

# Differentiating occupational asthmatics from non-occupational asthmatics and irritant-exposed workers

W. Anees<sup>1</sup>, D. Blainey<sup>2</sup>, V. C. Moore<sup>1</sup>, K. Robertson<sup>2</sup> and P. S. Burge<sup>1</sup>

<sup>1</sup>Occupational Lung Disease Unit, Department of Respiratory Medicine, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK, <sup>2</sup>Department of Respiratory Medicine, Broomfield Hospital, Chelmsford, Essex CM1 7ET, UK.

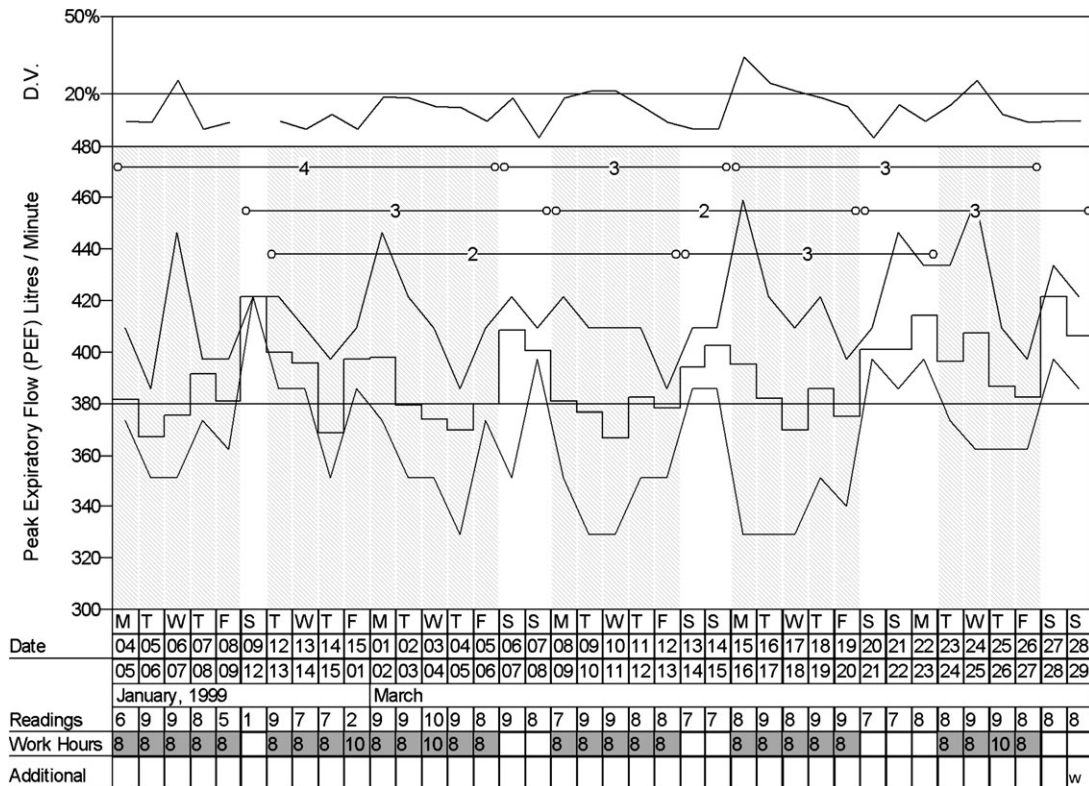
Correspondence to: P. S. Burge, Occupational Lung Disease Unit, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, UK. Tel: +44 121 424 2745; fax: +44 121 772 0292; e-mail: sherwood.burge@doctors.org.uk

