Thorax 1996;51:857–863

Occupational lung disease • 8

Series editor: P S Burge

The diagnosis of occupational asthma from serial measurements of lung function at and away from work

P Bright, P Sherwood Burge

The diagnosis of occupational asthma has serious consequences for a worker, who is often left with much less money and no job (at least in the UK).[1] It is important that the diagnostic process is available and accurate. In most instances the diagnosis of occupational asthma can be strongly suspected from the history alone, by finding a temporal relationship between symptoms and occupational exposure. Some asthmatics substantially under or over report symptoms in relation to changes in lung function and not all workers can be relied on to tell the truth. It is therefore wise to obtain further proof of the diagnosis of occupational asthma before counselling workers to avoid exposures which might cost them their jobs. Managers usually require proof of a problem before money is allotted to remove or control occupational sensitising agents. For those still at work the most appropriate next step in the diagnostic process is the serial measurement of lung function in relation to work. Peak expiratory flow (PEF) has usually been selected as the most appropriate parameter to measure because of the availability of portable meters for its measurement. It is likely that similar changes will be shown in forced expiratory volume in one second (FEV_1). Although some believe that the FEV_1 is more sensitive in detecting the airflow obstruction, particularly in the late asthmatic reaction,[2 3] not all agree.[3 4] If occupational asthma exists there should be measurable changes in PEF in relation to occupational exposure. The problem lies in differentiating the effects of work exposure from the spontaneous diurnal variation in airway calibre and its other determinants such as treatment, exercise, respiratory infection, exposure to non-specific irritants, and the errors inherent in its measurement.

Occupational Lung Disease Unit, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5ST, UK
P Bright
P S Burge

Correspondence to:
Dr P S Burge.

Definitions

ASTHMA

Asthma is defined physiologically in terms of reversible airflow (and hence peak flow) obstruction. There is no agreement as to the degree of reversibility required, how it should be calculated, nor how often it has to be present. The daily diurnal variation is preferably calculated as the amplitude/predicted. The daily mean or maximum can also be used as the denominator. The denominator is of importance for records from workers with low peak flows where diurnal variation is more dependent on the low mean value than on true variability.[5] In a random adult population Higgins *et al*[6] found the upper 90% confidence interval to be 17.6% (expressed as percentage mean adjusted to the increased value for the first day of the record); 60% of asthmatic subjects had a variability over this value in a seven day record.[6] A population study using less frequent measurements found the upper 95% confidence interval of diurnal variation to be 118% (expressed as maximum/minimum).[7] The calculation of diurnal variation also depends on the number of daily readings made, increasing for each additional measurement from two to eight.[8] The reading on waking is most often the lowest reading. The highest daily reading is very variably timed after waking, tending to be earlier on working days in those with occupational asthma.[9] Infrequent readings increase the chance of missing the true daily maximum.

OCCUPATIONAL EFFECT

No statistical or categorical method for separating occupational from non-occupational asthma has defined a minimum physiological effect that is considered significant. One definition of occupational asthma requires a fall in FEV_1 of $>20\%$ after a non-irritant exposure during the working day or over the working week.[10] There is general agreement in the interpretation of bronchial provocation tests that a 15% fall in FEV_1 or PEF over a reading at the same time following a control exposure constitutes a significant change.[11] The mean of all readings on a rest day may be very similar to the mean of all readings on a test day, even when one value shows a 20% fall, and often shows a change of much less than 10%. The calculation of mean differences between work and rest days is very dependent on the interval between work exposure and the start of deterioration (immediate versus late effects) and the speed of recovery. If recovery takes 2–3 days and a worker only has two days break from work at weekends, the mean values on rest days may even be lower than those on work days when severe occupational asthma exists.[12] Until large studies are completed of workers who have both kept good quality PEF records and have had a diagnosis made by independent methods, it will not be possible to define the minimum change in PEF on work days which constitutes occupational asthma. At present it is best to analyse the PEF record in terms of an occupational effect – that is, the work exposure results in lower readings than would have occurred if the worker had not been exposed to the offending agent at work.

