

Occupational asthma in apprentice adolescent car painters

Eifan AO, Derman O, Kanbur N, Sekerel BE, Kutluk T. Occupational asthma in apprentice adolescent car painters.

Pediatr Allergy Immunol 2005; 16: 662–668. © 2005 Blackwell Munksgaard

Occupational asthma (OA) is one of the leading causes of pulmonary diseases and has been extensively studied in adults. Childhood employment, a significant problem in many developing countries, should be studied to determine and evaluate its effects on psychosocial and lung health. In order to investigate the presence of work-related asthma-like symptoms and OA in apprentice adolescent car painters, 72 adolescents between the ages of 15–20 yr studying in Vocational Training Centres of Ankara were investigated using questionnaire, pulmonary function test (PFT), serial peak expiratory flow (PEF) measurements and methacholine inhalation tests. As a control group, 72 adolescents studying in Industrial and Commercial Training Centres located in the same environment were investigated with questionnaire and PFT. Almost 50% of the study group had work-related asthma-like symptoms for which occupational dermatitis history was predictive [odds ratio: 2.9 (1.026–8.13) (95% confidence interval)]. Seventeen of 22 with serial PEF measurements showed a variability of $\geq 20\%$ and three (4.2%) of 12 tested with methacholine inhalation test had a $PC_{20} \leq 8$ mg/ml, which led to the diagnosis of OA. There was no statistically significant difference between study and control groups in terms of PFT. In conclusion, the high prevalence of work-related asthma-like symptoms among adolescent car painters clearly indicates the need for routine follow-up of adolescent workers for lung health.

**Aarif Omar Eifan, Orhan Derman,
Nuray Kanbur, Bulent Enis Sekerel
and Tezer Kutluk**

Department of Pediatrics, Hacettepe University
Faculty of Medicine, Ankara, Turkey

Key words: childhood employment; isocyanate;
methacholine; questionnaire

Tezer Kutluk, MD, Professor in Pediatrics, Unit of
Adolescent Medicine, Department of Pediatrics,
Hacettepe University Faculty of Medicine, 06100
Ankara, Turkey
Tel.: +90 312 3051142
Fax: +90 312 3243284
E-mail: tkutluk@tr.net, tkutluk@hacettepe.edu.tr

Accepted 16 August 2005

Occupational asthma (OA) is a major cause of pulmonary disease and the most common cause of non-acute lung disease in the industrialized world (1). The incidence of OA has been on the increase in developed countries, while in developing and underdeveloped countries the incidence is still unknown.

Occupational asthma is defined as asthma caused or made substantially worse by agents inhaled in the occupational environment (2). Isocyanates are among the most frequent agents responsible for OA in most industrialized countries, and painters are the most common risk group (3).

Childhood employment is a problem mostly seen in developing countries. Large numbers of working children aged 15–18 years are engaged

in occupations like agriculture and in the automotive industries. As for legal safeguards, the law requires medical examination of children up to 18 years of age, and that only for industrial employment (4). But no standards have been set down for medical fitness.

Work duration, i.e. duration of exposure, is a well-known risk factor for the development of OA and it thus follows that adolescent workers are less likely to have OA compared with adults because of the shorter duration of their exposure. However, given the occurrence during the adolescent period of the growth spurt and proportionally the growth in lung volume and development of the respiratory system, it becomes necessary to evaluate health hazards in this group of workers. The aim of this study was

to investigate the presence of work-related asthma-like symptoms and OA in adolescent car painters, and to document their predictors.

Materials and methods

Study design

Apprentice car painters (study group) and the control group were investigated with questionnaire and pulmonary function tests (PFT). Those in the study group with work-related asthma-like symptoms were further surveyed with peak expiratory flow rate (PEFR) monitoring followed by methacholine inhalation test if a PEF variability of $\geq 20\%$ was present.

Study population

The study group consisted of apprentice adolescent car painters. There were 85 apprentice adolescent car painters registered for car-painting courses during the 2002–2003 academic year at the only three Vocational Training Centres (Ozkan, Ostim and Ahi Erdek) located in Ankara, Turkey. Only 72 of them who actively attended the course once a week from 08:00–17:00 hours and who were employed at different car painting shops in the city of Ankara accepted to participate and were included in the study. As the control group, 72 students studying in Industrial and Commercial Vocational Training Centres located in the same environment and who had no history of car paint exposure were also included. Eighteen students in the control group were working as computer parts assemblers. All study subjects provided written informed consent to participate in the trial, which was approved by Hacettepe University's Ethics Committee.