<b>Background</b>	Serial peak expiratory flow (PEF) records have been recommended as a first-line investigation in workers suspected as having occupational asthma (OA).
<b>Aims</b>	To determine which PEF variability index best differentiates workers with OA from non-occupational asthmatics and unaffected irritant-exposed workers.
<b>Methods</b>	PEF was measured at least four times daily for at least 3 weeks in three groups of subjects: (i) forty healthy grain-exposed farmers and dockers, (ii) forty-two consecutive workers with independently confirmed OA and (iii) forty-eight non-occupational asthmatics. Indices of PEF variability were compared between groups.
<b>Results</b>	The difference in mean PEF between rest and work periods best separated the occupational asthmatic workers from the others. The upper 95% confidence limit of this index for grain-exposed workers was 2.8% of predicted PEF (16 l/min) and 3.3% (15 l/min) for non-occupational asthmatics. Sensitivity for diagnosing OA using this index was 70%. An increase in diurnal variation on workdays of >7% had a sensitivity of only 27% for the diagnosis of OA. The difference between maximum PEF on workdays and minimum PEF on rest days had a sensitivity of <10% against non-occupational asthmatic controls.
<b>Conclusions</b>	Difference in mean PEF between workdays and rest days is the best simple index for differentiating subjects with OA from those with non-OA or irritant-exposed healthy subjects. Differences >16 l/min are unlikely to be due to significant irritant exposure in healthy workers.
<b>Key words</b>	Grain; irritants; Oasys; OA; PEF.

## Introduction

Serial peak expiratory flow (PEF) monitoring has been recommended as a first-line investigation in workers suspected as having occupational asthma (OA) [1]. Although several studies have shown PEF records to be a sensitive and specific tool for the diagnosis of OA [2–5], there is a degree of intra- and inter-expert variability in the interpretation of PEF records [6–8]. In particular, there is often disagreement on the relevance of records that show small but consistent deteriorations in PEF during work exposure, particularly when PEF diurnal variability is within normal limits (Figure 1). Some would regard these features as indicating an irritant response rather than true OA, even in workers who have work-related respiratory symptoms suggestive of OA.

While there is no doubt that exposure to an irritant agent can lead to significant bronchoconstriction in asthmatic subjects, it is less clear what magnitude of response can occur in healthy individuals exposed to significant levels of irritants found in typical occupational settings. It is also unclear which index of PEF variability best distinguishes workers with OA from those with non-OA or irritant-exposed healthy workers. Coté *et al.* [9] found that the best index of PEF variability for separating workers with OA from those without was the difference in average maximum PEF during rest weekends compared to average minimum PEF during workdays. However, this index in reality only differentiates those with high diurnal variation from those with low diurnal variation. The upper 95% confidence limit for this index in



**Figure 1.** PEF chart from a secretary with a positive challenge to the material her room was cleaned with. Her PEF record shows a small work-related deterioration in PEF and mean diurnal variation of 15% on workdays. Shaded areas are workdays and unshaded areas are rest days. Dashed line is predicted PEF, solid line is daily mean PEF and upper and lower dotted lines represent maximum and minimum daily PEF, respectively. Mean PEF difference between rest and work periods is 23 l/min (6.1% of predicted PEF). Oasys-2 score is 3.0.

Coté's study (derived from 15 non-occupational asthmatics) was fairly low and is unlikely to be specific in non-occupational asthmatics who have a higher degree of diurnal PEF variability. Two alternative indices for identifying OA include assessment of change in diurnal variation between work periods and rest periods and differences in mean PEF between rest and work periods.

The aim of this study was to assess the ability of various simple indices of PEF variability to differentiate between workers with proven OA from those with non-OA and from healthy workers exposed to grain dust, a known respiratory irritant and to compare these simple indices with the occupational asthma system (Oasys—a computer program that scores serial PEF records on the likelihood of showing OA) score from the published discriminant analysis [10].

## Methods

PEF records from three groups of workers were identified: workers with OA, non-OA and healthy workers occupationally exposed to high levels of grain dust, a known respiratory irritant. Only PEF records deemed to be of

adequate data quantity for record interpretation as assessed by previously defined minimum PEF data quantity criteria were used [11]. These were (i)  $\geq 4$  readings on at least 75% of days, (ii)  $\geq 3$  complexes (equivalent to  $\sim 3$  weeks) in duration and  $\geq 3$  consecutive days at work in each work period for at least 75% of work periods.