Occupational asthma is best defined in this context as the combination of asthma and a work effect. There are some workers with a definite work effect where the diurnal variation is always within normal limits. Some of these have other defined diseases such as allergic alveolitis or occupational bronchitis, where a low diurnal variation in PEF is expected. Others have symptoms and other investigations indistinguishable from asthma;[13] whether such individuals should be called asthmatic or not is unclear – there is no other readily available label. There is some evidence that small consistent falls in lung function in relation to work predict progressive deterioration in FEV_1 (perhaps occupational bronchitis), at least in cotton and grain workers.[14–16]

Data quality

The principal problem with serial self measurement is the quality of the data. Poor quality can result from the measuring device, the expiratory effort, the meter reading, or the manual or logged data transfer. An ideal meter would assess the quality of the expiration in real time and produce feedback to the subject to correct deficiencies. At present there are no portable meters that achieve this. Recent European and American guidelines for meters suitable for self monitoring of lung function are available.[17 18] Accuracy refers to any systematic difference between the true measurement (for instance, from a computer driven syringe pump) and that recorded on the meter. It depends particularly on linearity and frequency response when measuring PEF. The American Thoracic Society recommends that monitoring meters should have an accuracy of ± 20 l/min or 10%, whichever is the greater.[17] The European guidelines give figures only for pneumotachometers where the accuracy should be within 5 l/min or 5%, whichever is the greater. Precision is the numerical difference between separate measurements of repeated identical exhalations. For PEF it should be less than 10 l/min between meters and 20 l/min within a meter over time (or 5% and 10%, respectively, if greater).

LINEARISATION OF METER READING

Peak flow meters used to be calibrated with a constant gas flow. The development of accurate computer driven pumps which can reproduce the pattern of expiratory flow seen in humans has shown that some meters are substantially non-linear, tending to over-read around 300 l/min and under-read over 600 l/min.[19] The usual effect of this in the occupation setting is to underestimate diurnal variation as the lower readings are often in the area where the meter over-reads. In one study diurnal variation (as percentage predicted) increased from below to above 20% in 12% of records.[8] Altitude can also affect PEF[20] but it will only become a confounding factor if there are substantial changes during the working day, or between rest and work days.

Some workers feel intimidated by doctors and fill in results where none have been done; a few probably deliberately prefabricate records. In our experience deliberate falsification is difficult to achieve realistically and probably rare. It can sometimes be detected by inspection of the original record, by finding a clean record completed with one pen and often having rows of identical readings (but beware of recopied records). More commonly some readings are done correctly, while others are invented. When readings are prefabricated they are usually not extreme and tend towards the mean for that worker, reducing the likelihood of diagnosing occupational asthma.[21] Quirce *et al*[22] compared meters that recorded the time and PEF of blows with hand written records and found that only 55% of records were completely accurate for timing and value of readings and 23.5% of readings were prefabricated. We have found that only 7.4% of readings did not accord between electronically recorded and manual records.[23] It is therefore our experience that PEF measurements are a reliable method of diagnosing occupational asthma, despite the inclusion of some prefabricated readings on some individuals.

NUMBER PREFERENCE

Number preference in reading measurements off an analogue scale is known to occur in many situations – for example, in the reporting of blood pressure. Mechanical PEF meters have scales calibrated to the nearest 10 l/min; measurements given to the nearest 5 l/min are likely to be approximations. More importantly, some subjects report their PEF to the nearest 20, 25, or 50 l/min. Reporting to the nearest 50 l/min is likely to produce a more dramatic effect on the PEF record. It is possible to detect number preference by producing a histogram of the tens digit of the PEF in a record. Number preference to the nearest 50 l/min would appear as an excess of zeros and fives. Although some records show number preference throughout, more commonly the number preference is intermittent and may indicate learning or failing compliance. We have recently investigated number preference in 33 PEF records recorded electronically to the nearest l/min. The maximum ratio of zero and five tens digits to the remaining tens digits was 0.42. This ratio was calculated from 268 manual records using mini-Wright meters. 10.5% had ratios above 1.0, including values as high as 171, suggesting that number preference was sometimes present. When a set of 150 manually recorded records with original ratios under 0.75 had number preference induced by rounding the PEF values to the nearest

50 l/min, there was no significant change (paired *t* test) in the mean diurnal variation (amplitude % predicted) for the whole record. The proportion of the record with a diurnal variation of more than 15% could vary by up to 50%. Rounding also decreased the discrimination between those with and without occupational asthma, particularly in those with less marked work related changes.

