁶			
(1) Physician diagnosis of EAA (probable or definite) (n = 19)	3	16	19
(2) Onset of at least 2 pulmonary symptoms (cough, wheeze, chest tightness, shortness of breath) and one systemic symptom (fever, weight loss) (n = 19)	3	14	17
(3) A history of symptoms improving regularly on days away from work and deteriorating on return to work (n = 19)	3	16	19
(4) Restrictive pattern on spirometry: FVC <80% predicted and FEV ₁ /FVC >70% (n = 19)	1	3	4
(5) Pulmonary transfer factor <80% predicted (n = 19)	2	12	14
(6) Chest radiograph or CT scan showing interstitial, reticulonodular or mosaic pattern (n = 19)	2	13	15
(7) Biopsy evidence of non-caseating granulomas and/or lymphocytosis on bronchoalveolar lavage (n = 16)	1	8	9

onset of asthma-type symptoms since January 2003. Eight of the 74 also met the EAA case definition. Taking into account the overlap of disease, 87 employees (10.4% of the workforce) met case definitions for one or more of EAA, OA and HF (fig 3). Hereafter the analysis will refer to these 87 workers.

Unexpectedly, a "control" who was asymptomatic on the screening questionnaire was diagnosed as having OA, supported by a diagnostic PEF record (fig 1). During clinical investigation he denied many symptoms. His spirometric parameters were abnormal (FEV₁ 68%, FVC 74% predicted).

Workers who met the case definition for EAA and OA were compared with the asymptomatic controls (table 2). Those with EAA had restrictive disease with the lowest FEV₁ and FVC, those with OA had obstructive spirometry (on average), and the controls had values above predicted as would be expected for a healthy worker population. There was no difference in the smoking history, demographic characteristics or the length of exposure when defined by duration of employment in the three groups. However, almost all of those with OA (97%) and all with EAA (100%) worked in the manufacturing areas, significantly higher than the proportion in the control group (61%). Also, a higher proportion of those with EAA and OA had worked directly with MWF compared with the controls.

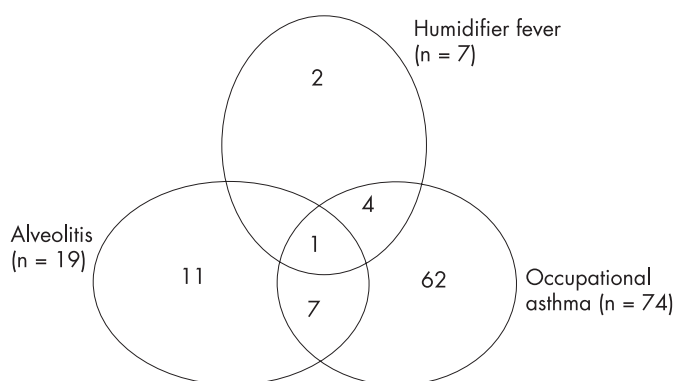


Figure 3 Case-defined work-related respiratory disease (n=87) showing overlap of disease at phase III.

Skin tests for atopic status were performed on 13/19 workers with EAA and 61/66 workers with OA; 3/13 (23%) with EAA and 33/61 (54%) with OA were atopic, showing the risk of OA to be associated with atopy.

Work location of the 87 workers with work-related respiratory disease (phase III)

The 87 workers with disease were distributed across 22 work locations in the factory (fig 4), with no workers with disease in 35 other work locations (as defined by their operational codes). Geographically, the cases of disease were clustered at the northern end of the factory. The work location with the highest number of cases was an engine assembly area (Assembly 1), but this also had the largest number of employees. As the numbers working in each location varies, the prevalence of disease is shown in fig 5. Four work locations all involved in machining (Machining 1, 2, 3 and 5) had a significantly higher rate of disease compared with the rest of the factory (fig 5). These four work locations were all in the northern half of the factory served directly by the largest common MWF sump (200 000 litres) or directly adjacent to it. A map of the factory showing the prevalence of disease for the work locations together with the location of the four main sumps and two washers shown to generate mist (Map 1) is given in the online supplement available at <http://thorax.bmj.com/supplemental>.

Table 5 shows the distribution of cases across the five work location groups (see Map 2 in the online supplement available at <http://thorax.bmj.com/supplemental> for the location of these five areas within the factory). Working in machining using MWF from the largest common sump was associated with an increased risk of having disease of more than four times (27.3%) compared with workers who worked all over the manufacturing area (7.9%) (odds ratio (OR) 4.39, 95% CI 2.00 to 9.60). Further analysis by type of disease showed that machining using MWF from the large sump significantly increased the odds of developing OA (OR 4.36, 95% CI 1.69 to 11.24); for EAA the OR was increased but this was not statistically significant (OR 2.62, 95% CI 0.73 to 9.38).

