Diurnal variation in peak expiratory flow rate among workers exposed to toluene diisocyanate in the polyurethane foam manufacturing industry

H S Lee, W H Phoon

Abstract

The diurnal variation in peak expiratory flow rate (PEFR) was studied in 26 mixers from eight factories making polyurethane foam, who were exposed to toluene diisocyanate (TDI), and 26 unexposed controls matched for age, race, and smoking. They were all men. The mean diurnal variation in PEFR of the mixers was 6.2%, which was significantly higher than the 4.3% for controls. Six mixers had a diurnal variation of > 15% on at least one day compared with none among the controls. There was, however, no overt case of occupational asthma. All but one of the 24 environmental samples taken exceeded the short term exposure limit of 0.02 ppm for TDI. This accounted for the high prevalence (50%) of irritative symptoms such as cough and eye irritation. Forced expiratory volume in one second (FEV₁) and FEV₁/forced vital capacity (FVC) (%) was negatively correlated with duration of exposure to TDI. Foam workers may still have high exposure to TDI, high prevalence of irritative symptoms, increased diurnal variation in PEFR and evidence of chronic airway obstruction, particularly in those with ≥ 10 years of exposure.

A diurnal variation in peak expiratory flow rate (PEFR) has been reported for workers exposed to tobacco dust,¹ grain dust,² and polyvinylchloride resin dust.³ Studies of PEFR have been carried out on patients with suspected occupational asthma from isocyanates.⁴ As far as we know no reports exist on the diurnal variation in PEFR in workers exposed to isocyanates.

We studied the diurnal variation in PEFR in a group of workers exposed to toluene diisocyanate (TDI) in the polyurethane foam manufacturing industry and in a control group.

Materials and methods

MANUFACTURING PROCESS

The study was conducted in eight factories manufacturing polyurethane foam for use in mattresses, cushions, and packing materials.

The foam was formed by mixing polyol with TDI together with a small amount of amine (less than 0.05%), organometal catalyst, and freon. The isomer ratio of the TDI was 80% 2,4-TDI: 20% 2,6-TDI in all the factories.

The process was manually operated in six of the factories. The chemicals were manually weighed, mixed, stirred, and poured into a wooden box, where a block of foam was immediately formed. The foam was then moved to a store and the process repeated. A ventilation hood or booth was provided for the foaming process in four of the six factories.

The other two factories produced foam slab by an automated process. The raw materials were pumped from holding tanks, mixed, and discharged into a conveyor moving through a tunnel equipped with exhaust ventilation. A long slab of foam was formed in the tunnel and cut into smaller blocks at the end of the conveyor.

Foaming was carried out for four to six hours every day in the factories with the manual process but only half a day a week in the two automated factories. These two factories had automated the process within the past three years. Before that, the process had also been manual and was carried out daily.

STUDY POPULATION

Only workers directly involved in the foaming or mixing process were selected for the study. They were the most exposed group of workers in the plants. Only about two to five workers per plant were directly involved in the process. For the purpose of this study they are called "mixers".

A total of 52 male workers were studied, consisting of all the mixers (26; exposed to TDI) from eight foam mattress factories. The controls were matched with the mixers for age ($\pm$ five years), race, and smoking state. The controls were selected from workshop maintenance and field staff from three

Table 1 Assessments of TDI in air (personal sampling)

Factory	Type of process	Sampling time (min)	No of samples	TDI in air (ppm) Mean (range)
A	Manual	50	2	0.035 (0.03-0.04)
B	Manual	69	2	0.095 (0.09-0.10)
C	Manual	30	4	0.26 (0.19-0.31)
D	Manual	68	3	0.37 (0.23-0.50)
E	Manual	71	3	0.08 (0.04-0.12)
F	Manual	62	3	0.09 (0.06-0.12)
G	Automated	30	4	0.21 (0.06-0.47)
H	Automated	92	3	0.04 (0.01-0.08)
Total			24	0.16 (0.01-0.50)

government departments with no exposure to known asthma inducing agents.

PEFR RECORDING

Each participant was given a mini-Wright peak flow meter and instructed in its correct use. He was asked to perform three blows after maximal inspiration on each occasion and to record the results on a form. The highest of the three readings was taken. Six daily recordings (every three hours) during waking hours were made for one week (six working days and one off day). Recording started on a Wednesday, and were made both at the workplace and at home.

The diurnal variation in PEFR was calculated as the difference between the highest and lowest PEFR values as a percentage of the highest PEFR on each day. For each worker the mean diurnal variation for the one week period was calculated.

