STUDY TITLE:

ANALYSES OF EXISTING PEAK EXPIRATORY FLOW IN WORKERS WITH OCCUPATIONAL ASTHMA

Part of the quality development programme of the Oasys computer assisted analytical tool for occupational asthma from the Regional NHS Occupational Lung Disease Unit, University Hospitals Birmingham NHS Foundation Trust, Birmingham UK.

Short title/Acronym:	Analysis of existing PEF in workers with occupational asthma
Sponsor:	University Hospitals Birmingham NHS Foundation Trust
IRAS reference:	277792

STUDY SYNOPSIS

TITLE	ANALYSES OF EXISTING PEAK EXPIRATORY FLOW IN WORKERS WITH OCCUPATIONAL ASTHMA
SHORT TITLE	Analysis of existing PEF in workers with occupational asthma
Protocol Version Number and Date	V2.0 10/01/2023
Methodology	Retrospective observational (cross-sectional) study, with new analysis of existing clinical data
Study Duration	2 years
Study Centre(s)	University Hospitals Birmingham NHS Foundation Trust
Research questions	1. Do different inhaled exposures at work cause different patterns of peak flow response? 2. What is the specificity of self-completed respiratory questionnaire responses using Oasys analysis of PEF as the reference standard?
Number of Subjects/Patients	Existing clinical data from around 800 patients to be used
Main Inclusion Criteria	Records from workers with possible occupational asthma who have kept frequent measurements of their breathing using peak flow meters over several weeks at work and at who have at least one positive score for occupational asthma using the Oasys program, from 1990 onwards
Statistical Methodology and Analysis	Each of these variables will be compared between relevant workplace exposure groups (e. high molecular weight agents chemicals) using T test or ANOVA for normally distributed data, non-parametric comparisons for non-normally distributed data and X2 for counts

Protocol Agreement Page

The clinical study as detailed within this research protocol (Version 1.0; 28th June 2022), or any subsequent amendments will be conducted in accordance with the UK Policy Framework for health and social care research, the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

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Glossary of Terms and Abbreviations

APR	Annual Progress Report
CA	Competent Authority
CI	Chief Investigator
NHS R&D	National Health Service Research & Development
Participant	An individual who takes part in a clinical trial
PI	Principle Investigator
PEF	Peak expiratory flow
QA	Quality Assurance
SOP	Standard Operating Procedure

Index

1. Introduction

1.1 Background

Occupational asthma is the commonest identified occupational lung disease in many western countries. It accounts for about 15% of adult-onset asthma [1], and leads to significant morbidity, unemployment and costs to the country and to the individual [2]. Serial measurements of peak expiratory flow (PEF) are the best method of confirming the diagnosis. Their analysis using the Oasys system, developed in our department [3-10], are supported by national and international evidence-based guidelines [11-13]. Oasys has a number of quality and diagnostic outcomes, one of which is the Area Between Curves (ABC) score. This plots of the PEF in 2-hourly blocks from waking to sleeping separately for all readings made on work and rest days. The ABC score is the area between the two curves (in litres/min/hour). The specificity (for occupational asthma) of a score >15litrs/min/hour is 94% [5,6].

Occupational asthma has many forms. High molecular agents acting through IgE sensitisation was the first to be established. We see few of these patients who can usually be diagnosed from history, lung function and specific IgE, the commonest current example is in bakers exposed to flour and enzymes [14,15]. There is a latent interval from first exposure to first symptom during which sensitisation occurs, followed by low dose elicitation. Similar latent intervals and low dose elicitation is seen with a number of low molecular weight agents where IgE mechanism are usually not demonstrable. Isocyanate sensitisation would be the commonest example [16,17], most accept this as occupational asthma with sensitisation. Acute irritant-induced asthma occurs following a large exposure to a known respiratory irritant (commonly chlorine) in a previously normal individual [18]. Asthma is induced within 24 hours of exposure, and may persist indefinitely, but without sensitisation and low dose elicitation. Work-aggravated asthma is a much more confusing term, implying that the asthma would have occurred anyway but is aggravated by current occupational exposures. Some use it as a way of removing responsibility for any disease from those responsible for the exposures, which are assumed to be non-specific [19]. The clearest example is when a worker with current asthma at the time of first exposure deteriorates within hours of first exposure to a known asthma precipitant, such as cold air in a cold store or sulphur dioxide. Less clear examples would include childhood asthmatics whose asthma has completely resolved before first exposure. We believe that there is another group, sometimes labelled as low-dose irritant occupational asthma [20]. In this situation there is no acute exposure, there is a latent interval from first exposure to first symptom, and low dose elicitation occurs but the agent is assumed to be acting as an irritant (for instance diesel exhaust). We have shown that this group cannot be differentiated from those with sensitisation from latent intervals, smoking, childhood asthma, smoking or atopy [21,22]. They however are not eligible for industrial disease compensation, are more often left exposed at work and may have a poor prognosis.