Challenge results

Of the two workers challenged, the worker with alveolitis had a late reaction to used MWF with a 14.6% fall in FEV₁ following

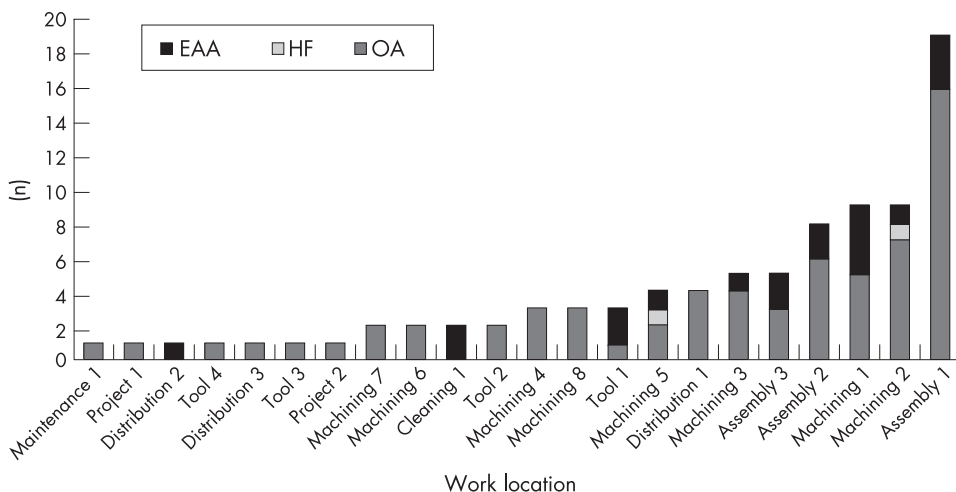


Figure 4 Work location of 87 workers with work-related respiratory disease. EAA, extrinsic allergic alveolitis; OA, occupational asthma; HF, humidifier fever.

indirect exposure and a 22% fall after direct exposure, with <1% change following unused MWF exposure. He had normal methacholine reactivity throughout. The worker with OA had a borderline reaction to the indirect exposure (immediate 13.7%, late 11.2% with a lower FEV₁ the following morning) and a significant dual asthmatic reaction with direct exposure (immediate 21.7%, late 13%; fig 6). His methacholine reactivity deteriorated from 2400 µg (normal >2000 µg) before the challenge to 300 µg the day after the positive challenge.

Environmental results

Results of air monitoring between May 2002 and October 2003 showed that concentrations of MWF in air were generally below the then HSE guidance value of 1 mg/m³.²³ In October 2003 the levels of mineral oil mist in air were between 1 and 4 mg/m³ with an average concentration of just above 1 mg/m³, also generally below the exposure guidance value of 3 mg/m³.²⁴ Personal samples of mineral oil mist taken at the same time indicated exposures of 1–1.7 mg/m³, with an average exposure of 1.3 mg/m³.

Samples of MWF taken from the largest common sump in August 2004 showed no bacterial, mycobacterial or fungal growth, with no increased endotoxin levels. DNA extraction identified *Acinetobacter* spp and *Ochrobacter anthropi*, but no

Mycobacterium spp. *Acinetobacter* spp and *Ochrobacter anthropi* were grown from washing machines.²⁰

Factory records showed a steep rise in tramp oil in the MWF in the large communal sump around April 2003, just after the hydraulic oil used in machines was changed (fig 2). A complicating factor was the highest number of workers reported onset of breathlessness in March 2003, just before the tramp oil increased.

DISCUSSION

The current investigation of employees in a car manufacturing plant in the UK detected 19 workers with EAA according to a strict case definition. During the investigation we also uncovered a large unknown outbreak of OA, with 74 workers diagnosed on the basis of serial peak flow records which are both reasonably sensitive and very specific for identifying patients with OA.^{21 22 25} A total of 87 workers met case definitions for OA and/or EAA and/or HF, an overall prevalence in the workforce of 10%. Half of the workers with OA had symptoms before 2003 (the date for new onset was defined as January 2003 or later based on the 12 index cases of EAA), suggesting that the outbreak of OA may have begun earlier than the outbreak of EAA.

