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Evaluation of an expert system for the interpretation of serial peak expiratory flow measurements in the diagnosis of occupational asthma in a field trial

The grain dust study

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Oasys-2 is a computer based analytical tool for the evaluation of serial measurements of peak expiratory flow (PEF). This study aimed to evaluate Oasys-2 in an epidemiological setting.

The study reviewed extant PEF records from 104 grain workers, and prospectively studied 228 further workers. Prospective PEF records were kept by 61% of the study group; 88% of returns from both parts contained $\geq$ 4 readings/day. As the two independent experts lacked agreement on the minimal data quantity required to diagnose occupational asthma, a data reduction exercise was completed in non-grain workers with independently validated diagnoses to establish the relationship between data quantity and diagnostic sensitivity and specificity. Specificity > 87% and sensitivity > 70% was achieved with $\geq$ 3 complexes, $\geq$ 4 readings per day and $\geq$ 3 consecutive days at work. Sixty seven per cent of PEFs met these criteria, many failures lacked 3 consecutive grain exposed days.

There was a poor correlation between PEF records, RASTs and questionnaire responses. Thirty-three PEF records showed a work related effect, 39 had questionnaire responses suggesting occupational asthma, but only 7 were common to both groups. The PEF records identified a different group of affected workers from questionnaires and RASTs, and the group with work-related PEF measurements showed more obstructive spirometry than those identified by the other methods.

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CONTENTS

INTRODUCTION

Oasys-2 is a computer based analytical tool for the evaluation of serial measurements of peak expiratory flow (PEF). It has been evaluated in clinic populations and has been found to have a sensitivity of 75% for the diagnosis of occupational asthma when evaluated against gold standard diagnostic methods independent of PEF measurement {1}. Its specificity is 94%. In the clinic situation around 50% of attendees provide an adequate record for diagnosis after postal instruction, rising to 85% after personal instruction and encouragement {2}. Oasys-2 has not been evaluated adequately in an epidemiological setting.

Workers exposed to grain have a variety of occupational respiratory diseases, including allergic and irritant asthma, grain fever, alveolitis and occupational COPD. The HSE has an ongoing study of farmers and dockers, including questionnaires, specific IgE measurements and lung function measurements. The existing populations in these studies were used to evaluate Oasys-2 in the field situation.

Grain-1 was a cross-sectional study whose participants had already kept serial PEF measurements before the current study began. We evaluated these for quality and made recommendations to improve quality for the prospective collection of serial PEF measurements in a second cohort (Grain-2).

AIMS

- The evaluation of the Oasys-2 software program using data from phase 1 of the HSE grain dust study
- The evaluation of the Oasys-2 software program using data from phase 2 of the HSE grain dust study
- Comparison of Oasys-2 reports against questionnaire and clinical data from the HSE grain dust study

GRAIN 1

METHODS

The study included the collection of peak flow records occurring before the current grant. One hundred and fifty composite peak flow records were received from 104 participants in the Grain 1 study who had been asked to make recordings every 2 hours from waking to sleeping for 2 weeks. Each peak flow series was plotted on Oasys-2, a computer program that plots and analyses serial measurements of peak expiratory flow for occupational effect, and evaluated using expert opinion as to data quality and the likelihood of occupational effect. Records were scored on Oasys-2, where a score of > 2.5 (out of a maximum of 4) was classified as definite occupational effect. The criteria used for adequacy were the subjective impressions of two experts.

Each worker completed the grain questionnaire using the Venables criteria {3} for the diagnosis of asthma. When 2 or more of the bronchial hyper-reactivity questions were answered positively, and the symptoms were better on rest days, occupational asthma was diagnosed. Those with positive and negative questionnaires were compared with peak flow records showing an occupational effect (Oasys-2 score >2.5).

The plotted records were assessed by two in dependent experts for adequacy for making an assessment for the presence or absence of asthma and separately for the presence or absence of occupational asthma.