There is recent evidence that some groups of low molecular weight agents causing occupational asthma where specific IgE has not been demonstrated may have similarities with occupational asthma from high molecular weight agents [23]. This particularly applies to acrylates, for which we have reasonable data [24].

1.2 Rationale and Risks/Benefits

At present Oasys analysis is only able to identify whether any disease which can be monitored by PEF is worse following work exposures. It does not identify the mechanism

of reaction (irritant vs. allergy), nor the likelihood that one agent is more likely to be the cause rather than another. The latter requires in-hospital specific challenges usually taking at least a week. If Oasys could separate these there would be substantial cost savings. The questionnaire study should provide data on the specificity of work-related asthma symptoms from a respiratory questionnaire in identifying occupational asthma in outbreak situations. If high this would again lead to significant cost savings.

1.3 Study overview

We wish to use existing records to see if different exposures at work cause different patterns of peak flow response. This would include comparing exposures to agents which are thought to act as irritants (such as chlorine-based cleaning agents, mild steel welding fume and diesel exhaust), can be differentiated from those where hypersensitivity is likely (such as flour, isocyanates and acrylates). Also we wish to try an identify how big a difference there has to be in PEF to identify a specific cause when a worker is exposed to more than one possible cause, when there are days with predominantly one rather than the other exposure. In an adjunct analysis we will investigate the sensitivity and specificity of responses to work related asthma questionnaires (undertaken by patients as part of routine care) against their PEF measurements, and grouped by different exposures.

We will use existing data on workplace exposures contained in patients' electronic medical records (including self-completed respiratory questionnaire responses), and any other confirmatory tests already done such as blood tests for specific IgE or the results of specific inhalation tests. No new data will be collected, and no new diagnoses will be made. With respect to PEF analysis, the Area Between Curves (ABC) score and pattern will be used for comparison of the different exposure groups. The ABC plot is one of the outputs from the Oasys analysis system which we use routinely in the occupational lung disease clinic for the diagnosis of occupational asthma. There are several outputs including the diurnal variation in PEF on days at and away from exposure, the magnitude of the difference between work and rest days (the ABC score) and the timing of response (immediate, flat and late) and he timing of recovery (1, 2, >2 days.

We wish to extend our comparison of PEF record analysis to distinct groups of low molecular weight exposures. The groups to be analysed depend on the quality of our data, but are likely to include acrylates [24], isocyanates [25,26], metal-working fluids [27-29], glutaraldehyde [30-32] and metals [33-35].

2. Trial Objectives and Design

2.1 Research questions

(1) Do different inhaled exposures at work cause different patterns of peak flow response?
(2) What is the specificity of self-completed respiratory questionnaire responses using Oasys analysis of PEF as the reference standard?

2.2 Trial Objectives

(1)To determine whether different exposures at work cause different patterns of peak flow response
(2) To determine whether exposure to supposed irritants differ from supposed sensitizers in workers reacting to either exposure
(3) To determine how big a difference in PEF is needed to identify a specific cause when a worker is exposed to more than one possible cause?

(4) To determine whether the specificity of questionnaire responses of work-related asthma symptoms, using positive Oasys analysis of PEF records as the reference standard?

2.3 Study Design

Observational (cross-sectional) study using retrospective data, collected as part of routine clinical practice.

3. Subject Selection

3.1 Study Population

Patients with possible occupational asthma who have undergone peak expiratory flow monitoring at the UHB NHS Foundation Trust occupational lung disease unit since 1990, and who have Oasys records available in the unit's clinical database (derived from their electronic patient record)

3.2 Participant Identification

Records from all workers with possible occupational asthma who have kept frequent measurements of their breathing using peak flow meters over several weeks at work and at home as part of their investigation to confirm their diagnosis and who have at least one positive score for occupational asthma, will be identified from the Oasys database on trust computers (derived from- and part of the electronic patient record) from 1990 to the present day.