Group 1 were healthy workers occupationally exposed to grain dust and consisted of healthy farmers exposed during harvesting, and dockworkers exposed while loading and unloading grain from ships and lorries. These subjects were identified retrospectively from the Health and Safety Executive grain dust survey of 27 farms and two docks in the South East of England. In total, 228 grain workers were identified, of whom 140 completed a respiratory symptom questionnaire, spirometry [12] and a serial PEF record. Ninety-eight (of whom 40 had no asthmatic symptoms as defined by the Venables questionnaire) of these subjects kept 120 PEF records that satisfied the minimum PEF data quantity criteria. Total grain dust measurements were carried out by the Health and Safety Laboratory using Institute of Occupational Medicine filtration samplers (SKC Ltd, Dorset, UK). Twenty-seven per cent of farm samples and 19% of dock samples showed levels  $>10 \text{ mg/m}^3$  (the UK maximum exposure limit) with grain dust

levels  $\geq 30 \text{ mg/m}^3$  being recorded in all work situations. Personal exposures to airborne endotoxin reached  $>600 \text{ EU/m}^3$  at every workplace. Healthy workers were selected from this group providing that they had no asthmatic symptoms as defined by the Venables questionnaire [12] and no evidence of airways obstruction, forced expiratory volume in 1 s ( $\text{FEV}_1$ )  $\geq 80\%$  predicted and  $\text{FEV}_1/\text{forced vital capacity}$  higher than predicted—1 SD.

Group 2 were workers with definite OA and were consecutive workers seen at the Birmingham Chest Clinic who had a diagnosis of OA confirmed independently of their PEF records. None had been exposed to grain. Diagnostic criteria were a good history suggestive of OA plus one of the following: (i) positive specific inhalation challenge test to an agent to which the worker was occupationally exposed ( $n = 30$ ), (ii)  $\geq 3.2$ -fold change in non-specific bronchial hyperresponsiveness in relation to exposure at work ( $n = 3$ ) and (iii) presence of specific immunoglobulin E to an occupational agent with known high specificity ( $n = 9$ ).

Only subjects whose first PEF record was of adequate data quantity at the time of initial investigation were included. None had previously been used in evaluating Oasys-2 [10].

Group 3 were non-OA subjects and were a group of physician-diagnosed occupational asthmatic/non-occupational asthmatic subjects who kept PEF records while away from work and who therefore could not have an occupational effect on the PEF measurements Mondays to Fridays 0900–1700 h were analysed as being at work. Differences in PEF indices between ‘rest’ and ‘work’ periods were therefore not as a result of genuine occupational exposure.

All PEF records were plotted using the Oasys-2 computer program after day interpretation [10], once periods containing documented respiratory tract infections, major lapse or learning effects had been removed and PEF data had been linearized [13].

Various indices of PEF variability were calculated (Box 1).

Atopy was defined as one or more positive skin prick test  $\geq 3 \text{ mm}$  to a non-occupational antigen with negative diluent control. Non-specific reactivity was measured in those with OA and non-OA either with methacholine using the Yan method (normal  $>2000 \mu\text{g}$ ) or with histamine using the Wright nebulizer technique (normal  $>8 \text{ mg}$ ). Non-specific reactivity was not measured in the grain-exposed workers.

Measures of PEF variability were expressed as mean and standard deviation. Upper 95% confidence limits for healthy grain workers and non-occupational asthmatics were calculated as mean plus 1.96 SDs. Sensitivity of a PEF index to diagnose OA was the percentage of workers with OA whose PEF index exceeds the corresponding upper 95% confidence limit.