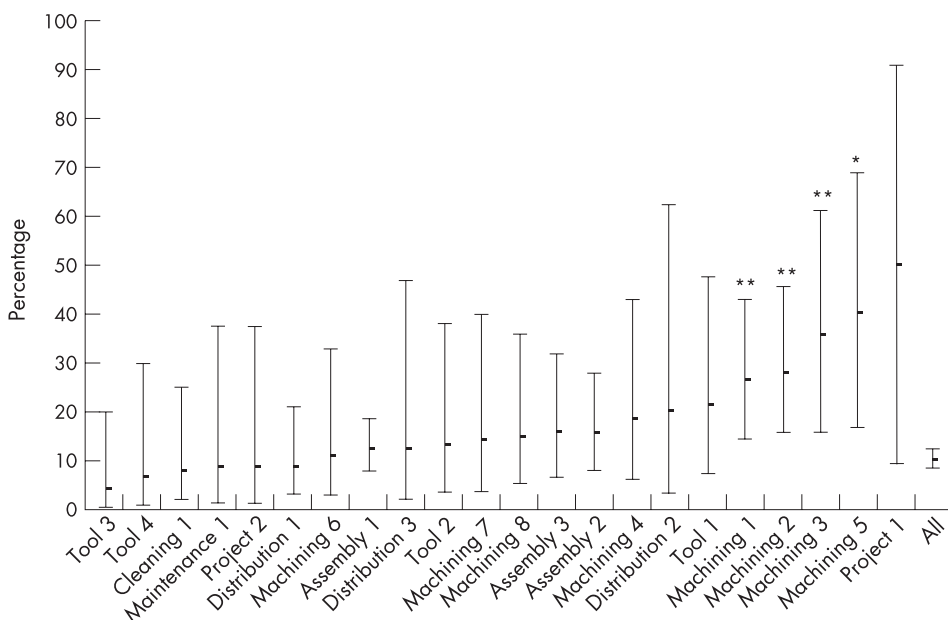


Figure 5 Percentage (with 95% confidence intervals) of workers with work-related respiratory disease by work location; *p<0.05, **p<0.01 work location higher than rest of workforce.

Table 5 Percentage of workers with work-related respiratory disease (meeting the case definition) by grouped work location together with odds ratio (OR) of disease across work locations (phase III)*

Work location	Total population (n)	Met case definition for EAA, OA and/or HF		Met case definition for EAA (8 also had OA)		Met case definition for OA	
		n (%)	OR (95% CI) vs "works all over"	n (%)	OR (95% CI) vs "works all over"	n (%)	OR (95% CI) vs "works all over"
(1) Machining using large MWF sump	66	18 (27.3%)	4.39 (2.00 to 9.60) p<0.001	5 (7.6%)	2.62 (0.73 to 9.38) p=0.138	12 (18.2%)	4.36 (1.69 to 11.24) p=0.002
(2) Machining using single/local MWF sumps	150	19 (12.7%)	1.70 (0.81 to 3.57) p=0.164	2 (1.3%)	0.43 (0.08 to 2.26) p=0.321	16 (10.7%)	2.34 (0.97 to 5.65) p=0.058
(3) Assembly and other manufacturing	320	36 (11.3%)	1.48 (0.76 to 2.88) p=0.246	7 (2.2%)	0.72 (0.22 to 2.29) p=0.573	29 (9.1%)	1.96 (0.87 to 4.38) p=0.103
(4) Works all over plant	165	13 (7.9%)	1	5 (3.0%)	1	8 (4.8%)	1
(5) Outside/office building	135	1 (0.7%)		0 (0%)		1 (0.7%)	
Total	836	87 (10.4%)		19 (2.3%)		66 (7.9%)	

* Denominators are total population in each work location.

We also identified workers with HF and work-related chronic bronchitis, as well as single cases of histologically confirmed lipid pneumonitis and Langerhans' cell histiocytosis and immunologically confirmed bronchopulmonary aspergillosis. The variety of different presentations of work-related respiratory disease related to exposure to MWF in the current study is consistent with other outbreaks of EAA in the USA. Zacharisen *et al* reported cases of EAA, asthma and bronchitis in a car engine manufacturing plant.²⁶ Hodgson *et al* found that many workers with EAA also had asthma, and there was at least one case of usual interstitial pneumonia and a case of sarcoidosis at the plant which produced titanium and steel parts for the aerospace industry.¹⁷ Similarly, in the present investigation 8 of the 19 workers who met the case definition for EAA also had peak flow variability consistent with the case definition for OA. EAA can produce findings of airways obstruction on spirometry, possibly due to associated bronchiolitis. It is conceivable that such airways obstruction would also show a work-related pattern.

Before further interpreting the results, it is important that the methodological limitations are discussed. First, with 87 cases of

work-related respiratory disease observed at the factory, the size of the control group (n = 50) may seem rather low. The number of controls had to be decided at the start of the investigation as the data collection had to happen for all at the same time, before the remedial action at the factory commenced. At that time the number of known (index) cases of EAA was only 12 and we were unaware of any cases of OA, so the sample size of 50 controls was thought to be reasonable. Second, a lower proportion of the control group worked in the manufacturing area compared with cases of OA and EAA and, as a consequence, they had less potential to be exposed to MWF. This was because the control population was selected from the asymptomatic workers identified from the screening questionnaire. The selection bias in the control group probably does not affect the results presented in this paper, as the focus of the paper is more about the epidemiology of those with respiratory illness. The results from this control group does reaffirm that working in the manufacturing area is associated with an increased risk of disease.