3.3 Inclusion Criteria

Records from workers with possible occupational asthma who have kept frequent measurements of their breathing using peak flow meters over several weeks at work and at home (minimum of 3) as part of their investigation to confirm their clinical diagnosis, and who have PEF records suggestive of occupational asthma (ie. Oasys software analysis is positive, using at least one of its scoring systems), and identified from the Oasys database on trust computers from 1990 to the present day.

3.4 Exclusion Criteria

1) Patients for whom PEF records were inadequate for analysis (eg. too few readings, insufficient number of days at work)
2) Records of patients whose occupational exposures are unknown

3.5 Informed consent

We do not intend to gain informed consent from individual patients. All the data to be used is already in the clinical domain. Our analyses will not alter any diagnoses already made. It would not be feasible to go back to a large number of patients from 1990 to obtain consent. Our unit is one of only 5 in the UK, and many patients come from distant locations within the UK. It is therefore likely that many patients would be uncontactable due to death, relocation, or discharge from the service.

3.6 National data opt out

We will perform a search of the messaging exchange for social care and health (MESH), using patients' NHS numbers in order to check for patients who have opted out of using their data for secondary purposes (eg. research) and these patients will not then be eligible to take any further part in the study. In order to adhere to the Principle of Transparency in the UK GDPR 2021, we will put a poster in the clinical area (outpatient waiting room of the occupational lung disease unit) signposting patients to the Trust Research Privacy notice.

4. Data Management

4.1 Participant Identification Numbers

Included patients will be assigned unique study identification numbers (eg. OASYS01, OASYS02, OASYS03 etc). A master file (Excel spreadsheet) will be kept in a password protected folder on the respiratory medicine shared drive (o:drive) containing each included patients' hospital number cross-referenced with their study ID. A separate site file (Excel spreadsheet) will contain only data pseudo-anonymized by unique study ID.

4.2 Data Collection

From the whole occupational lung disease clinical database (which also includes the Oasys clinical database – ie. those patients (c. 50%) who have completed PEF records), in order to describe the tertiary clinic population as a whole in terms of annual incidence, most frequently encountered cause and frequency of use of PEFs as the gold standard in clinical diagnosis, we will gather the following limited data for all patients with occupational asthma diagnosed within the service 1990-2022 (c. 1600-1700):

1) Date of diagnosis
2) Diagnosis (eg. Occupational asthma by sensitization, irritant induced occupational asthma)
3) Causative agent
4) Job role at time of diagnosis
5) Confidence in diagnosis (ie. Diagnosis based upon PEFs or not, any specific challenge test done, or specific IgE done?)

Data from the Oasys patient database will gathered, and any missing data will be sought from the remaining elements of the NHS trust electronic patient record. We will collect baseline demographic and diagnostic data:

1) Age
2) Gender
3) Smoking status
4) Atopic status
5) Pre-existing asthma
6) Non-specific reactivity
7) Treatment during the PEF record
8) Presence of work related symptoms (based upon clinical questionnaire filled out by a subgroup of patients identified in workplace outbreaks of asthma, as part of their routine clinical care within the NHS occupational lung disease unit)

and diagnostic data from the PEF record:

1) The causative agent and exposure
2) The ABC score (a score derived from the area between the curves (ABC) of PEF on days at and away from work, calculated automatically when PEFs entered into Oasys software).
3) Diurnal variation on work and rest days (the difference between PEFs in morning and evening)
4) The pattern of reaction (immediate, flat and late) and speed of recovery (1,2,>2 days) from visual inspection of the Oasys records

4.3 Data processing

We will separate those whose exposures are generally regarded as irritant from those generally regarded as due to hypersensitivity. We will also identify a group who have kept records including >1 different exposure. Groups will comprise:

1) High molecular weight allergens (mainly flour, latex, enzymes and laboratory animals)
2) Intermediate agents separately
3) Woods
4) Metal-working fluids
5) Solder fluxes
6) Low molecular weight allergens separately
7) Isocyanates
8) Acrylates
9) Metals (mostly chrome and cobalt)
10) Glutaraldehyde
11) Cleaning agents
12) Agents with exposure in office environments
13) Agents with exposure in school environments
14) Agents encountered in healthcare environments
15) All other low molecular weight agents

Those with records with more than one exposure who have had one agent identified as the cause (for instance from specific inhalation tests), a comparison of days with either exposure will be used for the comparison of PEF responses of different exposures.