RESULTS

Record Quality

The mean number of recorded readings per day is shown in table 1a. Record duration and number of peak flow records with no work or rest days are shown in table 1b. Seventy nine percent of those who kept records were able to keep at least 4 readings/day, and 93% kept records for at least 10 of the 14 days requested. A small number of records contained no days at or off work, but very few records had more than one complex (a period at work, followed by a period off work, followed by a period at work).

Table 1a
Quantity of peak flow data recorded: readings per day

Mean readings/day	No. of PEFs
>=8	63
4-<8	70
<4	17

Table 1b
Quantity of peak flow data recorded: record duration

Record duration	No of PEFs	No rest days	No work days
14	80	3	1
10-13	59	1	1
<10	11	1	0

There was good agreement between the observers as to whether records were of adequate quantity to make a diagnosis of asthma. However there was significant disagreement on whether records actually showed asthma or not, with disagreement tending to be systematic. The situation was the opposite for occupational effect. There was major disagreement on whether records were of adequate quantity to diagnose occupational effect. However, where there was agreement on adequacy, there was generally good agreement as to whether the record showed occupational effect or not, both between observers and Oasys-2.

Only 17 records were thought subjectively to have adequate quantity for the diagnosis of occupational effect. Records with at least one complex were scored by Oasys-2, 23 had a score >2.5.

Questionnaire and Peak Flow Diagnosis

Thirty-one questionnaires fulfilled the Venables criteria for work-related bronchial reactivity. The relationship between questionnaire and peak flow diagnoses is shown in table 2.

There were 6 workers with questionnaire diagnoses of work-related bronchial reactivity with peak flow confirmation, however there was a much larger number (17) whose Oasys-2 scores were positive but questionnaires negative, raising the possibility of false positive Oasys-2 scores. As few records were subjectively assessed as of adequate data quantity (mostly due to the small number of complexes), a further study was undertaken to assess objectively the minimum data quantity required for optimal sensitivity and specificity of Oasys-2.

Table 2
Relationship between questionnaire and peak flow diagnosis of occupational effect

Peak flow diagnosis of occupational effect	Questionnaire diagnosis of occupational asthma	
	No	Yes
No	102	25
Yes	17	6

FURTHER STUDY: ASSESSMENT OF DATA QUANTITY REQUIRED FOR OASYS-2

INTRODUCTION

A separate study was undertaken to define minimum data quantity for assessing occupational effect using Oasys-2. This study was performed using data obtained from 97 workers with occupational asthma whose diagnosis had been confirmed independently of peak flow measurements. They were seen at the Birmingham Chest Clinic, but were not exposed to grain and were nothing to do with the grain study. These records were labelled as "Gold Standard Positive" records. Data was systematically removed from these records to assess the effect of record duration, number of daily readings, and number of consecutive workdays in each work period, on sensitivity for diagnosing occupational effect from a PEF record. This process was also undertaken on 60 non-occupational asthmatic subjects to assess the effect of data quantity on specificity for diagnosing occupational effect from a PEF record. Recommendations for minimum PEF data quantity criteria were obtained from this study that maximised sensitivity and specificity for diagnosing occupational effect from PEF records.

RESULTS

The effects of data reductions are shown in tables 3-5. Table 3 shows the effects of reducing the duration of the record, using the number of complexes (periods at work separated by a period off work, a work-rest-work complex, or its counterpart a rest-work-rest complex). The specificity for records with only one complex was poor at 65%, often related to a learning effect at the start of a record, which was generally a work period. Specificity continued to improve for records of up to 4 complexes in duration.