**Box 1. PEF variability**

**1. Mean workday diurnal variability:**

$$\frac{\text{maximum daily PEF} - \text{minimum daily PEF (average of all workdays)}}{\text{predicted PEF}}$$

**2. Work–rest difference in diurnal variability: mean diurnal variability of workdays (as calculated above) minus mean diurnal variability of rest days;**

**3. Mean rest–work PEF differences: mean PEF on all rest days minus mean PEF on all workdays (absolute value in l/min);**

**4. Mean rest–work PEF differences expressed as a per cent of the predicted PEF;**

**5. Maximum rest – minimum work PEF expressed as per cent predicted:**

$$\frac{\text{average of maximum PEF on all rest days} - \text{average of minimum PEF on all workdays}}{\% \text{ predicted PEF}}$$

**6. Oasys-2 score (using the published discriminant analysis).**

**Results**

Fifty-two PEF records from 40 grain-exposed workers, 42 records from 42 occupational asthmatic workers and 48 records from non-occupational asthmatics were identified. Table 1 shows the characteristics of the subjects. Sixty-six per cent of the occupational asthmatics had been on inhaled steroids while keeping their PEF records. The OA group were exposed to a variety of agents, the most being to metal agents (26%), followed by biocides (16%), isocyanates (10%), flour (7%), colophony (7%), oil mists (7%), latex (5%), chloramines (5%), acrylates (5%) and other agents (12%).

The mean and upper limits of the assessed PEF indices for healthy grain workers and non-occupational asthmatics are shown in Table 2, along with the mean values in workers with confirmed OA and the sensitivity of these measures for identifying OA. Workday PEF diurnal variability was above the 95% confidence limit for the grain-exposed workers in only 40% of workers with confirmed OA, an increase in PEF variability during work periods by 7% compared to rest periods (the upper limit of change occurring in non-occupational asthmatics) was very insensitive for diagnosing OA. Of the statistical indices, the difference between mean work PEF and mean rest PEF expressed as per cent predicted PEF was the best at differentiating between workers with OA and both

**Table 1.** Subject characteristics

	Healthy grain-exposed workers ( <i>n</i> = 40)	Non-OA ( <i>n</i> = 48)	OA ( <i>n</i> = 42)
Age (years)	44.5 ± 10.4	49.4 ± 11.1	43.7 ± 9.3
Atopy	26%	33%	53%
Current/ex-smokers	36%/18%	30%/37%	14%/29%
FEV1 % predicted	107.6 ± 12.9	80.6 ± 11.6	86.3 ± 20.6
FEV1/forced vital capacity (%)	80.5 ± 3.8	69.9 ± 13.6	72.4 ± 16.8
Non-specific reactors	Not applicable	59%	63%

**Table 2.** PEF data comparison between healthy grain-exposed workers, non-occupational asthmatics and workers with confirmed OA

Index of PEF variability		Grain-exposed healthy subjects ( <i>n</i> = 40)	Non-OA ( <i>n</i> = 48)	OA ( <i>n</i> = 42)	Sensitivity for OA using upper limit from	
					Grain-exposed	Asthmatic
1. Workday diurnal variability (as % predicted)	Mean (SD)	9.1% (4.0)	13.5% (7.4)	16.1 (9.2) (median = 15.1)		
	Upper limit	16.9%	–	–	40%	–
2. Difference between mean workday diurnal variability and mean rest day diurnal variability	Mean	0.2% (2.6)	–0.1% (3.7)	5.4% (8.3) (median = 2.7)		
	Upper limit	5.3%	7.2%	–	31%	27%
3. Mean rest–work PEF difference (l/min)	Mean	–1.4 l/min (8.7)	0.4 l/min (7.3)	32.6 l/min (36.2) (median = 22.1)		
	Upper limit	15.7 l/min	14.7 l/min	–	67%	68%
4. Mean rest–work PEF difference (as % of predicted)	Mean	–0.3% (1.6)	0.1% (1.6)	6.9 (6.1) (median = 5.1%)		
	Upper limit	2.8%	3.3%	–	74%	70%
5. Maximum rest – minimum work PEF difference (as % of predicted)	Mean	8.6% (4.1)	13.9 (8.3)	19% (10.7) (median = 17.2)		
	Upper limit	16.6%	30.2%	–	51%	9%
Specificity of Oasys-2 score >2.5		96% (50/52)	92% (44/48)	–	–	–
Sensitivity of Oasys-2 score >2.5				79% (33/42)		