REMOVAL OF CONFOUNDING FACTORS
The separation of the effects of occupational exposure requires the elimination of as many confounding factors as possible, particularly learning and laze effects and the response to respiratory infections.[24] It is common for the worker to become more proficient at peak flow measurement during the first few days of the record, during which the diurnal variation is often higher and the mean lower. Sometimes the maximum is also higher, as it is uncomfortable to make maximal inhalations on each occasion. There is evidence that individuals often fail to achieve the maximum value obtained during coaching, with a mean loss of about 20 l/min[25] which is unlikely to upset the analysis unless it is systematically different on rest and work days. Some records show a gradual decline in PEF across work and rest periods (laze effects). The reasons for this are unknown but could include dirt in the meter, less effort in blowing, deteriorating asthma, or a change in treatment. The changes are usually gradual and make only a minor difference to the analytical programs.[26]

Number of daily readings and duration of record

International guidelines for PEF measurement in relation to occupational asthma have been developed[27] and recommend making at least three measurements on each occasion, the best two to be within 20 l/min. Readings should be made 4–9 times a day to include periods at and away from work. The European guidelines recommend a minimum of four readings per day.[27] We have found that the results of discriminant analysis are more stable in records where there are at least six readings per day. Records are helped by having a two week period away from work with records at work before and after this. The international guidelines recommend visual interpretation of plotted records as the most appropriate method of analysis, but recognises the problems of observer variability and recommends that more objective methods using computer analysis should be developed for record interpretation.

The ideal duration of the record depends on the severity of the occupational asthma, the presence of non-occupational airflow obstruction from asthma or COPD, and the regularity of exposure to the offending agents at work. Too short a record often results in uncontrollable confounding from learning and other effects; too long a record probably increases the risks of poor compliance and change in exposure. In practice it is best to start with a four week record to include regular periods off work. If this is equivocal, records are helped by having a two week period away from work with records at work before and after this. Longer records are particularly required for workers with unstable asthma where there are many provoking factors outside the work situation. Occupational asthma can probably be excluded from a good quality two week record where the PEF is within the normal range, the diurnal variation is less than 10%, and there is no variation between readings on work days and at least four days away from work. Great care is needed if the worker gives a history of severe reactions at work, where medically supervised readings before, during, and after a short period at work are preferable.[28-30]

Plotting

Serial PEF measurements can be plotted either in the traditional serial method as used in the monitoring of asthma severity, or as daily maximum, mean and minimum. The latter was the original method used to develop the diagnostic method for occupational asthma.[31 32] The plots are to a fixed scale with one day = 5 mm and 20 l/min PEF = 1 cm, facilitating pattern recognition. Each "day" begins with the first reading at work and continues to the last reading before work the next day. In this way the reading on waking is analysed with the previous day's readings. Sometimes this refinement makes little difference but it is a great help in night shift workers and can help separate work effects in those with longer recovery patterns. It accentuates the differences between work and rest days and makes it easier (at least for the non-expert) to detect smaller changes. In addition, the plot is enhanced by the inclusion of the number of readings for each day, a warning if the first reading was more than one hour after waking, and a calculation of the daily diurnal variation. No studies have compared the expert assessment of records using different methods of plotting.

Methods of interpretation of serial peak flow charts

CONFOUNDING FACTORS
The control for confounding factors is fundamental before meaningful analysis of the effect of work can take place. Varying treatment is the most difficult to control for and is best eliminated by making the PEF record on the same treatment throughout. The effect of bronchodilator use can be minimised by making readings before inhalation. Without control some individuals will increase treatment in anticipation of, or following, deterioration at work, thereby minimising any change in PEF. If less treatment is taken on days away from work the maximum PEF may be lower which, if combined with an increase in the minimum daily PEF on the same days, should alert the reporter to the problem.[12] Periods on and off corticosteroids need analysing separately. Respiratory infections are the most serious as they can cause large changes in PEF. If the worker takes time off with the infection it appears that the period away from work is worse than the period at work. A worker may