Table 3
Sensitivity and specificity of oasys-2 when the record duration was sequentially reduced

Number of Complexes	1	2 ≈2 weeks	3	4 ≈3 weeks	5	6 ≈4 weeks
Sensitivity	73.3	70	83.3	76.7	80	81.8
Specificity	64.7	82.4	88.2	94.1	91.2	93.8

Table 4 shows the effect of work periods with less than 5 consecutive days, and rest periods of 1 and 2 days. The sensitivity declined particularly for work periods of less than 3 days. Rest periods of 1 day appeared adequate. However the reduction process for 1 day rest periods was from records originally with 2-3 rest days allowing recovery before the next workday, a situation that might not mimic real life 1 day rest periods.

Table 4
Sensitivity and specificity of Oasys-2 when the consecutive workday and rest day duration was sequentially reduced

Number of work-rest-work days	5-2-5	4-2-4	3-2-3	2-2-2	1-2-1	5-1-5
Sensitivity	76.7	76.7	70	56.7	46.7	73.3
Specificity	90	90	90	100	90	90

Table 5 shows the effects of reducing the numbers of readings per day. Although sensitivity was reduced for days with less than 8 readings, the effect was not marked. Diurnal variation is however closely related to the number of readings per day, being significantly underestimated for records with less than 4 evenly spread readings per day {4}.

Table 5
Sensitivity and specificity of oasys-2 when the numbers of readings per day were sequentially reduced

Number of readings per day	8	4	3	2	1 (5 pm)	1 (6 am)
Sensitivity	85.3	82.4	76.5	82.4	79.4	55.9
Specificity	95.7	87	87	82.6	87	73.9

CONCLUSION

From this work we concluded that an adequate record for Oasys-2 analysis contains at least 3 complexes, at least 4 evenly spread readings/day, and at least 3 consecutive workdays in each work period. These criteria were applied to set 2 of the grain 2 study.

GRAIN-2

METHODS

Returned PEF records were divided into two sets (1 and 2). Set 1, consisting of 120 records was analysed independently by 2 observers on two separate occasions. 8 of these records were split to form two records due to part of the record being carried out in one year, then the second part after a year break. This was considered too long a break to be taken as one record, so the 120 records were became 128 records after splitting. On the first occasion the observers had knowledge of when the subject was at work but not specifically whether they were working with grain. On the second occasion further information on days with grain exposure was available. The experts first had to indicate whether they felt the records were of adequate quantity to make a judgement as to likelihood of asthma or occupational effect. They then indicated the probability of asthma or occupational effect. Records were also analysed by Oasys-2 and results for probability of occupational effect compared against the experts.

Using the minimum PEF data quantity criteria, the process of assessing adequacy of grain records and probability of asthma/occupational effect was repeated by the 2 observers on set 2 of grain 2. This set consisted of another 64 records not previously seen by the observers but in whom no specific-grain exposure days were available. The results of the observers' assessments of set 2 records were compared to results from set 1 to see whether the minimum PEF data quantity criteria improved agreement between experts.

The questionnaires were used to divide the PEF records into different groups:

- Non-asthmatic PEF records (two out of the 3 main asthma questions answered negatively n=109). They could have sensitisation (classed by having a positive RAST) to storage mite or grain antigens.
- Asthma using the Venables criteria; any two of the 3 main asthma questions without rest day improvement (n=12)
- Asthma using the Venables criteria and rest day improvement (n=8)

RESULTS

There is questionnaire data on 228 workers in total. 140 (61.4%) of these kept 192 PEF records, of which 129 were of adequate data quantity.

Adequacy of Peak Flow Records From Grain Workers

98/140 (70%) workers provided 129 PEF records that were of adequate quantity. 63 records (32.8% of all records from 54 workers) were inadequate. Reasons for inadequacy are shown in figure 1.

128 records were provided with the grain days marked; only 13 of these were of good enough quantity to assess the effects of grain exposure on PEF. The reason for this in the majority of cases was that there were not enough consecutive days with grain exposure.

The two experts agreed on the presence or absence of asthma in 82% of records and on the presence or absence of occupational effect in 93% of records assessed as adequate.