Questionnaire

We used a modified questionnaire containing questions required for establishment of OA, which was recommended by the American Thoracic Society (ATS) (5) and has been previously validated and applied (6). It was composed of 22 questions and was completed by the participants during their class hours. Work-related symptoms (cough, shortness of breath, wheezing, chest tightness), occupational history, smoking habits and personal/family history of respiratory and allergy diseases were noted and reviewed with the participants before the data was collected. We collected the following information: Did these symptoms

begin and exist within the overall period working as a car painter? Were the symptoms related to work? Did the symptoms improve when the person was away from work? Participants were also questioned regarding specific symptoms for conjunctivitis, dermatitis, and rhinitis.

Pulmonary function tests

As a second stage, Purritan Bennet System Spirometer (Purritan Bennet System Vitalograph Ltd, Buckingham, UK), conforming to the ATS specification, was used to evaluate the pulmonary functions of the participants. Subjects were allowed several practice attempts. The best forced expiratory volume (FEV_1) and the best forced vital capacity (FVC) were taken from three technically satisfactory forced expiratory manoeuvres whereby the best two readings were within 5% of each other.

Peak expiratory flow rate monitoring

Serial PEFR records were made with the 'Asma-PLAN Peak Flow'. Subjects were trained in the use of the peak flowmeter and asked to record the measurements (taken four times daily over a 3-week period) on a diary card. The sum of the weekend records, at least 5–7 days, was accepted as away from work, with the remaining PEFR records reflecting work days. On each occasion participants were asked to blow three times and record all readings. Only the best of the three attempts was kept for analysis. Records were plotted in graphic form incorporating work days and holidays. Graphs identified as indicating OA required complete agreement among the two observers as to whether they showed a real pattern of deterioration during days of work with recovery during holidays and/or examination of daily and weekly PEFR variability using the formula $[(PEFR_{\max} - PEFR_{\min}) / (PEFR_{\max} + PEFR_{\min}) / 2] \times 100\%$. When the PEFR graph showed a work-related change in 2 of the 3 week and the daily/weekly PEFR variability was $\geq 20\%$, it was considered to be suggestive for OA.

Non-specific bronchial provocation test with methacholine

Methacholine challenge test was performed using a modified protocol of Cockcroft et al. (7), which has been previously used and standardized (8). Briefly, in each test an aerosol of saline was inhaled first, followed by 5-min intervals of methacholine inhalation in twofold increasing concentrations, from 0.03 to 8 mg/ml.

Definitions

In accordance with the American College of Chest Physicians consensus statement (9), we diagnosed OA and likely OA as follows: (A) Diagnosis of asthma and (B) onset of asthma after entering the workplace; (C) association between symptoms of asthma and work; and (D) one or more of the following criteria: (1) workplace exposure to an agent known to give rise to OA; (2) work-related changes in FEV₁ or PEFR; (3) work-related changes in bronchial responsiveness; (4) positive response to specific inhalation challenge tests; or (5) onset of asthma in association with symptomatic exposure to an agent in the workplace.

Occupational asthma: meets A + B + C + D2 or D3 or D4 or D5 of the surveillance case definition.

Likely OA: meets A + B + C + only D1 of the surveillance case definition.

Statistical analysis

For comparisons between the two groups, statistical analysis was performed with Student's *t*-test for normally distributed data and the Mann-Whitney *U*-test for skewed data. Chi-square was used to compare the percentage of the groups. A two-sided $p \leq 0.05$ was accepted as statistically significant. Logistic regression analyses were performed to investigate the independent effects of different variables. Univariate regression models included age of patient, family atopy, work duration, smoking, and presence of occupational rhinitis and dermatitis, and only those with a $p \leq 0.25$ were included for the logistic regression model. Statistical analyses were performed using the Statistical Package for the Social Sciences, SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

Results

The study profile is shown in Fig. 1. A total of 144 students (72 study subjects and 72 in control group) were included in the study. Characteristics of the participants are summarized in Table 1. The mean working duration of the study group was 3.12 ± 0.21 years (range: 0.6–8 years) with a mean of 62.62 ± 1.34 h/week (range: 18–90 h). Painters were using compressor-driven spray guns with bottom-loaded depots filled with paints. Although most of the shops rest the spray-booth (a closed system circuit with respirator) for painting, it is only used to paint expensive cars and generally used by the main workers.