4.4 Data Entry

The research team (who are also part of the clinical care team) will identify patients from the electronic patient record (via the Oasys database), and a master file (Excel spreadsheet) will be kept with hospital number and unique study ID number for all included patients. A separate site file will be created for research data, pseudo-anonymized with study ID (thus not containing any hospital numbers). Both the master file and site file will be kept on a shared drive (the "o:drive") belonging to the respiratory medicine department at UHB NHS Foundation Trust. These will be kept in a password protected folder, and will only be accessible to the research team who will all be responsible for data entry. The accuracy of this data will be assured by ensuring that source data is cross referenced against research data by two members of the research team.

5. Data Confidentiality and Security

5.1 Data confidentiality statement

The research team will comply with the requirements of the Data Protection Act (2018) & UK GDPR (2021) with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

5.2 Physical security arrangements

Both the master file and site file will be kept on a shared drive (the "o:drive") belonging to the respiratory medicine department at UHB NHS Foundation Trust. These will be kept in a password precede folder, and will only be accessible to the research team. The master file will contain patient hospital number and unique study ID, the site file will thus contain pseudo-anonymised data with study ID only.

5.3 Access to clinical records

Access is to any who have legitimate access to our hospital clinical records. For the purpose of this study, only the CI/PI and co-investigators will have access. No extra data will be obtained.

5.4 Data storage

Data will be kept in password protected folders on trust computers (currently the respiratory department O:drive of the hospital IT system). The clinical team (who are also the research team) identified above will analyse the data. Once the study has ended, the pseudo-anonymised data will be kept for 10 years, as per Medical Research Council guidance. It will be kept in a password protected folder within the shared respiratory medicine drive on NHS Trust computers. No paper files will be used or retained.

5.5 Data quality assurance

The accuracy of the research data will be assured by ensuring that source data is cross referenced against research data by two members of the research team.

5.6 Data custodian

The custodian of the data will be the chief investigator Professor Sherwood Burge.

5.7 Data archiving

Research data will be kept in a password protected folder within the shared respiratory medicine drive on NHS Trust computers. No paper files will be used or retained. The UHB NHS Foundation Trust Research Archiving policy will be adhered to, and the CI will make an archive plan, which will include deciding when to archive after the study has finished, preparing master file (Excel spreadsheet with patient hospital number and associated study ID number) and site file (pseudo anonymised data in spreadsheet) within the folder for archive, by encrypting and making sure is saved as read-only text.

6. Statistical Considerations

6.1 Primary Outcome

Differences in ABC score* between groups (ie. irritant or sensitizer exposed individuals)

*where ABC score is a metric outputted from Oasys software and used to diagnose occupational asthma. It is derived from the area between the curves on days at work and days away from work.

6.2 Secondary Outcomes

1) Differences in the pattern of asthmatic reaction (immediate, flat, late) on PEF
2) Recovery time (1,2, >2 days) from asthmatic reactions based upon PEFs
3) Diurnal variation in PEF home vs work
4) Sensitivity and specificity of questionnaire responses (for the questionnaire analysis)

6.3 Sample Size

We will include all records which fulfill the inclusion and exclusion criteria, and confine subgroup analyses to groups with a minimum of 30 included records

6.4 Statistical Analysis

Each of the outcome variables will be compared between relevant groups using T test or ANOVA for normally distributed data, non-parametric comparisons for non-normally distributed data and Chi-squared for categorical data.

For the comparison of groups of low molecular weight exposures groups will be matched for the major confounding factors affecting PEF variability, particularly the use of inhaled corticosteroids taken during the record (recorded on the Oasys report). It may be possible to control for exposure during the record (original or reduced) depending on the extent of the data. We will not control for baseline PEF, as this may be affected by the recovery after exposure which is one of the variables we wish to study.