be more susceptible (due to the effects of the infection) or less susceptible (due to the effects of treatment) to the effects of the working environment for some time after the acute infection. Upper respiratory tract infections can produce effects as large as those due to work, with a maximum mean fall in PEF of around 20% lasting for an average of seven days.[24] The most appropriate solution is to remove that part of a record affected by respiratory infection before analysis for a work effect. There can be problems in differentiating between respiratory infection and occupational rhinitis when symptoms alone are used. Workers without prior asthma who develop occupational asthma also wheeze with non-specific triggers such as exercise, perfumes, cold air, etc, causing the PEF to fall. Provided that the record is long enough it is unlikely that confounding will occur as such triggers should be evenly distributed between work and rest days. The possible exception is exercise, which may be a fundamental part of some jobs, in which case it may be impossible to separate the effects of sensitisation and exercise from PEF records alone.

Exposure to the offending agent is usually not measured and is likely to vary from day to day. Days when exposure is known not to occur should be analysed as days away from exposure. Varying daily exposure is likely to be a major determinant of the inconsistent work effects seen in some records. A special confounding factor can occur when waking readings are omitted on days away from work, resulting in higher daily minimum readings on days off work. Many workers get up later on rest days, in which case they should be instructed to make the first measurements on waking rather than rising. Provided that two hourly readings are being made, the effect on the daily mean PEF is likely to be minimal.[33]

Methods of interpreting serial peak flow records can be divided into three. It is important when comparing the sensitivity and specificity of the methods between studies to appreciate that they may be using either of the above types of plot and that cases used in studies are rarely the more difficult ones with subtle work related effects. Foreknowledge of the population of workers under study may influence interpretation of records by experts. As noted earlier, some authors quote "work effects" as a positive result while others require asthma defined by a certain percentage diurnal variation in addition to work effects.

SUBJECTIVE ASSESSMENTS

Visual assessment by experts has been found to be superior to statistical analysis. The actual results of individual studies are, however, very dependent on the type of record studied; workers with large changes related to work and no treatment are much easier to identify than those on high dose inhaled corticosteroids with an element of fixed airway obstruction.[31 32 34] Subjective assessments may be supported by more objective criteria arrived at empirically. Burge *et al*[31 32] described the results of a study on workers exposed to colophony or isocyanates using the maximum, mean, and minimum plots. They required 75% of the working week to show specific (but undefined) patterns. The sensitivity was 77% and specificity 100%. Perrin *et al* "visually" analysed records on workers with cedar asthma and found a sensitivity of 86% and specificity of 89%. Agreement was needed by two out of three readers for two out of three weeks at work.[35]

Agreement between readers is important but is not always appreciated. Looking at relatively clear cut cases in the studies to date, Liss and Tarlo[36], for example, quoted agreement as measured by a kappa score of 0.62–0.83 for inter-reader agreement, while Malo *et al*[37] quoted intra-reader agreement as 83–100%.

QUANTITATIVE AND STATISTICAL APPROACHES

Rule based systems establish a criterion for a work effect – for example, the number of times a given decrease in PEF occurs on work and rest days. Although some success has been reported,[36 38 39] there are two problems with this approach. Basing diagnoses on a specific percentage fall in PEF will produce bias against those with a low peak flow for other reasons – for example, smokers and workers in certain industries such as those exposed to oil mist tend to have a low peak flow which only recovers after an extended time away from work. Criteria based on percentage falls in PEF are again very dependent on the accuracy and linearity of the peak flow meters used.

Some studies have used more sophisticated statistical methods. Henneberger *et al*[40] used *t* tests to compare the mean peak flow and mean diurnal variation of work days versus rest days. Compared with the visual interpretation of the record by three experts, mean peak flow had a sensitivity of 86% and specificity of 71%, while for the diurnal variation sensitivity was 43% and specificity 86%. The number of subjects was small, however, the method of plotting the peak flow was not stated, and two types of peak flow meter were used. Perrin *et al*[35] used a number of statistical indices but found none as satisfactory as visual interpretation of the record. Paggiaro *et al*[27] also used several indices of daily and day to day variability. They found that the mean peak flow, the coefficient of variation, and the maximum amplitude were all statistically different on days at work compared with days away from work for those with occupational asthma, but not for those with non-occupational asthma. The same group later commented, using the same indices, that peak flow monitoring allows only the detection of typical cases of occupational asthma.[41] Burge analysed records with an ANOVA, analysing the effect of work after adjusting for the effects of treatment, day of exposure, and hour of the day.[38] The analysis lacked sensitivity in electronics workers who tended to take more treatment on work days and lacked specificity in isocyanate exposed workers whose long recovery patterns meant that many days away from work were worse than initial days at work. These problems are inherent in statistical analyses.