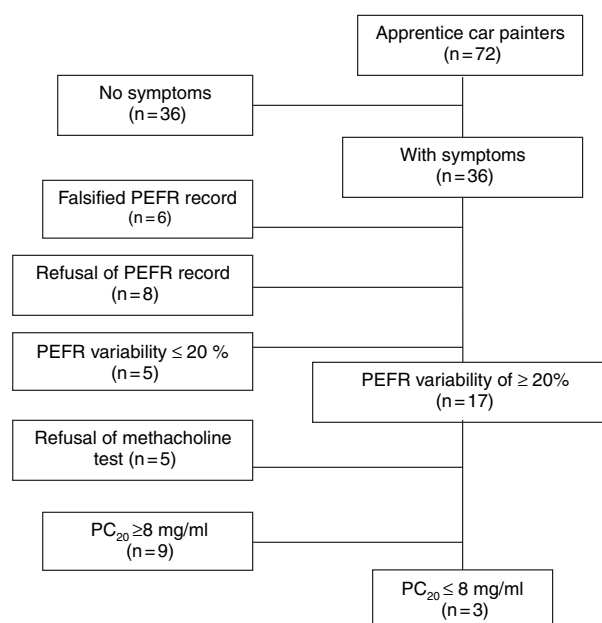


Fig. 1. Trial profile.

Table 1. Characteristics of study and control groups

	Car painters (n = 72)	Control group (n = 72)	P-value
Age (years)	17.47 ± 0.14	17.24 ± 0.13	0.169
Sex (male) (%)	100	100	1.000
Height (cm)	170.05 ± 0.86	172.41 ± 0.70	0.053
Working duration (years)	3.12 ± 0.21	1.52 ± 0.28*	<0.001
Working duration (h/week)	62.62 ± 1.34	25.52 ± 4.44	<0.001
Smokers [n (%)]	30 (41.6)	18 (25)	0.034
Smoking duration (years)	1.91 ± 0.31	0.83 ± 0.21	0.011
Number of cigarettes/day	5.45 ± 0.98	2.46 ± 0.64	0.019
Parental smoking [n (%)]	52 (72)	47 (65)	0.369

Values are given as mean ± SEM unless otherwise stated

*Eighteen students from control group were working after-class hours.

There were no significant differences between the two groups in terms of age and height. The study group had a longer working duration and were heavy smokers compared with the control group. The prevalence of respiratory symptoms in the study and control groups is shown in Table 2. The prevalence of current and ever wheezing were significantly higher in car painters than in the control group, with current nocturnal cough recorded as the most common complaint ($p = 0.015$). Fifty percent ($n = 36$) of the exposed group reported work-related complaints like breathlessness, wheezing, chest tightness, cough and sneezing after their exposure to car paints. Eleven of these 36 painters and one subject reported current and ever wheezing respectively.

Table 2. Prevalence of respiratory symptoms in car painters and control group

	Car painters (n = 72)		Control group (n = 72)		P-value
Ever wheezing	23	31.9	12	16.7	0.033
Wheezing in the last year	17	23.6	11	15.3	0.206
With breathlessness	16	22.2	3	4.2	0.002
Without upper resp. infect.	5	6.9	—	—	0.023
Nocturnal awakening in the last year					
Chest tightness	11	15.3	7	9.7	0.313
Breathlessness	11	15.3	6	8.3	0.197
Coughing attack	26	36.1	13	18.1	0.015
Physician diagnosis					
Asthma	1	1.4	—	—	0.316
Bronchial asthma	—	—			
Bronchitis	—	—	5	6.9	0.023
Allergic bronchitis	—	—	3	4.2	0.216
Family atopy	6	8.3	7	9.7	0.771
Work-related complaints	36	50	4/18*	22.2	0.026
Symptom regression on weekends	26	36.1	5/18	27.8	0.506
Symptom regression on long holiday	35	48.6	6/18	33.3	0.244
Occupational dermatitis	33	45.8	7/18	38.9	0.596
Occupational rhinitis	24	33.3	4/18	22.2	0.362
Wheezing before employment	3	4.3	3/18	17.6	0.086
Use of protective measures					
Mask	31	43.1	5/18	27.8	0.237
Gloves	27	37.5	7/18	38.8	0.913
Coat	39	54.2	14/18	77.8	0.069

*Eighteen students from control group were working after-class hours.