For the determination of specificity of work-related asthma symptoms from questionnaires we will use the data from an outbreak of occupational asthma in a car engine factory [27] with occupational asthma from aerosols of metal-working fluid which we have completed, and questionnaires were undertaken as part of routine clinical care. At least one positive score (eg. ABC score) from Oasys analysis will be used as the positive reference.

7. Ethical and Regulatory Considerations

This protocol and any subsequent amendments, along with any accompanying material provided to the patient in addition to any advertising material will be submitted by the Investigators to a Research Ethics Committee (REC) and Health Research Authority (HRA). Written Approval from both will be obtained and subsequently submitted to the UHB NHS Foundation Trust Research & Development Department to obtain Confirmation of Capability and Capacity (Trust Approval). The study will only commence once these permissions have been granted.

7.1 Substantial amendments

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with UHB NHS Foundation Trust R&D department so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended. Any subsequent substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site. All correspondence with the REC will be retained.

7.2 REC annual review

An annual progress report (APR) will be submitted to the REC by the chief investigator within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

7.3 Ethical issues

We can summarize the main ethical issues as follows:

(i) Equipoise

It is currently not known whether asthma caused by different agents (eg. irritants or respiratory sensitizers) have different patterns on peak flow monitoring. A detailed answer to this question will allow, perhaps, earlier diagnosis and isolation of causes for occupational asthma, and therefore should lead to better health and employment outcomes later on in many cases.

(ii) Data confidentiality

This study is a data only project, using routinely collected clinical data. We will need access to the patients' medical records from our NHS occupational lung disease unit, and results of serial PEF records and specific inhalation tests kept on trust clinical computers as part of standard medical records. The research team including chief investigator are clinical care team members as well, and identifiable data will not be viewed or shared beyond this team. We will process pseudo-anonymized data from the point of data collection onwards.

(iii) Informed consent
We do not intend to gain informed consent from individual patients for this study. Since patients have been seen in the service since 1990, many patients are either dead or discharged and not locatable. We will present summary data in tables. We will search all the patients to see whether any have opted out of having their records used for research (the NHS Opt Out), using our medical informatics department at the Trust.

8. Data Monitoring

8.1 Monitoring of study

The study will be monitored and/or audited by University Hospitals Birmingham NHS Foundation Trust under their remit as Sponsor and other regulatory bodies to ensure adherence to Good Clinical Practice and the UK Health Policy Framework for Health and Social Care.

Monitoring of study data shall include source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of accuracy of data manipulation. A nominated designee of the Sponsor shall carry out monitoring of study data as an on-going activity.

Study data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority where applicable as required.

Accidental protocol deviations can happen at any time. They will be adequately documented and communicated to the chief investigator, who will report them to the Sponsor immediately. Any frequently recurring deviations will be considered unacceptable, and could be considered a serious breach.

8.2 Study oversight

The chief investigator will have formal oversight of the study, and will meet the co-investigators every 3 months formally, to discuss compliance with protocol and any procedural issues.

9. Sponsorship and Indemnity

University Hospitals Birmingham NHS Foundation Trust will act as the Sponsor to this study. Delegated responsibilities will be assigned to the Chief Investigator and the NHS Trust taking part in this study.

University Hospitals Birmingham NHS Foundation Trust holds standard NHS Hospital indemnity and insurance cover with NHS Litigation Authority for NHS Trusts in England, which apply to this study.

10. Dissemination

10.1 Study report

A final report will be written by and submitted to the REC. Authorship will be determined by the criteria set out by the International Committee of Medical Journal Editors, but it is envisaged that this will include all four members of the research team.

10.2 Publication

Results will be published in a suitable subject-specific peer reviewed journal such as Occupational and Environmental Medicine or Thorax. Anonymity of patients will be retained for publication, and wherever possible, group summary statistics will be used. Informed consent would be required and gained from patients providing any detailed illustrative cases if suitable.