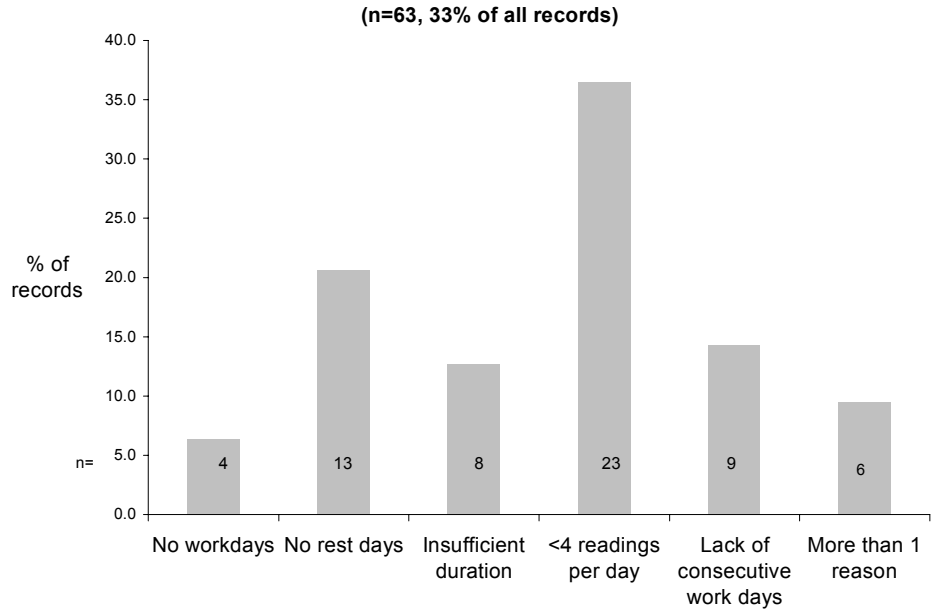

Figure 1
Reasons that records were assessed as inadequate for Oasys-2 analysis

Comparison of a History of Occupational Asthma According to the Venables Criteria and PEF Record Interpretation

8 subjects who had kept adequate PEF records reported symptoms suggestive of occupational asthma. Only 1 of these workers had an Oasys-2 score >2.5. The 2 expert observers independently completely agreed with Oasys-2 in all these cases. Specific RAST's to grain and storage mite were measured in 6 of these workers, all were negative, including the worker with a positive peak flow record.

The relationship between work-related asthmatic symptoms and Oasys-2 scores is shown in table 6. There were less work-related symptoms and positive peak flow records than in the first grain study, but again no relationship between positive questionnaires and positive peak flow records.

Table 6
The relationship between work-related asthmatic symptoms and Oasys-2 scores in those who kept adequate peak flow records

Peak flow diagnosis of occupational effect	Questionnaire diagnosis of occupational asthma	
	No	Yes
No	112	7
Yes	9	1

Interpretation of PEF Records with Oasys-2 Score >2.5 in Workers Without Occupational Asthma According to the Venables Criteria

Excluding the above worker, 15/191 records had Oasys-2 scores >2.5, however only 10 of these records from 9 workers were of good enough quantity to be interpreted. One or both of the experts agreed with the positive interpretation in 9/10. None of the 9 workers were asthmatic according to the Venables criteria, though the experts felt that 7/10 records showed increased PEF variability suggestive of asthma. An example is shown in figure 2.