Table 3. Pulmonary function tests of apprentice car painters and control group

	Car painters (n = 62)	Control group (n = 60)	P-value
FCV (l)	4.77 ± 0.09	4.77 ± 0.09	0.99
FEV ₁ (l)	4.17 ± 0.08	4.24 ± 0.08	0.52
PEF (L/S)	9.71 ± 0.26	10.23 ± 0.24	0.14
FVC (%)	102.35 ± 2.17	101.09 ± 2.22	0.88
FEV ₁ (%)	101.98 ± 1.91	100.40 ± 1.75	0.54
PEF (%)	118.00 ± 2.76	122.58 ± 2.76	0.24
FEV ₁ /FVC (%)	87.24 ± 0.75	88.85 ± 0.68	0.21
FEF ₂₅₋₇₅ (%)	110.79 ± 3.77	113.43 ± 3.01	0.41
Obstructive*	7 (11.3%)	3 (5%)	0.32

Values are given as mean ± SEM.

LS, litre/second.

*FEV₁/FVC <80%.

A total of 86% of the apprentice car painters and 83% of the control group provided satisfactory PFTs. Ten subjects in the study group and 12 subjects in the control group did not provide satisfactory PFTs. PFTs of both groups were not statistically different (Table 3). Seven painters and three subjects from the control group had obstructive airflow limitation (FEV₁/FVC <80%). The comparison of painters with vs. without complaints at their workplace showed no statistical difference in terms of age, working duration, smoking habits, PFT and exposure symptoms (data not shown). Logistic regression

analysis showed that only occupational dermatitis was predictive for the presence of work-related asthma-like symptoms [Odds ratio: 2.9 (1.026–8.13) (95% confidence interval)].

A total of 36 car painters with complaints at their workplace were to be further evaluated using serial PEFr monitoring. Twenty-eight subjects agreed to participate. However, the compliance with the recording was not perfect; six readings were considered falsified because the readings were more than 200 l/min of each other. Of the 22 PEFr readings that were accepted as not falsified, 17 (24%) demonstrated a 3-week work-related pattern positive PEFr variability of ≥20%, and of these 17 patients, nine (12%) patients had current wheezing, which is compatible with the diagnosis of OA. The graph of a patient with typical positive patterns of changes in PEFr at work and away is shown in Fig. 2. In 22 subjects monitored for PEFr, nine had wheezing for the last 12 months and one subject had wheezing before employment.

Apprentice car painters who had typical history of occupational exposure with a PEFr variability ≥20% were invited for non-specific bronchial provocation test (NBPT). Twelve subjects successfully performed the test and three of them had a positive NBPT. Of these three patients, two had a PEFr variability ≥20% and one patient had a direct visual PEFr pattern suggestive of OA.

Discussion

There is no pathognomonic test for the diagnosis of bronchial asthma. The diagnosis depends primarily on history, clinical findings, PFTs and the response to therapy. This sometimes makes it difficult to diagnose asthma in clinics. However, the childhood epidemiological surveys carried out in Turkey revealed somewhat similar prevalence of asthma-like symptoms as observed in Europe and North America, but the physician-diagnosed asthma is rather low (10). As far as we know, there is no survey carried out for OA in working adolescents, but there are a number of studies performed among adults.

Fifty per cent of the apprentice car painters had work-related asthma-like symptom history triggered by occupational agents: 36% had cough, 24% wheezing, 15% dyspnoea and 15% chest tightness. To our knowledge, there is only one research performed in adults to survey the prevalence of OA among car painters in our country (6). In that study, Uçgun et al. found 97% of workers had wheezing symptoms, 63% cough, 47% dyspnea and 63% chest tightness.