10.3 Public and patient involvement

We intend to disseminate the results by oral presentation to an existing West Midlands occupational asthma PPI group, run by Dr Gareth Walters (co-investigator)

11. References

1. Blanc PD, Annesi-Maesano I, Balmes JR, Cummings KJ, Fishwick D, Miedinger D, Murgia N, Naidoo RN, Reynolds CJ, Sigsgaard T, Torén K, Vinnikov D, and Redlich CA, The Occupational Burden of Nonmalignant Respiratory Diseases. An Official American Thoracic Society and European Respiratory Society Statement, Am J Respir Crit Care Med, 2019;199:1312-1334
2. Ayres JG, Boyd R, Cowie H, Hurley JF, Costs of occupational asthma in the UK, Thorax, 2011;66:128-133
3. Burge CBSG, Moore VC, Pantin CFA, Robertson AS, Burge PS, Diagnosis of occupational asthma from time point differences in serial PEF measurements, Thorax, 2009;64:1032-1036
4. Moore VC, Jaakkola MS, Burge PS, A Systematic Review of Serial Peak Expiratory Flow Measurements in the Diagnosis of Occupational Asthma, Annals of Respiratory Medicine, 2010;1:31-44
5. Moore VC, Jaakkola MS, Burge CBSG, Robertson AS, Pantin CF, Vellore AD, Burge PS, A New Diagnostic Score for Occupational Asthma, Chest, 2009;135:307-314
6. Moore VC, Jaakkola MS, Burge CBSG, Pantin CFA, Robertson AS, Burge PS, Do long periods off work in peak expiratory flow monitoring improve the sensitivity of occupational asthma diagnosis? Occup Environ Med, 2010;67:562-567
7. Moore VC, Jaakkola MS, Burge CBSG, Pantin CF, Robertson AS, Vellore AD, Burge PS, PEF analysis requiring shorter records for occupational asthma diagnosis, Occup Med (London), 2009;59:413-417
8. Park D, Moore VC, Burge CBSG, Jaakkola MS, Robertson AS, Burge PS, Serial PEF measurement is superior to cross-shift change in diagnosing occupational asthma, Eur Respir J, 2009;34:574-578
9. Burge PS, Pantin CFA, Newton DT, Gannon PFG, Bright P, Belcher J, McCoach J, Baldwin DR, Burge CBSG and the Midlands Thoracic Society Research Group, Development of an expert system for the interpretation of serial peak expiratory flow measurements in the diagnosis of occupational asthma, Occup Environ Med, 1999;56:758-764
10. Gannon PF, Newton DT, Belcher J, Pantin CF, Burge PS, Development Of OASYS-2: A System For The Analysis Of Serial Measurement Of Peak Expiratory Flow In Workers With Suspected Occupational Asthma, Thorax, 1996;51:484-489
11. Fishwick D, Barber CM, Bradshaw LM, Harris-Roberts J, Francis M, Naylor S, Ayres J, Burge PS, Corne JM, Cullinan P, Frank TL, Hendrick D, Hoyle J, Jaakkola M, Newman