Another methodological issue is that the date of onset of symptoms was established retrospectively from the

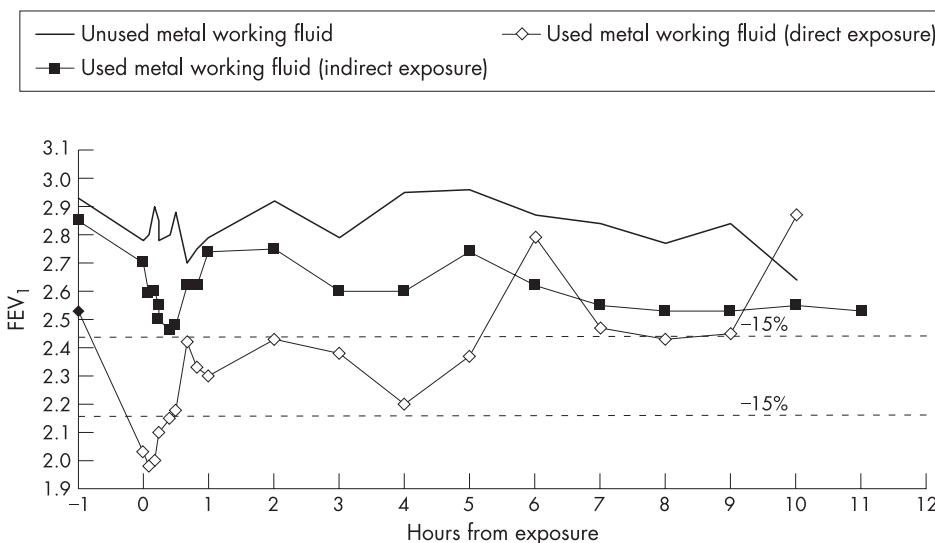


Figure 6 Bronchial provocation challenge test with unused and used metal working fluid on a worker with occupational asthma. FEV₁, forced expiratory volume in 1 s.

self-completed questionnaire more than 15 months after the onset of the outbreak. Only 70 of the 146 workers with work-related breathlessness were able to identify the month of onset. There were no contemporary surveillance data. With these caveats, there appears to be a peak incidence in March 2003, just before a new hydraulic oil for metal working machines was introduced in April 2003. The new hydraulic oil was more soluble in the MWF, increasing the concentration of tramp oil in the MWF. However, as the change in hydraulic oil occurred after the start of the outbreak, there is no clear evidence that this change is significant. The outbreak also coincided with reports of increased misting in the factory during the winter period when the roof louvers were closed.

Although factory records historically showed little bacterial growth, our own microbiological investigations in the factory found *Acinetobacter* spp and *Ochrobactrum anthropi* cultured from the washer fluid. DNA from these bacteria was also identified in the MWF from the largest sump, although there was no culture. No *Mycobacterium* spp were identified either from culture or from DNA extraction. The Health and Safety Laboratory has carried out a parallel immunological investigation of the workers at the factory in the current investigation which is reported in detail elsewhere.²⁰ MWF from the largest common sump at the time of the outbreak and extracts from cultures of *Acinetobacter* spp, *Ochrobactrum anthropi* and *Mycobacterium* spp were used to look for the presence of precipitating antibodies.²⁰ In those with EAA, 59% had precipitating antibodies to at least one of the microbial species *Acinetobacter* or *Ochrobactrum* or to used sump oil, whereas precipitating antibodies were found in only 10% of those with OA and 5% of asymptomatic workers (controls).²⁰ This is unlike other outbreaks of alveolitis where precipitating antibodies are commonly found in affected and asymptomatic subjects.²⁷ No workers tested positive for precipitating antibodies to *Mycobacteria* species. These results indicate that bacterial contamination of MWF—and in particular *Acinetobacter*—had at least a contributory role in the cases of EAA.

The overall levels of mist from both MWF and mineral oil sources were unremarkable, with most levels below the then MWF guidance value of 1 mg/m³ and the mineral oil in air guidance value of 3 mg/m³.^{23, 24} The Health and Safety Executive (the UK regulatory body for health and safety) has since withdrawn these guidance values.²⁸

The highest number of cases was in one of the assembly areas which was about 30 metres from the common sump, suggesting that the causative aerosol was relatively widespread. Two washers vented inside the factory and were also in the northern end of the factory. Given the wide distribution of disease in the factory, the most likely cause was an aerosol from either the metalworking and/or washing operations, although no material within this mist has been confirmed as a specific causal agent.

The potential of other exposure factors as a cause of this outbreak was considered. Metal particles can produce an intrapulmonary inflammatory response²⁹ and some specific metals are well recognised causes of OA. These are mainly platinum salts, chrome, cobalt and, to a lesser extent, zinc and nickel. At the factory the engines were made of aluminium alloy. There was no platinum, chrome or nickel. There was one machine where hard metal valve rings were machined. Cobalt levels in the MWF were insignificant and levels were checked in the urine of workers and were normal. There is some doubt as to whether aluminium alone can cause OA. The main work on aluminium and asthma comes from smelters where aluminium sodium fluoride is a possible cause. It has never been described in those working with cold aluminium. There were no sources of nitrogen oxides (no heating of the metal). However, the potential for other chemical constituents to be either causal or

to have had a co-effect cannot be discounted. The Health and Safety Executive has compiled a list of the constituents and contaminants of the MWF and wash fluids at the factory which were considered in the original investigation as possible causes of either EAA or OA (see online supplement available at <http://thorax.bmj.com/supplemental>).