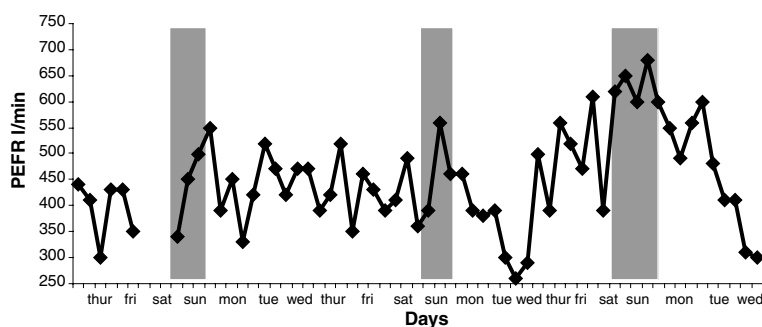


Fig. 2. Daily PEFR plot from a worker with a PEFR variability of $\geq 20\%$ and a positive NBPT ($PC_{20} = 0.5$ mg/dl). The shaded area represents rest days, unshaded areas are days at work.

But in researches carried out in other countries, workers exposed to isocyanate were reported as having respiratory symptoms due to OA at a prevalence of 5–25% (3, 11, 12). Malo et al. (13) found the positive predictive value of the questionnaire to be 63% and negative predictive value 83%, and stated that the questionnaire alone was inadequate for the diagnosis of OA. In Turkish, there is no appropriate literal translation for the word ‘wheezing’. Thus, instead of relying only on wheezing symptoms for the diagnosis of OA, we decided to include all painters (50%) with any respiratory symptoms on contact with the paint in order to increase the predictive value of the questionnaire. Comparing with researches carried out in European and North American countries, the high rate of respiratory symptoms found in our study might be the result of the higher prevalence of smoking (almost 40%).

Many researchers of OA found normal FEV_1 values taken before and after the working hours (14, 15). In patients with red cedar asthma, 80% had a normal FEV_1 and 39% had normal maximal mid-expiratory flow rates at the time of diagnosis (16). In our study, we took PFT in the mornings on the days painters attended the classes in their vocational centres. We considered visiting the workplace to take PFT of each apprentice painter before and after working hours but understood that it would reduce the number of participants in the study. So without considering the PFT results, all those who admitted to having respiratory symptoms in the workplace, 36 (50%), were monitored by PEFR.

In Turkey, the rate of unemployment is high, and workers may hide their problems in order not to be considered as malingerers. Although 36 apprentice painters had work-related symptoms and were suspected as having OA, only 28 participated in taking serial PEFRs. Furthermore, six of them falsified the serial PEFR records. This may have been due to fear of losing their job, not improbable given the adolescent’s psychological state. Our study was

comprised of subjects of middle and late adolescence age, during which period there is an establishment of a stable sense of identity, waning of peer group influence, introspection and realistic planning for economic independence (17). The desire to be seen as healthier in comparison with their peer groups might have led to their falsifying the records, or they may have feared that the records would show that they were unfit and they would lose their job. Burge et al. (18) were the first to state the reliability of PEFR in OA diagnosis. Numerous studies have found serial measurement of PEFR to be both sensitive and specific in the diagnosis of OA, with values ranging from 73% to 100% and 74–100% respectively (18–20). According to these studies, detection of PEFR variability favours the presence of asthma. Interestingly, of 17 patients who had a PEFR variability of $\geq 20\%$, nine of them had current wheezing. It is likely that due to the lack of a suitable word in Turkish for ‘wheezing’, the remaining eight of 17 workers perceived the symptom differently and did not report it in the questionnaire.

Many authorities have described bronchial responsiveness as the hallmark of asthma. The absence of bronchial hyper-responsiveness as assessed shortly (minutes, hours) after a work-shift in a worker who complains of symptoms virtually excludes OA. However, even in the presence of OA, bronchial responsiveness may be normal in a worker who has been away from work for several days (a weekend/weeks or a month) (7, 21). There are several possibilities to explain those who had positive PEFR variability but absence of bronchial hyper-responsiveness. Serial PEFR monitoring might not have been carried out as instructed. For this reason, the results should be acceptable only if a deliberate action was not conducted. That is why it was not hard for those who did not participate in taking serial PEFR while admitting to having work-related symptoms in the questionnaire. Bronchial hyper-responsiveness went undetected probably because of their not having been exposed within

a few days before the test was carried out. Small-scale car painting shops have a limited amount of work and most of these shops paint the cars in the open air to avoid the expense of renting respirators; thus, the exposure concentrations of isocyanate might have been too low to produce the effect. Another possibility might be attributed to the method we used to test the bronchial hyper-reactivity. The protocol used in this study to determine bronchial hyperresponsiveness was when $PC_{20} \leq 8$ mg/ml, whereas in other centres, the significant NBPT is set at a cut-off value of $PC_{20} \leq 16$ –32 mg/ml (22, 23). If we had used the higher cut-off value, we may have had a larger group of apprentices with bronchial hyperresponsiveness.