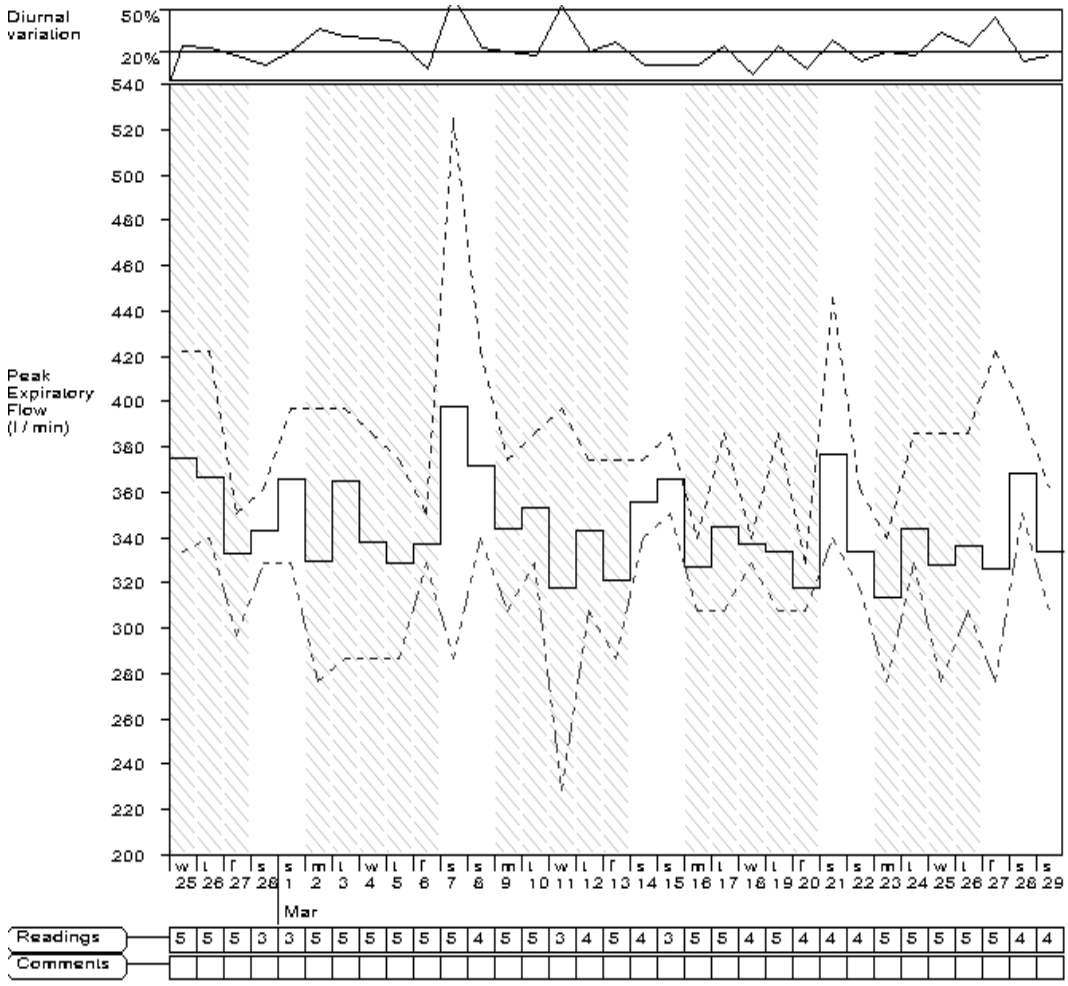

Figure 2
Oasys-2 plot of a grain worker with negative RAST's to grain and storage mites, and no respiratory symptoms

The patient's FEV1/FVC was 71%. The plot shows; top panel, diurnal variation in peak flow, often over 20%, within the asthmatic range. Middle panel, daily maximum (top line), mean (middle bar) and minimum (lower line) peak expiratory flow. Days at work have a shaded background, days away from work a clear background. Visual inspection shows deterioration in 3 out of 5 work periods and improvement in 4/5 rest periods. Oasys-2 scores it as 3.4, within the definite occupational effect range. The bottom panel shows the numbers of readings per day.

Spirometric data was available in 7 of the 9 subjects who had positive Oasys-2 scores and who were non-asthmatic (with no work-related symptoms) according to Venables criteria. The FEV1/FVC ratio was lower in subjects with Oasys scores >2.5 compared to non-asthmatics with Oasys scores <2.5 (Mann-Whitney U test, 2-tailed p=0.051) (table 7).