During bronchial challenge tests two workers (one with OA and one with EAA) confirmed reactions to the used MWF taken from the common sump but not the clean MWF. The used MWF will contain material from the aluminium alloy castings, microbial contamination and added biocides, pH adjusters, etc. The lack of reaction to the unused MWF indicates that the chemical constituents alone were unlikely to have caused the disease.

As a consequence of this outbreak UK policy has changed, firstly for the users of MWF and secondly for those affected by EAA. First, the “lessons learned” from this outbreak have been published by the Health and Safety Executive on their website (this is available in the online Appendix at <http://thorax.bmj.com/supplemental>), detailing the practical implications for other users of MWF.²⁸ This outbreak showed that adhering to the guidance standards of oil mist did not prevent respiratory disease^{23, 24} and has led to their withdrawal by the Health and Safety Executive. Furthermore, the Health and Safety Executive has since issued new guidance on safe working practices that includes a requirement for respiratory surveillance. They have subsequently carried out a national survey of large users of MWF in 2005/6 to identify the extent to which guidance was being followed, with many deficiencies noted.³⁰

Second, there is an anomaly in that OA due to oil mists is compensatable in the UK through a no-fault compensation system from the UK Government’s Department for Work and Pensions, but EAA due to anything other than fungal or avian antigens is not.³¹ OA is known to adversely affect income and clinical outcome,^{32, 33} whereas the impact of EAA is likely to be at least as important. In July 2006 the Industrial Injuries Advisory Council (who advise the Department of Work and Pensions of the list of prescribed diseases for compensation) recommended that the occupational coverage for EAA should include exposure to mists from MWF.³⁴ This has now had ministerial approval and “work involving exposure to MWF” as a cause of EAA was added to the list of prescribed diseases on 6 April 2007.³¹

Finally, it is of interest to note what happened after the outbreak at the factory. After the assessment at the factory in June 2004 a series of control measures was introduced including:²⁸

- replacing MWF in the large common sumps;
- cleaning machines with individual sumps (both metalworking and washing) which were heavily contaminated with bacteria and then refilling them with fresh fluid;
- treating other less contaminated sumps with biocide;
- supplying employees with respiratory protection with powered respirators for those with known disease; and
- instituting respiratory surveillance for all employees.

Continued surveillance using occupational PEF records was carried out for those with OA, and a few had persistent OA despite the extensive control measures. The factory went into administration in April 2005. The machinery was subsequently bought by Nanjing Automobile (Group) Corporation and removed to China. Nanjing has been warned about the risks.

CONCLUSIONS

This investigation of an outbreak of EAA in a car manufacturing plant detected a large number of affected workers—not

only EAA but also OA—and is the largest reported outbreak in Europe. Mist from used MWF is the likely cause although oil mist levels were generally below guidance values, emphasising that it was time to reconsider the standards and issue new guidelines. Our study suggests that, in workplaces using MWF and wash fluids, there is a need to carry out risk assessments, ensure that fluid quality is monitored and maintained, improve the control of mist and carry out respiratory health surveillance on exposed workers.

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Additional information is given in the online supplement available at <http://thorax.bmj.com/> supplemental

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For ONLINE APPENDIX for Thorax/2006/072199

CONSTITUENTS AND CONTAMINANTS WITH THE POTENTIAL TO
CAUSE OR EXACERBATE RESPIRATORY DISEASE IN THE AEROSOL
MISTS AT THE FACTORY

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CONSTITUENTS OR CONTAMINANTS, WHICH MAY HAVE PLAYED A PART IN CAUSING OR EXACERBATING SYMPTOMS OF BOTH EXTRINSIC ALLERGIC ALVEOLITIS(EAA) AND OCCUPATIONAL ASTHMA(OA)

Constituent or Contaminant and links to respiratory disease	Quantities found or identified in metalworking or wash fluids/mists	Comment
<p>Bacteria - linked to both occupational asthma (OA) and extrinsic allergic alveolitis (EAA).</p>	<p>In 2004 high bacteria levels were counted in fluid samples from a number of washing machines and small sumps belonging to stand – alone metalworking machines. Two of these washing machines 38969 and 700315 were capable of expelling large quantities of contaminated mist in the area where most of those diagnosed with disease were working when they first became breathless</p>	<p>Some workers diagnosed with EAA demonstrated a serological¹ response both to a crude metalworking fluid extract, taken in April 2004, from the large Mayfram sump, and to predominant bacteria, <i>Ochrobactum anthropi</i> and <i>Acinetobacter sp</i>², present as DNA fragments in the sump.</p> <p>In 2005 Two workers diagnosed with EAA have demonstrated adverse respiratory effects when challenged with samples of fluid from the Mayfram sump taken by HSE in September 2004..</p> <p><i>Ochrobactum anthropi</i> has been linked to an outbreak of EAA in a car component factory in the USA³.</p>

¹ Sera were taken from those diagnosed with EAA.