One statistical method that gained brief popularity was cosinor analysis, where a sinusoidal curve is fitted to the PEF record allowing the calculation of the mesor (a type of mean), the amplitude (half the maximum to minimum daily variation), and the acrophase (the timing of the maximum relative to midnight). These measurements can be made on different parts of the record, on individuals, and on groups of individuals. Randem *et al*[9] used this method in workers diagnosed as having occupational asthma from colophony. Comparisons were made between work and rest parts of individual records and between those receiving and not receiving medication. The most consistent differences for all three indices were in comparing seven day working weeks to seven day resting weeks. Only amplitude and acrophase were statistically different when comparing five day working weeks with five day resting weeks. For other comparisons between work and non-work periods, the mesor tended to be lower for work periods, the amplitude higher, and the acrophase earlier, but the differences did not reach statistical significance. Those on medication tended to have a lower mesor, higher amplitude, and later acrophase, possibly because these individuals were the most severely affected. The earlier acrophase on work days was thought to be the result of blunting of the normal peak in the PEF that should occur between midday and late afternoon due to exposure to agents in the work place. Other investigators had noted an earlier acrophase in subjects exposed to environmental factors associated with asthma – for example, Gervais *et al*[42] found an earlier acrophase in children exposed to environmental pollutants. In the study by Cinkotai *et al*[43] the presence of bronchitic symptoms and age was positively associated with amplitude, while exposure to high levels of cotton dust was negatively correlated with amplitude.

Although cosinor analysis may give useful insights into the effect of exposure to occupational agents on the circadian rhythm of PEF, the technique is open to criticism especially if used as a diagnostic tool for individual patients. Cosinor analysis forces the diurnal variation in PEF into a sinusoidal pattern but, as illustrated by Cinkotai *et al*,[43] the group acrophase fell short of the true daily maximum.

A polynomial fitted the data better as it contained extra terms but still did not model the daily maximum well. Theoretically, cosinor analysis can predict a rhythm using only a small number of data points in each cycle provided these are well distributed throughout the cycle. For PEF data one third of the cycle is missing as the subject is asleep when the peak flow is likely to be at its lowest; hence, these critical data are not available to the model. Small numbers of data points will allow the erroneous compression of the diurnal variation into the sinusoidal pattern with apparently excellent goodness of fit measures. Cosinor analysis is only able to detect a diurnal variation in a proportion of subjects. In the study by Cinkotai *et al*[43] only 69 out of 161 subjects showed significant diurnal variation. In the study by Hetzel and Clark[44] only 145 out of 221 normal subjects had a detectable rhythm but a rhythm was detected in all asthmatic subjects, presumably because of their greater amplitude. Some subjects with occupational asthma – perhaps because of chronic exposure to high levels of environmental factors – have low PEF values with low diurnal variation which may not be detected by cosinor analysis. Waking time has a major effect on the timing of the acrophase[43] so must be controlled for in comparison studies.

COMPUTER METHODS AND NEURAL NETWORKS

The problem of interpreting a serial peak flow record is essentially one of pattern recognition. There is a large branch of computer science devoted to this technique and it has been applied to problems as diverse as enemy tank identification and the identification of wines by their smell. Pattern recognition systems have been developed and continue to be improved on for the identification of work effects in serial peak flow records. Unlike human experts, these techniques have the advantage of complete repeatability. All start from the plot of daily maximum, mean, and minimum, are based on expert interpretation unrelated to the final diagnosis, and are designed to detect an occupational effect rather than occupational asthma. The analyses split the record up into a series of overlapping elements containing either a period at work, a period away from work, and a period at work (a work-rest-work complex) or its counterpart (a rest-work-rest complex).