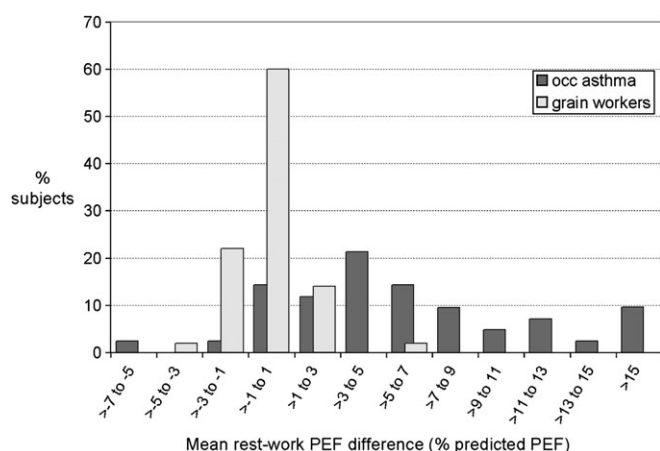
Upper limits for healthy grain-exposed and non-occupational asthmatics were derived from mean ± 1.96 SDs. Sensitivity for each index was the percentage of confirmed occupational asthmatics with values above the upper 95% confidence limit for the other two groups.

non-occupational asthmatic subjects and grain-exposed healthy workers (Figure 2). The upper 95% confidence limit of rest–work differences in mean PEF was 16 l/min or up to 3.3% of predicted PEF in non-occupational asthmatics or healthy grain-exposed workers.

## Discussion

Our study found that rest–work differences in mean PEF was the best statistical index differentiating between workers with OA and non-occupational asthmatic subjects or irritant-exposed healthy workers and approached the Oasys-2 score derived from a previously validated discriminant analysis [10]. A fall in mean PEF of >3–4% of the predicted value, or 16 l/min, is unlikely to occur by chance in

a non-occupational asthmatic or as a result of significant irritant exposure in an otherwise healthy individual, provided PEF records satisfy minimum data quantity criteria. The area between curve (ABC) score has been developed in a separate group of workers and also found that a similar value of 15 l/min/h differentiated between occupational and non-occupational asthmatics [14]; however, there were no healthy workers with irritant exposures to control for the effects of irritant exposure in that study. The ABC score is valid for short records (8 work and 3 rest days) provided that two hourly readings are available. The minimum data frequency and duration for optimal sensitivity and specificity of the mean rest–work PEF score have never been investigated. A large proportion of workers with OA had a PEF diurnal variation within normal limits



**Figure 2.** Distribution of mean PEF difference between rest and work periods (expressed as per cent predicted PEF) for healthy grain workers and workers with OA. This was the best index at separating workers with OA from non-occupational asthmatics and grain-exposed healthy individuals.

similar to findings in community studies of non-OA [15]. Any negative effects of work exposure on PEF are superimposed on the normal circadian increase after waking sometimes resulting in reduced diurnal variation on workdays in occupational asthmatics. We did not find that assessment of changes in maximum rest day PEF compared to minimum workday PEF as suggested by Côté *et al.* [9] to be as useful. The good results from the Côté study were due to the selection of controls who were less asthmatic than those with OA. The selection of asthmatic controls in the present study has overcome this.