² HSL Report dated 9 September 2004 “Results of bacterial identifications from environmental sampling” 12 August 2004.

³ Project Sensor News Volume 16, No 1, winter 2004 – 5, Michigan State University, College of Human Medicine, 117 West Fee Hall, East Lansing, MI 48824 - 1316

Constituent or Contaminant and links to respiratory disease	Quantities found or identified in metalworking or wash fluids/mists	Comment
Endotoxin - linked to short term health effects and exacerbation of pre – existing asthma	In 2004 high endotoxin levels were recorded in samples taken by HSL from a number of machines and locations ⁴ . These were frequently the same locations where high levels of bacteria had been recorded e.g. in and around 38969 (camshaft wash)	May have had a role in some of the disease diagnosed. As they were found in wash 39869 they may have been spread over considerable area.
Fungi – linked to extrinsic allergic alveolitis and other respiratory conditions, but limited evidence of any link to occupational asthma	At all times, generally low levels of common fungi were found in all sumps and washing machines, although in August 2004 moderate levels were found in air in various parts of the factory (for example, on 12 August 2004 1.4×10^3 were found in air near washer 700315, and 1.2×10^3 in air in CPK 24 at the other end of the factory)	May have had a role in some respiratory disease.

⁴ See HSL Report dated 19/8/04

Constituent or Contaminant and links to respiratory disease	Quantities found or identified in metalworking or wash fluids/mists	Comment
<p>Cobalt - linked to hardmetal disease, a severe lung disease, and asthma, both normally from exposure to cobalt dust. There was no exposure to cobalt dust at the factory, but it is possible there was some cobalt in metalworking and wash fluids from the metals being machined or metalworking tools used</p>	<p>A number of samples⁵ of fluids were taken from metalworking and washing machine sumps; generally levels were found < 0.1mg/l (or below the detection limit)</p> <p>Concentrations of cobalt in air sampled⁶ were below 0.01mg/m³</p> <p>Levels of cobalt in urine from those diagnosed with respiratory disease was not consistent with occupational exposure⁷</p>	<p>Respiratory disease from exposure to cobalt is normally associated with exposure to cobalt dust in the hard metal and diamond polishing industries</p> <p>The Occupational Exposure Standard (OES)⁸ was 0.1mg/m³ (8 hr time weighted average)</p>
<p>Other metals – including other hard metals, Iron, Chrome, Manganese and Nickel - either as constituents of metals being machined or metalworking tools used – linked to a variety of health effects on the skin and lungs, but not EAA or OA</p>	<p>Concentrations of these metals in air were sampled⁹ at very low exposures, generally <0.01</p>	<p>Such exposures are not generally associated with any health effect, and were always below any Maximum Exposure Limit (MEL)¹⁰ or OES</p>

⁵ See HSL Environmental Monitoring Requests - samples collected on 12/8/04, 16/8/04, 23/8/04, and 14/9/04

⁶ See HSL Environmental Monitoring Request – samples collected on 25/1/05

⁷ See letter from University of Surrey, dated 26 July 2005

⁸ Occupational Exposure Standards (OESs) were in force at the time of the outbreak and represent concentrations of hazardous substances in air at which there is no indication of risk to the health of workers exposed by inhalation day by day. OESs have now been replaced by Workplace Exposure Limits (WELs). The actual levels at which all relevant OESs and WELs were set remained unchanged over the period of the outbreak.

⁹ See Environmental Monitoring Request – samples collected on 25/1/05

¹⁰ Maximum Exposure Limits (MELs) were in force at the time of the outbreak for substances which may cause the most serious health effects, such as occupational asthma, and for which “safe levels of exposure” cannot be determined. A MEL is also set for substances, for which although safe levels may exist, it is not reasonably practicable to reduce to those levels. MELs have now been replaced by WELs.