Discriminant analyses have been developed to mimic the effects of an expert and tested against a wide range of workers' records. OASYS-2, one such system, has a sensitivity of 69% and a specificity of 94% when applied to records from workers with a final diagnosis made independently of the peak flow record.[45] A neural net version with increased sensitivity is under development.[46] Time series analysis techniques, developed primarily for financial forecasting, seem promising.[47] The technique is employed to look for deviations from the rest pattern during work periods. The method is limited as serial peak flow records do not contain the density of data needed and therefore confidence intervals tend to be rather wide.

Practical aspects

Obtaining records suitable for analysis involves repeated and usually unsupervised exposures to a work environment which may be causing occupational asthma. It is clearly not suitable for workers with anaphylactic type reactions, for whom carefully controlled bronchial provocation testing with suitable minute levels of exposure are more appropriate if a specific diagnosis is required. Serial peak flow measurement requires commitment from workers and is difficult to achieve in some work places where full respiratory protection is required. It is usually possible to make recordings on waking, on arrival at work, during each formal rest period at work, on leaving work, at home after work, and on retiring to bed. Such records are unlikely to be evenly spaced in time, but this probably does not matter provided that there are at least six readings per day (although it provides a problem for spectral analysis).[48] It is best to aim for two hourly readings, particularly in those with mild reactions or those whose peak flow pattern is chaotic. After very minimal instruction adequate records are produced by about 50% in the occupational setting, and after further instruction about 80% produce adequate records.[49] Most workers who fail to keep an adequate record transcribed manually also fail to produce adequate records with a logging meter. Some workers keep much better records on work days than rest days. Rest day records are often the most important as there are usually fewer of them. Some workers seem to take very few days off work and, in these cases, records over annual holidays are often required.

The future

Self recorded lung function always lacks credibility to the sceptic. Logging meters overcome some of the problems. Such meters should record all blows and provide quality control in real time so that the worker knows whether further blows are required. The meters should obviously be technically satisfactory and linear. In our experience, compliance with logging meters is often less than with conventional peak flow meters. Logging meters are heavier and some are quite complicated. Many require an FEV_1 manoeuvre which can be more difficult. We have tried to incorporate the waking, sleeping, starting and stopping work markers into such logging meters with very limited success, mainly due to the inability to edit the input, which needs to be timed by the worker rather than the person logging the data (unlike their use for registering symptoms in drug trials).

Further work is needed on the analysis of long periods off work. If significant improvementoccurs during a 2–4 week period off work, with deterioration on return to work, occupational asthma is likely whatever the rest of the record shows. It is possible that further analysis of the diurnal variation changes and average hourly plots may produce further insights. It is unclear whether irritant reactions can be distinguished from those due to hypersensitivity; further work is needed to elucidate this.