Taylor AJ, Nicholson P, Niven R, Standards of care for occupational asthma, Thorax, 2008;63:240-250
12. Nicholson PJ, Cullinan P, Newman Taylor AJ, Burge PS, Boyle C, Evidence based guidelines for the prevention, identification, and management of occupational asthma, Occup Environ Med, 2005;62:290-299
13. Baur X, Sigsgaard T, Aasen TB, Burge PS, Heederik D, Henneberger P, Maestrelli P, Rooyackers J, Schlunssen V, Vandenplas O, Wilken D on behalf of the ERS Task Force on the Management of Work-related Asthma, Guidelines for the management of work-related asthma, Eur Respir J, 2012;39:529-545
14. Hendrick DJ, Davies RJ, Pepys J, Bakers Asthma, Clin Allergy, 1976;6:241-250
15. Pepys J, Wells ID, D'Souza MF, Greenberg M, Clinical and immunological response to enzymes of Bacillus subtelis in factory and consumers, Clin Allergy, 1973;3:143-160
16. Pepys J, Pickering CAC, Breslin ABX, Terry DJ, Asthma due to inhaled chemical agents-tolylene di-isocyanate, Clin Allergy, 1972;2:225-236
17. O'Brien IM, Harries MG, Burge PS, Pepys J, Toluene di-isocyanate-induced asthma. I. Reactions to TDI, MDI, HDI and histamine, Clin Allergy, 1979;9:1-6
18. Brooks SM, Weiss MA, Bernstein IL, Reactive airways dysfunction syndrome (RADS). Persistent asthma syndrome after high level irritant exposure, Chest, 1985;88:376-384
19. Chiry S, Cartier A, Malo J-L, Tarlo SM, Lemière C, Comparison of Peak Expiratory Flow Variability Between Workers with Work-Exacerbated Asthma and Occupational Asthma, Chest, 2007;132:483-488
20. Vandenplas O, Wiszniewska M, Raulf M, de Blay F, Gerth van Wijk R, Moscato G, Nemery B, Pala G, Quirce S, Sastre J, Schlünssen V, Sigsgaard T, Siracusa A, Tarlo SM, van Kampen V, Zock J-P, Walusiak-Skorupa J., EAACI position paper: irritant-induced asthma, Allergy, 2014;69:1141-1153
21. Anees W, Blainey D, Moore VC, Robertson K, Burge PS, Differentiating occupational asthmatics from non-occupational asthmatics and irritant-exposed workers, Occup Med, 2011;61:191-195
22. Burge PS, Moore VC, Robertson AS, Sensitization and irritant-induced occupational asthma with latency are clinically indistinguishable, Occup Med, 2012;62:129-133
23. Suojalehto H, Suuronen K, Cullinan P, Lindström I, Sastre J, Walusiak-Skorupa J, Munoz X, Talini D, Klusackova P, Moore V, Merget R, Svanes C, Mason P, dell'Omo M, Moscato G, Quirce S, Hoyle J, Sherson D, Preisser A, Seed M, Rifflart C, Godet J, de Blay F, Vandenplas O, European network for the Phenotyping of Occupational Asthma (E-PHOCAS) investigators., Phenotyping occupational asthma caused by acrylates in a multicentre cohort study., J Allergy Clin Immunol Pract, 2019;10.1016/j.jaip.2019.10.017
24. Walters GI, Robertson AS, Moore VC, Burge PS, Occupational asthma caused by acrylic compounds from SHIELD surveillance (1989–2014) , Occup Med, 2017;67:282-289
25. Burge PS, O'Brien IM, Harries MG, Peak flow rate records in the diagnosis of occupational asthma due to isocyanates, Thorax, 1979;34:317-323
26. Walters GI, Kirkham A, McGrath EE, Moore VC, Robertson AS, Burge PS, Twenty years of SHIELD: decreasing incidence of occupational asthma in the West Midlands, UK? Occup Environ Med, 2015;72:304-310
27. Robertson W, Robertson A, Burge CB, Moore V, Jaakkola MS, Dawkins PA, Burd M, Rawbone R, Gardner I, Kinoulty M, Crook B, Evans GS, Harris-Roberts J, Rice SB, Burge PS, Clinical investigation of an outbreak of alveolitis and asthma in a car engine manufacturing plant, Thorax, 2007;62:981-990
28. Burge C, Robertson A, Burge S, Serial peak flow measurements in occupational asthma; methods for monitoring response to exposure control using Oasys, Eur J Respir Dis Suppl, 2005;26 Suppl 4:150s

29. Burge PS, Moore VC, Burge CBSG, Vellore AD, Robertson AS, Robertson W, Can serial PEF measurements separate occupational asthma from allergic alveolitis? Occup Med, 2015;65:251-255
30. Di Stefano F, Siriruttanapruk S, McCoach J, Burge PS, Glutaraldehyde: an occupational hazard in the hospital setting, Allergy, 1999;54:1105-1109
31. Gannon PFG, Bright P, Campbell M, O'Hickey SP, Burge PS, Occupational asthma due to glutaraldehyde and formaldehyde in endoscopy and X-ray departments, Thorax, 1995;50:156-159
32. Curran AD, Burge PS, Wiley K, Clinical and immunological evaluation of workers exposed to glutaraldehyde, Allergy, 1996;51:826-832
33. Walters GI, Moore VC, Robertson AS, Burge CBSG, Vellore A-D, Burge PS, An outbreak of occupational asthma due to chromium and cobalt, Occup Med, 2012;62:533-540
34. Walters GI, Robertson AS, Moore VC, Burge PS, Cobalt asthma in metalworkers from an automotive engine valve manufacturer, Occup Med, 2014;64:358-364
35. Bright P, Burge PS, O'Hickey SP, Gannon PF, Robertson AS, Boran A, Occupational asthma due to chrome and nickel electroplating, Thorax, 1997;52:28-32