Specific bronchial challenge tests are still considered as the gold standard in the confirmation of the diagnosis of OA (24, 25). We could not confirm our diagnosis by using specific bronchial challenge because of the unavailability of these tests in our institution and as well as in our country.

Cartier (21) stated in his review that symptoms of OA resulting from exposure begin within a few weeks or years. This is recorded as 3–240 months in the study of Park and Nahm (26). Uçgun (6) reported the average period of symptoms due to exposure to be 2 years. The prevalence among those having worked less than 20 years and more than 20 years was reported as 2.2% and 27.3%, respectively, in the study of Mastrangelo et al. (27). In our study, according to surveillance case definition, we managed to diagnose three (4.2%) patients with likely OA who had worked as a car painter for 3 yr on average, which demonstrates that a long period of exposure is not necessarily required for the symptoms to occur.

Although atopy is not considered a predisposing factor of sensitization to substances of low molecular weight (21, 25), such as isocyanate, we found that occupational dermatitis was predictive for the presence of work-related asthma-like symptoms. The potential role of skin exposure in development of diisocyanate sensitivity has been documented by several investigators. Liu et al. (28) quantified diisocyanate skin exposure in auto body shops, while Petsonk et al. (29) reported an increased prevalence of diisocyanate asthma among workers with evidence of isocyanate skin exposure. This implicates the skin as a potential route of sensitization to isocyanates.

In his recent articles, Frew (30, 31), emphasized OA as being a valuable model in which to test the various hypotheses and encouraged further work on the mechanisms of OA because it can be induced by a variety of agents that

appear to affect the airway via different mechanisms. As it is known that the response of the immune system decelerates with age, it is understandable that the sensitization of isocyanate can occur in different age groups at different periods of time. This is an interesting topic, which needs further investigation. There are some unavoidable limitations to the present findings. Foremost are the small sample size and the vast number of dropouts from the study group which made quantitative analysis difficult, and the absence of further diagnostic techniques. Therefore, we could not confirm a diagnosis of asthma among car painters.

In conclusion, our study has demonstrated that in the case of apprentice adolescent car painters who work in unfavourable/unhealthy conditions, an average of 3 years of working duration is sufficient for developing OA. Adolescents who plan to undertake such work for many years should be closely followed for early diagnosis and treatment of OA.

References

1. TARLO SM, LEUNG K, BRODER I, SILVERMAN F, HOLNESS DL. Asthmatic subjects symptomatically worse at work: prevalence and characterization among a general asthma clinic population. *Chest* 2000; 118: 1309–14.
2. CHAN-YEUNG M, MALO JL. Aetiological agents in occupational asthma. *Eur Respir J* 1994; 7: 346–71.
3. MEREDITH S. Reported incidence of occupational asthma in the United Kingdom, 1989–90. *J Epidemiol Community Health* 1993; 47: 459–63.
4. Turkish Government Statistical Institute and International Labour Organization. Report of Child Employment in Turkey 1999: 1–60.
5. FERRIS BG. Epidemiology standardization project (American Thoracic Society). *Am Rev Respir Dis* 1978; 118: 1–120.
6. UÇGUN I, ÖZDEMİR N, METİNTAS M, METİNTAS S, ERGİNEL S, KOLSUZ M. Prevalence of occupational asthma among automobile and furniture painters in the center of Eskisehir (Turkey): the effects of atopy and smoking habits on occupational asthma. *Allergy* 1998; 53: 1096–100.
7. COCKCROFT DW, MINK JT. Isocyanate-induced asthma in an automobile spray painter. *Can Med Assoc J* 1979; 121: 602–4.
8. SEKEREL BE, SARAÇLAR Y, TUNCER A, ADALIOĞLU G, CETİNKAYA F. Standardization of methacholine inhalation challenge. *Turk J Pediatr* 1997; 39: 165–72.
9. CHAN-YEUNG M. Assessment of asthma in the workplace. ACCP consensus statement. American College of Chest Physicians. *Chest* 1995; 108: 1084–117.
10. ASHER M, ANDERSON H, STEWART A, CRANE J. Worldwide variations in the prevalence of asthma symptoms. The International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Resp J* 1998; 12: 315–35.
11. CULLEN MR, REDLICH CA, BECKETT WS, et al. Feasibility study of respiratory questionnaire and peak flow recordings in autobody shop workers exposed to