1 Gannon PFG, Weir DC, Robertson AS, Burge PS. Health, employment and financial outcomes in workers with occupational asthma. *Br J Ind Med* 1993;**50**:491–6.
2 Berube D, Cartier A, L'Archeveque J, Ghezzo H, Malo J. Comparison of peak expiratory flow rate and FEV_1 in assessing bronchomotor tone after challenges with occupational sensitizers. *Chest* 1991;**99**:831–6.
3 Moscato G, Galdi E, Scibilia J. Occupational asthma, rhinitis and urticaria due to piperacillin sodium in a pharmaceutical worker. *Eur Respir J* 1995;**8**:467–9.
4 Moscato G, Dellabianca A, Paggiaro P, Bertoletti R, Corsico A, Perfetti L. Peak expiratory flow monitoring and airway response to specific bronchial provocation tests in asthmatics. *Monaldi Arch Chest Dis* 1993;**48**:23–8.
5 Weir DC, Burge PS. Measures of reversibility in response to bronchodilators in chronic airflow obstruction: relation to airway calibre. *Thorax* 1991;**46**:43–5.
6 Higgins BG, Britton JR, Chinn S, Cooper S, Burney PG, Tattersfield AK. Comparison of bronchial reactivity and peak expiratory flow variability measurements for epidemiologic studies. *Am Rev Respir Dis* 1992;**145**:588–93.
7 Quackenboss JJ, Lebowitz MD, Krzyzanowski M. The normal range of diurnal changes in peak expiratory flow rates. Relationship to symptoms and respiratory disease. *Am Rev Respir Dis* 1991;**143**:323–30.
8 Gannon PFG, Newton DT, Pantin CFA, Burge PS. Effect of the number of peak expiratory flow readings per day on diurnal variation. *Eur Respir J* 1992;**5**(Suppl 15):200s.
9 Randem B, Smolensky MH, Hsi B, Albright D, Burge PS. Field survey of circadian rhythm of PFR of electronics workers suffering from colophony-induced asthma. *Chronobiol Int* 1987;**4**:263–71.
10 Smith DD. Medical-legal definition of occupational asthma. *Chest* 1990;**98**:1007–11.
11 Pepys J, Hutchcroft BJ. Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *Am Rev Respir Dis* 1975;**112**:829–59.
12 Burge PS. Single and serial measurements of lung function in the diagnosis of occupational asthma. *Eur J Respir Dis* 1982;**63**(Suppl 123):47–59.
13 Bright P, Burge PS. Diurnal variability versus work/rest changes on serial peak flow measurements in the diagnosis of occupational asthma. *Eur Respir J* 1993;**6**:497s.
14 Becklake MR. Relationship of acute obstructive airway disease to chronic (fixed) obstruction. *Thorax* 1995;**50**(Suppl 1):S16–21.
15 Glindmeyer HW, Lefante JJ, Jones RN, Rando RJ, Weill H. Cotton dust and across-shift change in FEV_1 as predicators of annual change in FEV_1. *Am J Respir Crit Care Med* 1994;**149**:584–90.
16 Chan-Yeung M, Dimich-Ward H, Enarson DA, Kennedy SM. Five cross-sectional studies of grain elevator workers. *Am J Epidemiol* 1992;**136**:1269–79.
17 American Thoracic Society. Standardisation of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;**152**:1107–36.
18 Quanjer PH, Tammeling JE, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Official statement of the European Respiratory Society. *Eur Respir J* 1993;**6**(Suppl):5–40.
19 Miller MR, Dickinson SA, Hitchings DJ. The accuracy of portable peak flow meters. *Thorax* 1992;**47**:904–9.
20 Pedersen OF, Miller MR, Sigsgaard T, Tidley M, Harding RM. Portable peak flow meters: physical characteristics, influence of temperature, altitude and humidity. *Eur Respir J* 1994;7:991–7.
21 Burge PS, Gannon PFG, Bright P. Peak expiratory flow monitoring is not a reliable method for establishing the diagnosis of occupational asthma (letter). *Am J Respir Crit Care Med* 1996; (in press).
22 Quirce S, Contreras G, Dybuncio A, Chan-Yeung M. Peak expiratory flow monitoring is not a reliable method for establishing the diagnosis of occupational asthma. *Am J Respir Crit Care Med* 1995;**152**:1100–2.
23 Gannon PFG, Dickinson SA, Hitchings DJ, Burge PS. The quality of self recorded peak expiratory flow (PEF). *Eur Respir J* 1993;**6**:492s.
24 O'Brien C, Bright P, Nicholson C, Burge PS. Patterns of peak expiratory flow response to upper respiratory infections in asthmatics. *Eur Respir J* 1995;**8**:272s.
25 Gannon PFG, Belcher J, Pantin CFA, Burge PS. The accuracy of self recorded peak expiratory flow. *Eur Respir J* 1992;**5**(Suppl 15):170s.
26 Bright P, Burge PS. Characterisation of "laze" and "learning" effects on plots of serial peak flow records. *Eur Respir J* 1995;**8**:271s.
27 Paggiaro PL, Moscato G, Giannini D, di Pede F, Bertoletti R, Bacci E, *et al.* The Italian Working Group on the use of peak expiratory flow rate (PEFR) in asthma. *Eur Respir Rev* 1993;**3**:438–43.
28 Stenton SC, Dennis JH, Walters EH, Hendrick DJ. Asmagenic properties of a newly developed detergent ingredient: sodium iso-nonanoyl oxybenzene sulphonate. *Br J Ind Med* 1990;**47**:405–10.
29 Vandenplas O, Malo J, Cartier A, Perreault G, Cloutier Y. Closed-circuit methodology for inhalation challenge tests with isocyanates. *Am Rev Respir Dis* 1992;**145**:582–7.
30 Cloutier Y, Malo J. Update on an exposure system for particles in the diagnosis of occupational asthma. *Eur Respir J* 1992;**5**:887–90.
31 Burge PS, O'Brien IM, Harries MG. Peak flow rates in the diagnosis of occupational asthma due to colophony. *Thorax* 1979;**34**:308–16.
32 Burge PS, O'Brien IM, Harries MG. Peak flow rate records in the diagnosis of occupational asthma due to isocyanates. *Thorax* 1979;**34**:317–23.
33 Venables KM, Davison AG, Browne K, Newman Taylor AJ. Pseudo-occupational asthma. *Thorax* 1989;**44**:760–1.
34 Siracusa A, Forcina A, Brugnami G, Ranciaro A, Fiordi T, Marabini A. Monitoring of peak expiratory flow rates during occupational asthma treatment. *Med Lav* 1992; **83**:157–66.
35 Perrin B, Lagier F, L'Archeveque J, Cartier A, Boulet L-P, Cote J, *et al.* Occupational asthma: validity of monitoring of peak expiratory flow rates and non-allergic bronchial responsiveness as compared to specific inhalation challenge. *Eur Respir J* 1992;**5**:40–8.
36 Liss GM, Tarlo SM. Peak expiratory flow rates in possible occupational asthma. *Chest* 1991;**100**:63–9.
37 Malo J, Cote J, Cartier A, Boulet L-P, L'Archeveque J, Chan-Yeung M. How many times per day should peak flow rates be assessed when investigating occupational asthma? *Thorax* 1993;**48**:1211–7.