Constituent or Contaminant and links to respiratory disease	Quantities found or identified in metalworking or wash fluids/mists	Comment
<p>Mycobacteria – these have been linked to outbreaks of EAA in the United States have been found in metalworking fluids after large outbreaks of EAA in the USA</p>	<p>No Mycobacteria were detected in HSL samples¹¹ taken from sumps</p> <p>HSL cultured Mycobacteria for precipitin tests involving sera from those diagnosed</p>	<p>No significant reactions were recorded between sera and Mycobacteria</p>
<p>Tramp oil – consists of oils, such as machine hydraulic and lubricating oils, which leak into metalworking fluid. At the factory over the period of the outbreak hydraulic and lubricating oils were highly refined mineral oils, with an exposure guidance value of 3mg/m³. Exposure to mineral oil mist alone has been linked to respiratory irritation, shortness of breath, coughing and tachypnea, but not occupational asthma or extrinsic allergic alveolitis. Tramp oil may form mineral oil/water emulsions, which may easily become microbiologically contaminated and support the proliferation of microorganisms.</p>	<p>Between October 2003 and February 2004 concentrations of mineral oil mist¹² in air of between 1 and 4 mg/m³ and an average concentration of just above 1 mg/m³ were recorded. Personal samples taken over the same period indicated exposures of between 1 – 1.7 mg/m³, with an average exposure of 1.3 mg/m³. These levels were recorded after the outbreak had peaked and action taken to reduce tramp oil.</p> <p>The hydraulic oil in all systems was changed in April 2003, which resulted in increased levels of tramp oil.</p>	<p>It may be expected that levels of exposure to mineral oil over the period of the outbreak were somewhat higher than those after steps had been taken to reduce the amount of tramp oil in the metalworking fluid. No direct link between such exposure and either occupational asthma or extrinsic allergic alveolitis has been demonstrated either in this outbreak or others.</p> <p>Onsets of breathlessness peaked in March 2003</p>

¹¹ See HSL Reports dated 17/11/03 and 4/5/04

¹² At the time of the outbreak, the guidance value for exposure to mineral oil, or neat oil, mist was 3mg/m³. This value is not based on any possible health effects at this level of exposure, but like the water – mix guidance value, represents good practice.

CONSTITUENTS OR CONTAMINANTS, WHICH ALONE MAY HAVE PLAYED A PART IN CAUSING OR EXACERBATING SYMPTOMS OF OCCUPATIONAL ASTHMA (OA)

Generally these are constituents, which have been linked to occupational asthma, but not extrinsic allergic alveolitis. There is no pattern in the use of particular fluids, or additives, such as biocides, or changes in them or of them which correspond to patterns of disease onset.

Constituent or Contaminant and links to respiratory disease	Quantities found or identified in metalworking or wash fluids/mists	Comment
Cases of occupational asthma have been linked to ethanolamines , including mono- and tri-ethanolamine ¹³ .	Monoethanolamine was present in all the major metalworking and wash fluid concentrates used in the factory.	<p>Taking into account the dilution of the concentrate the amount of Monoethanolamine in mist would have been extremely low.</p> <p>The same metalworking fluids had been in use in the factory with no major formulation changes since 1994.</p> <p>A new aluminium wash fluid was introduced in 2003, but this contained the about same proportion of Monoethanolamine as the wash fluid it replaced.</p>
Triethanolamine - cases of asthma linked to ethanolamines, including mono- and tri-ethanolamine ¹⁴ .	Present in wash fluid for cast iron.	Used since 1994.

¹³ *American Review of Respiratory Disease* 115(5): 867-71, 1977 May, *Allergy* 1994; 49:877-881: 12 cases 1990 - 2005

¹⁴ *American Review of Respiratory Disease* 115(5): 867-71, 1977 May, *Allergy* 1994; 49:877-881: 12 cases 1990 - 2005

Constituent or Contaminant and links to respiratory disease	Quantities found or identified in metalworking or wash fluids/mists	Comment
<p>Tolytriazole biocide – suspect, but no cases of asthma have been linked with exposure to tolytriazole.</p>	<p>Present in very low proportions in metalworking and wash fluids</p>	<p>All fluids in use have been unchanged (apart from the removal of diethanolamine) since 1998.</p> <p>Amount in mist would be extremely low. Would be present in mist at low concentrations <math><0.001\text{mg}/\text{m}^3</math> at the guidance value for metalworking fluid concentrate ($1\text{mg}/\text{m}^3$). Exposures at the factory were generally below this value.</p>