- isocyanate-containing spray paint: observations and limitations. *Occup Med* 1996; 46: 197–204.
12. SARI-MINODIER I, CHARPIN D, et al. Prevalence of self-reported respiratory symptoms in workers exposed to isocyanate. *JOEM* 1999; 41: 582–8.
13. MALO JL, GHEZZO H, L'ARCHEVEQUE J, LAGIER F, PERRIN B, CARTIER A. Is the clinical history a satisfactory means of diagnosing occupational asthma? *Am Rev Respir Dis* 1991; 143: 528–32.
14. MALO JL, CARTIER A. Occupational asthma in workers of a pharmaceutical company processing spiramycin. *Thorax* 1988; 43: 371–7.
15. BURGE PS. Single and serial measurements of lung function in the diagnosis of occupational asthma. *Eur J Respir Dis Suppl* 1982; 123: 47–59.
16. CHAN-YEUNG M, LAM S, KOERNER S. Clinical features and natural history of occupational asthma due to western red cedar (*Thuja plicata*). *Am J Med* 1982; 72: 411–5.
17. NEEDLMAN RD. Adolescence. In: NELSON WE, BEHRMAN RE, KLIEGMAN RM, ARVIN AM, eds. *Growth and development. Textbook of Pediatrics*, 15th edn. Philadelphia: W.B. Saunders, 1996: 62–3.
18. 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.
19. COTE J, KENNEDY S, CHAN-YEUNG M. Sensitivity and specificity of PC20 and peak expiratory flow rate in cedar asthma. *J Allergy Clin Immunol* 1990; 85: 592–8.
20. 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: 40–8.
21. CARTIER A. Definition and diagnosis of occupational asthma. *Eur Respir J* 1994; 7: 153–60.
22. MALO JL, PINEAU L, CARTIER A, MARTIN RR. Reference values of the provocative concentrations of methacholine that cause 6% and 20% changes in forced expiratory volume in one second in a normal population. *Am Rev Respir Dis* 1983; 128: 8–11.
23. LAM S, WONG R, YEUNG M. Nonspecific bronchial reactivity in occupational asthma. *J Allergy Clin Immunol* 1979; 63: 28–34.
24. CARTIER A, BERNSTEIN IL, BURGE PS, et al. Guidelines for bronchoprovocation on the investigation of occupational asthma. Report of the Subcommittee on Bronchoprovocation for Occupational Asthma. *J Allergy Clin Immunol* 1989; 84: 823–9.
25. CHAN-YEUNG M, LAM S. Occupational asthma (state of the art). *Am Rev Respir Dis* 1986; 133: 686–703.
26. PARK HS, NAHM DH. Isocyanate-induced occupational asthma: challenge and immunologic studies. *J Korean Med Sci* 1996; 11: 314–8.
27. MASTRANGELO G, PARUZZOLO P, MAPP C. Asthma due to isocyanates: a mail survey in a 1% sample of furniture workers in the Veneto region, Italy. *Med Lav* 1995; 86: 503–10.
28. LIU Y, SPARER J, WOSKIE SR, CULLEN MR, CHUNG JS, et al. Qualitative assessment of isocyanate skin exposure in auto body shops: a pilot study. *Am J Ind Med* 2000; 37: 265–74.
29. PETSONK EL, WANG ML, LEWIS DM, SIEGEL PD, HUSBERG BJ. Asthma-like symptoms in wood product plant workers exposed to methylene diphenyl diisocyanate. *Chest* 2000; 118: 1183–93.
30. FREW AJ. What can we learn about asthma from studying occupational asthma? *Ann Allergy Asthma Immunol* 2003; 90: S7–10.
31. FREW AJ. Advances in environmental and occupational diseases 2003. *J Allergy Clin Immunol* 2004; 113: 1161–66.