A similar analysis of those workers with positive and negative RAST's to grain and or storage mites is shown in table 8. Those with positive antibodies had better spirometry than those with negative results, the differences were not statistically significant.

Table 7
Comparison of spirometric data in subjects without asthma according to Venables questionnaire responses, separated into those with and without positive Oasys-2 scores (adequate records only)

	Oasys-2 > 2.5, n=7	Oasys-2 ≤ 2.5, n=93	P value
FEV1 % predicted, median Inter quartile range	100.8 99.1 to 109.5	102.9 92.8 to 113.4	0.82
FEV1/FVC median, inter quartile range	71.1 67.6 to 76.0	78 73.5 to 81.4	0.051

Table 8
Comparison between workers with IgE antibodies, work related asthmatic symptoms from the Venables questionnaire, and spirometry

	RAST positive (n=29)	RAST negative (n=122)	p value
work-related asthmatic symptoms	5 (17%)	15 (12%)	p=0.54
FEV1 % predicted (median) Inter quartile range	108.7 96.2 to 114.1	100.3 92.3 to 112.7	p=0.12
FEV1/FVC (median) Inter quartile range	77.8 74.6 to 80.6	76.9 72.2 to 81.2	p=0.57

There was a very poor relationship between sensitisation to storage mites and grain and work-related asthmatic symptoms. Of 29 PEF records (27 workers) with sensitisation, 4 (14%) had asthmatic symptoms with rest day improvement. Of 122 without sensitisation, work-related asthmatic symptoms were found in 15 (12%).

Of the 13 records (from 13 workers) with grain days marked that were of adequate quantity, 3 had Oasys-2 scores >2.5. According to questionnaire responses, one worker was asthmatic, one had chronic bronchitis, neither indicated that symptoms were better on days away from work. The third was asymptomatic. The expert observers independently felt that these PEF records were diagnostic of occupational asthma when exposed to grain. However, spirometry was normal and none had positive RAST's to grain or storage mites. A similar analysis was made relating those with and without work-related asthmatic symptoms from the Venables questionnaire (table 9). There was no difference in spirometry between those without any asthmatic symptoms and those with non work-related asthmatic symptoms. The group with work-related asthmatic symptoms had a non-significant reduction in FEV1, but no difference in airflow obstruction, as measured by the FEV1/FVC. The only group with a median reduction in FEV1/FVC were those with PEF records showing an occupational effect.

Table 9
Comparison of spirometry and Oasys-2 scores between those with and without work-related asthma symptoms from the Venables questionnaire

	Work-related asthma (n=8) (a)	Asthma, not work-related (n=12) (b)	No asthmatic symptoms (n=109) (c)	p value (Kruskal-Wallace)
FEV1 % predicted (median) Inter quartile range	91.3 89.0 to 94.0	102.1 95.8 to 109.2	102.9 92.9 to 113.2	p=0.068 (a vs. b, p=0.14) (a vs. c, p=0.02)
FEV1/FVC (median) Inter quartile range	79.5 66.9 to 80.0	77.9 71.4 to 80.2	77.4 72.5 to 81.3	p=0.86 (a vs. b, p=0.73) (a vs. c, p=0.57)

DISCUSSION

The first grain study showed that most workers who returned a record were able to keep at least 4 readings a day for the majority of the 2-week period requested. There was however a very poor relationship between work-related asthmatic symptoms as shown by the Venables questionnaire {3} and work-related peak flow plots, with 17 (11%) asymptomatic workers having positive peak flow plots. This raises the possibility of poor specificity of Oasys-2; a situation not seen in previous evaluations {5}. In the second study an attempt was made to obtain records of at least 3 weeks with at least 4 readings per day. We were however unable to control the periods at work with grain exposure. Seventy percent of the workers surveyed returned at least one peak flow record, which is similar to returns from other occupational surveys {6,7,8,9}. Records suitable for Oasys-2 scoring were obtained from 67% of the workers returning records. Many of the inadequate records had factors out of the control of the worker, mainly related to lack of consecutive days with grain exposure, which is unfortunately a limitation of PEF records in general. Eight percent of records were of inadequate duration and 23% records had less than 4 readings/day, a situation where Oasys-2 performs relatively well {10}.