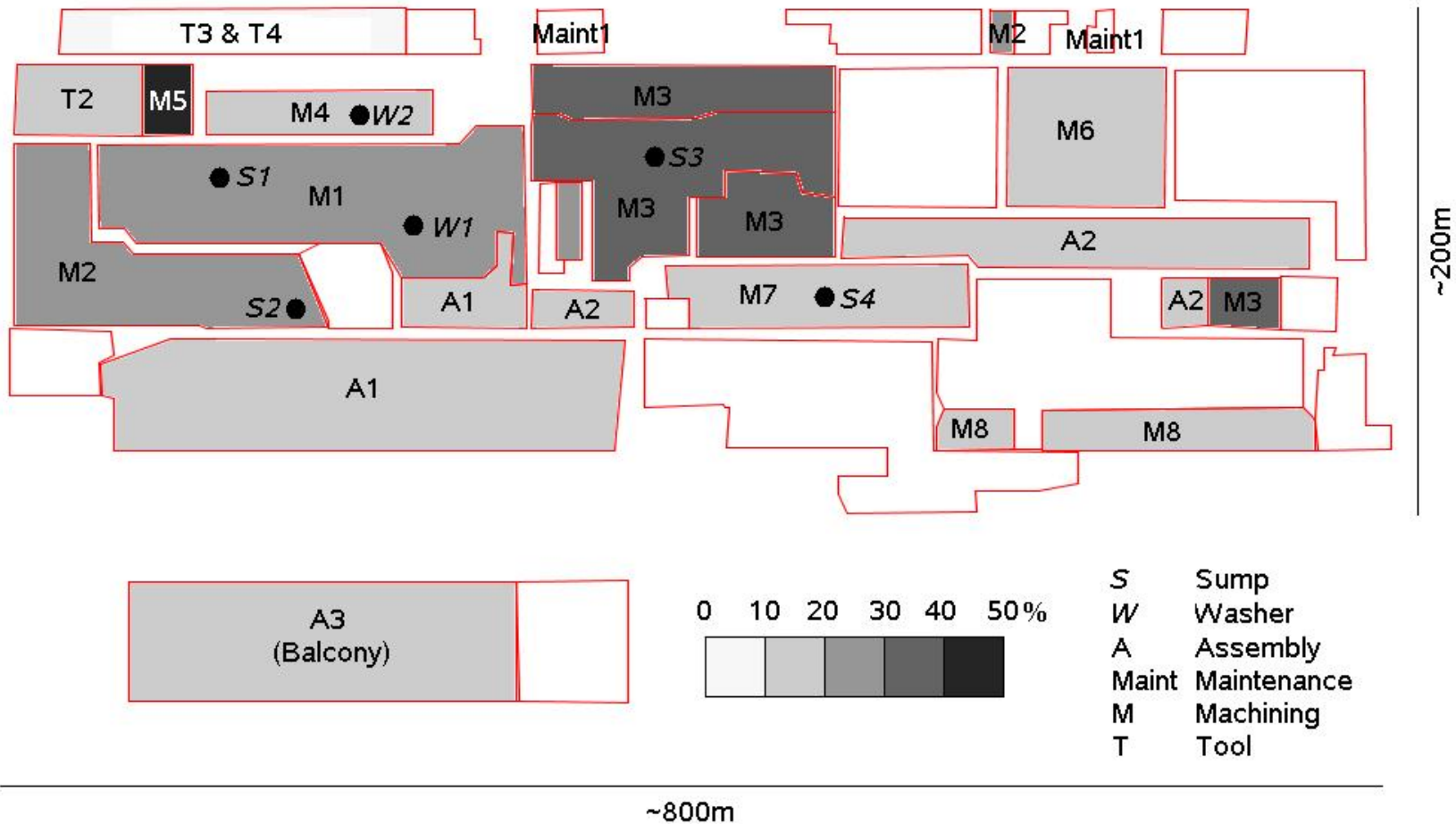
Constituent or Contaminant and links to respiratory disease	Quantities found or identified in metalworking or wash fluids/mists	Comment
Sodium Polyacrylate – polyacrylates have been linked to occupational asthma	Present as a small proportion of a metalworking fluid.	<p>Used unchanged since 1992 (apart from the removal of diethanolamine in August 2002).</p> <p>Polyacrylates named as suspected agents in 2 cases in nappy factory but kind of polyacrylate not named.</p> <p>About 50 cases due to monomeric acrylates e.g. cyanoacrylates, methacrylates have been reported in the last 15 years</p>
Tall Oil - suspected to be a sensitiser	Present in a metalworking fluid	<p>Used unchanged since 1994 (apart from the removal of diethanolamine in August 2002).</p> <p>Would be present in mist at low concentrations <0.1mg/m³ at the guidance value for metalworking fluid concentrate (1mg/m³). Exposures at the factory were generally below this value</p>
Formaldehyde ¹⁵ released by biocides in use. May cause sensitisation by inhalation and skin contact	Very low concentrations of between 0.0130 and 0.1122 mg/m ³ were measured ¹⁶ at points around the factory in August 2004.	<p>No new biocides have been introduced since 2000, with no changes in formulation since 2002.</p> <p>Formaldehyde had a MEL of 2ppm/2.5mg/m³ during the period of the outbreak.</p>

¹⁵ Formaldehyde is under review by HSE.

¹⁶ HSL Sample Numbers 03500/04 to 0309/04 taken on 23/8/04

Map of factory showing prevalence of work-related respiratory disease.

Codes show:- work locations in Figures 4 & 5 of the paper i.e. M1 is 'Machining 1'; four largest sumps (S), with S1 being the largest sump; and the two washers which vented into the factory (W1 and W2).



Map of factory showing the spatial distribution of the four work groupings (links to Table 5 in the paper).

(NB. The 5th work grouping – ‘working outside the main plant or in the office block’ is not shown, as they did not work in the main plant)