Grain dust is a recognized respiratory irritant and exposures in farm workers or dockyard workers can be considerable. All were exposed to measured values over the occupational exposure standard of  $10 \text{ mg/m}^3$ . Grain dust can also cause a number of clinical syndromes including asthma, asthma-like syndrome and chronic lung disease [16,17]. This is the first study, which has used such a group as a control for OA, providing robust data separating OA from asymptomatic irritant exposure. A  $>16 \text{ l/min}$  fall in mean PEF on workdays compared with days off work is unlikely to occur as a result of grain dust exposure in an otherwise healthy worker. We have not studied symptomatic grain workers who might have OA due to sensitization or work aggravated asthma where the grain dust is exacerbating pre-existing asthma. It is unlikely that a physiological method, such as serial PEF measurement, will be able to elucidate the mechanisms of airflow obstruction. Both irritant and allergic mechanisms can cause airflow obstruction of similar degree, and both cause similar immediate reactions, although late asthmatic reactions are more common in allergic than irritant asthma. Grain exposure is but one of many respiratory irritants; it is more likely that the level of exposure has a greater influence on the asthmatic response than the type of irritant, but data clarifying this are missing.

Several challenge-room studies of irritant agent exposure have reported absence of significant bronchoconstriction in healthy individuals. While some asthmatic subjects demonstrate significant physiological responses to sulphur dioxide concentrations as low as 200 ppb when exercising (ambient concentrations in UK usually  $<120 \text{ ppb}$ ), concentrations  $<1000 \text{ ppb}$  have not been reported to cause bronchoconstriction in healthy individuals [18]. Avol *et al.* [19] studied the effect of exposure to sulphuric acid aerosols (concentrations up to  $1520 \text{ mcg/m}^3$  for 1 h) in 21 asthmatic and 21 healthy individuals. Although a significant decrease in lung function was noted in asthmatics when exposed to higher concentrations of sulphuric acid, a significant decrease did not occur in healthy individuals, though there was an increase in cough. Neither group showed an increase in methacholine reactivity. However, reactions to ozone can occur in healthy individuals, associated with a neutrophilic airway inflammatory response [20].

We would suggest that a small but consistent deterioration in PEF during work periods in an otherwise healthy but currently symptomatic worker should not be dismissed as due to irritant exposures, if the fall in mean PEF is greater than  $\sim 16 \text{ l/min}$  or if the record has an Oasys-2 score  $>2.5$ . These workers should be investigated further. We have previously shown that the presence of increased numbers of eosinophils or neutrophils in induced sputum in workers with OA and a positive Oasys-2 score cannot be predicted from the magnitude of the mean rest-work PEF difference [21].

In conclusion, we have found that differences in mean PEF between rest and work periods is the best simple index for separating workers with OA from those without OA, even when within-day or within-record PEF variability is relatively small. Mean rest-work differences in PEF of  $>16 \text{ l/min}$  or 3–4% of predicted PEF are unlikely to occur in non-occupational asthmatics or irritant-exposed healthy workers.

### Key points

- The difference between peak expiratory flow on work and rest days may be small in workers with confirmed occupational asthma.
- A  $16 \text{ l/min}$  difference in peak expiratory flow between days away and at work separates occupational asthmatics from non-occupational asthmatics and irritant-exposed healthy subjects with good sensitivity.
- Changes in diurnal variation in peak expiratory flow between work and rest days are generally unhelpful. An increase in peak expiratory flow on workdays  $>7\%$  (the upper 95% confidence limit for non-occupational asthmatics) has a poor sensitivity for the diagnosis of occupational asthma.

## Funding

Cefic Long-Range Research Initiative (LRI) grant - the European Chemical Industry Council; Health and Safety Executive, UK; Colt Foundation PhD Fellowship to W.A.

## Acknowledgements

Our thanks to J. Swan and B. Crook from the Health and Safety Executive for providing data on grain-level measurements.

## Conflicts of interest

P.S.B. freely distributes the Oasys program through his website ([www.occupationalasthma.com](http://www.occupationalasthma.com)) and does not receive any income from this.