The analysis of the first grain study highlighted disagreements between experts in the diagnosis of asthma from PEF variability. There was disagreement on the required frequency and extent of increased diurnal variation required. This has also been demonstrated in previous studies {11}. A further study of different peak flow records has been carried out with experts in many countries. The weighted kappa value for a diagnosis of asthma was 0.29, the agreement for occupational effect was 0.71, showing better agreement for a diagnosis of occupational effect than for asthma {12}. It was easier to diagnose or exclude occupational asthma from PEF records as this differentiation was based on work-rest differences, rather than PEF variability. There were differences between experts, however, on what criteria constituted adequacy of a PEF record for diagnosing occupational asthma. An extra study was therefore undertaken to define minimal data quantity, using workers whose diagnosis had been confirmed objectively by methods other than peak flow measurements, and who were outside the grain handling and farming industries. The minimum criteria for optimal sensitivity and specificity were periods of at least three days of consecutive work exposure in each work period, with at least 4 evenly spaced PEF readings per day, with a record duration of about 3 weeks (3 complexes). Following the data quantity study, agreement between experts improved substantially.

Once these criteria were established the whole exercise was repeated with the second prospective grain study, carried out during harvesting or grain handling, 61% of workers returned PEF records, of which 70% fulfilled the adequacy criteria. This time there was good agreement between observers as to whether records were of adequate quantity or not and as before, good agreement as to whether they showed occupational asthma. In this study there were 9 (8%) asymptomatic workers fulfilling the adequacy criteria who had work-related deterioration in PEF. This could represent false positive PEF analysis by Oasys-2. However the experts blindly agreed with the interpretation in 8/9 records. Spirometric measurements (carried out before the peak flow measurements) were available for 7 of these; they had more airflow obstruction than workers with Oasys-2 scores of ≤ 2.5 suggesting that the PEF plots were detecting a real effect. Only one worker had both symptoms suggestive of occupational asthma using the Venables criteria and a work-related PEF analysis. An additional 7 (6%) had work-related asthma symptoms and a negative peak flow assessment. Oasys-2 has reduced sensitivity (about 69%), implying that at least some of these could have physiologically demonstrable occupational asthma using challenge tests. However the experts agreed with the negative interpretations in 7/7 of those with adequate PEF records. Sensitisation to grain and storage mite antigens was used to try and define whether the questionnaires or PEF plots were more likely to

be detecting true occupational asthma. There was no relationship between positive immunology and either the questionnaire or PEF plots. Each appeared to identify a separate group of workers. Workers with positive immunology had similar proportions with work-related asthmatic symptoms (17% vs. 12%), and had similar spirometry, not distinguishable from those with negative immunology. Similarly those with work-related asthmatic symptoms from the Venables questionnaire had similar assessments of airflow obstruction those with no asthmatic symptoms. This data supports Malo's and Vandenplas' findings that an improvement in asthmatic symptoms away from work is not a reliable (specific) indicator of occupational asthma and that objective confirmatory measures should be sought {13,14}.

In conclusion, peak flow measurements to adequate quantity for analysis using Oasys-2 were possible in an epidemiological setting. The group studied were not ideal for Oasys-2 to diagnose occupational asthma, due to the irregular exposures and different non-asthmatic pathologies likely to be present. The plots of PEF as analysed by Oasys-2 identified a group with airflow obstruction, not identified by Specific IgE measurements to grain or storage mites, nor by the questionnaire used. Validation of these findings should be made by observing the rate of FEV1 decline during subsequent grain surveys in these workers.

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