38 Burge PS. Prolonged and frequent recording of peak expiratory flow rate in workers with suspected occupational asthma due to colophony or isocyanate fumes. *MSc thesis*, London School of Hygiene:1978.
39 Cartier A, Bernstein IL, Burge PS, Cohn JR, Fabbri LM, Hargreave FE, *et al*. Guidelines for bronchoprovocation on the investigation of occupational asthma. *J Allergy Clin Immunol* 1989;**84**:823–9.
40 Henneberger PK, Stanbury MJ, Trimbath LS, Kipen HM. The use of portable peak flowmeters in the surveillance of occupational asthma. *Chest* 1991;**100**:1515–21.
41 Giannini D, di Pede F, Moscato G, Bacci E, Carletti A, Carrara M, *et al*. Sensitivity of peak flow monitoring to detect occupational asthma in relationship with specific bronchial challenge. *Eur Respir J* 1994;7:312s. .
42 Gervais P, Reinberg A, Fraboulet G, Abulker C, Vignaud D, Delcourt MER. Circadian changes in peak expiratory flow of subjects suffering from allergic asthma documented both in areas of high and low air pollution. In: Reinberg A, Halberg F, eds. *Chronopharmacology*. 1978;203–12.
43 Cinkotai FF, Sharpe TC, Gibbs ACC. Circadian rhythms in peak expiratory flow rate in workers exposed to cotton dust. *Thorax* 1984;**39**:759–65.
44 Hetzel MR, Clark TJH. Comparison of normal and asthmatic circadian rhythms in peak expiratory flow rate. *Thorax* 1980;**35**:732–8.
45 Gannon PFG, Newton DT, Belcher J, Pantin CFA, Burge PS. Development of OASYS-2, a system for the analysis of serial measurements of peak expiratory flow in workers with suspected occupational asthma. *Thorax* 1996; **51**:484–9.
46 Bright P, Burge P. Computer assisted interpretation of occupational peak flow plots; OASYS-N. *Eur Respir J* 1995;**8**:220s.
47 Belcher J, Gannon PFG, Pantin CFA, Burge P. Spectral analysis of peak expiratory flow from workers with suspected occupational asthma. *Eur Respir J* 1992;**5**:403s.
48 Belcher J, Hampton JS, Tunicliffe Wilson G. Parameterisation of continuous time autoregressive models for irregularly sampled time series data. *J R Stat Soc* 1994;**56**:141-55.
49 Gannon PFG, Newton DT, Burgess DCL, Burge PS. Interpretation of serial peak expiratory flow records for workers in an electroplating factory. *Eur Respir J* 1992;5(Suppl 15):403s.