## References

1. Moscata G, Godnic-Cvar J, Maestrelli P, Malo JL, Sherwood Burge P, Coifman R. Statement on self-monitoring of peak expiratory flows in the investigation of occupational asthma. *Eur Respir J* 1995;**8**:1605–1610.
2. Burge PS, O'Brien I, Harries M. Peak flow rate records in the diagnosis of occupational asthma due to isocyanates. *Thorax* 1979;**34**:317–323.
3. Burge PS, O'Brien I, Harries M. Peak flow rate records in the diagnosis of occupational asthma due to colophony. *Thorax* 1979;**34**:308–316.
4. Leroyer C, Perfetti L, Trudeau C, L'Archeveque J, Chan Yeung M, Malo J. Comparison of serial monitoring of peak expiratory flow and FEV1 in the diagnosis of occupational asthma. *Am J Respir Crit Care Med* 1998;**158**:827–832.
5. Perrin B, Lagier F, L'Archeveque 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**:40–48.
6. Liss GM, Tarlo SM. Peak expiratory flow rates in possible occupational asthma. *Chest* 1991;**100**:63–69.
7. Zock JP, Brederode D, Heederik D. Between- and within-observer agreement for expert judgement of peak flow from graphs from a working population. *Occup Environ Med* 1998;**40**:969–972.
8. Malo JL, Cote J, Cartier A, Boulet L, L'Archeveque J, Chan Yeung M. How many times per day should peak expiratory flow rates be assessed when investigating occupational asthma. *Thorax* 1993;**48**:1211–1217.
9. Côté J, Kennedy S, Chan Y. Quantitative versus qualitative analysis of peak expiratory flow in occupational asthma. *Thorax* 1993;**48**:48–51.
10. Gannon PFG, Newton DT, Belcher J, Pantin CF, 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**:484–489.
11. Anees W, Gannon PF, Huggins V, Pantin CFA, Burge PS. Effect of peak expiratory flow data quantity on diagnostic sensitivity and specificity in occupational asthma. *Eur Respir J* 2004;**23**:730–734.
12. Venables KM, Farrer N, Sharp L, Graneek BJ, Newman Taylor AJ. Respiratory symptoms questionnaire for asthma epidemiology: validity and reproducibility. *Thorax* 1993;**48**:214–219.
13. Miller MR, Dickinson SA, Hitchings DJ. The accuracy of portable peak flow meters. *Thorax* 1992;**47**:904–909.
14. Moore VC, Jaakkola MS, Burge CBSG *et al.* A new diagnostic score for occupational asthma; the Area Between the Curves (ABC score) of PEF on days at and away from work. *Chest* 2009;**135**:307–314, doi:10.1378/chest.08-0778 (published online first: 23 September 2008).
15. Higgins BG, Britton JR, Chinn S *et al.* The distribution of peak expiratory flow variability in a population sample. *Am Rev Respir Dis* 1989;**140**:1368–1372.
16. Senthilselvan A, Pahwa P, Wang P, McDuffie HH, Dosman JA. Persistent wheeze in grain elevator workers should not be ignored. *Am J Respir Crit Care Med* 1996;**153**:701–705.
17. Post W, Heederik D, Houba R. Decline in lung function related to exposure and selection processes among workers in the grain processing and animal feed industry. *Occup Environ Med* 1998;**55**:349–355.
18. Stacy RW, Seal E, Jr, House DE, Green J, Roger LJ, Raggio L. A survey of effects of gaseous and aerosol pollutants on pulmonary function of normal males. *Arch Environ Health* 1983;**38**:104–115.
19. Avol EL, Linn WS, Whynot JD *et al.* Respiratory dose-response study of normal and asthmatic volunteers exposed to sulfuric acid aerosol in the sub-micrometer size range. *Toxicol Ind Health* 1988;**4**:173–184.
20. Nightingale JA, Rogers DF, Barnes PJ. Effect of inhaled ozone on exhaled nitric oxide, pulmonary function, and induced sputum in normal and asthmatic subjects. *Thorax* 1999;**54**:1061–1069.
21. Anees W, Huggins V, Pavord ID, Robertson AS, Burge PS. Occupational asthma due to low molecular weight agents: eosinophilic and non-eosinophilic variants. *Thorax* 2002;**57**:231–236.