PULMONARY FUNCTION

Forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured on a dry wedge spirometer (Vitalograph) on Wednesday mornings (midweek) when workers began their shifts (before the foaming process). The spirometer was calibrated before use. The best FEV₁ and FVC readings were taken from three technically satisfactory forced expiratory manoeuvres where the best two recordings were within 5% of each other. All values were corrected to body temperature and pressure saturation (BTPS). Height (to the nearest cm) was measured without shoes. Predicted normal values for FEV₁ and FVC were calculated based on regression equations developed by Zee⁵ for local men.

RESPIRATORY QUESTIONNAIRE

Each subject was interviewed by trained field investigators using a structured questionnaire. Data were obtained on pulmonary symptoms, personal biodata, detailed work history including previous employment, medical history, atopy, and smoking habits.

ENVIRONMENTAL ASSESSMENTS

A total of 24 personal breathing zone samples were collected from mixers in the eight factories. Samples were collected in impingers containing a mixture of hydrochloric acid, glacial acetic acid, and distilled water and analysed for 2,4-TDI only by a colorimetric method.⁶ Sampling was carried out during the foaming process and sampling time ranged from 30 to 90 minutes depending on the duration of the process. The flow rate used was 1 l/min. The samples collected were immediately put into an icebox and sent for analysis.

STATISTICAL ANALYSIS

Analysis of variance (F test), *t* test for independent quantitative variables, χ^2 test, Fisher's exact test, and analysis of covariance were used where appropriate to compare data.

Results

ENVIRONMENTAL ASSESSMENT

All but one of the 24 personal breathing zone samples exceeded the short term exposure limit (STEL) for TDI of 0.02 ppm.⁷ The highest concentration was 0.5 ppm, which was 25 times the STEL. In all eight factories, the mean concentration of TDI in air exceeded the STEL (table 1).

STUDY POPULATION

The mixers comprised 23 Chinese, two Indians, and one Malay. Thirteen (50%) were non-smokers and

Table 2 Characteristics of study population

	Mixers (n = 26) Mean (SD)	Controls (n = 26) Mean (SD)
Age (y)	31.6 (8.6)	32.3 (8.9)
Exposure duration to TDI (y)	6.6 (6.3)	—
Height (cm)	168.9 (5.7)	169.2 (5.7)
Cigarette-years	93.3 (150.2)	101.9 (181.0)

Table 3 Prevalence of symptoms

	Mixers (n = 26)	Controls (n = 26)
Eye irritation	13 (50.0)*	2 (7.7)
Rhinitis	9 (34.6)	5 (19.2)
Cough	14 (53.8)**	2 (7.7)
Breathlessness	5 (19.2)	1 (3.8)
Wheeze	3 (11.5)	1 (0)

Data are given as No (%) with positive symptoms.

*p = 0.002 (χ^2 test); **p = 0.0008 (χ^2 test).

two were ex-smokers. Tables 2–4 summarise the personal data, prevalence of respiratory symptoms, and results of lung function tests and PEFR monitoring. None of the mixers had any history of asthma before working with isocyanates. Only one had a history of possible atopic dermatitis during childhood. About 50% of mixers experienced eye irritation (p = 0.002) or cough (p = 0.0008) during work compared with 7.7% among the controls. A history of wheeze was found in 11.5% of mixers compared with none among the controls. This difference was not statistically significant (table 3).

The average ratio of FEV₁/FVC (expressed as a percentage) was 83.0 for mixers. This was significantly lower (p = 0.01) than the 89.3% for controls (table 4). Mixers had a mean diurnal variation in PEFR of 6.2%, which was significantly higher than the 4.3% for controls (p = 0.02). Six mixers (23.0%) had a diurnal variation of more than 15% on at least one day compared with none among the controls (p = 0.01; Fisher's exact test). Only one mixer had a diurnal variation in PEFR greater than 20% on any one day. Bronchial provocation testing to TDI was negative.

The mixers were divided into those with less than 10 years of exposure and those with 10 or more years of exposure to TDI. Those with 10 or more years were compared with those with less than 10 years of exposure and the control group. As expected, those with 10 or more years of exposure were older (table 5). The prevalence of irritative symptoms (eye irritation and cough) was higher in the group with less than 10 years of exposure but this was not statistically significant.

Table 4 Average results of lung function tests and PEFR

	Mixers (n = 26) Mean (SD)	Controls (n = 26) Mean (SD)
FEV ₁ (l)	3.4 (0.7)	3.5 (0.5)
% Predicted FEV ₁	99.5 (15.0)	102.2 (11.7)
FVC (l)	4.0 (0.6)	3.9 (0.6)
% Predicted FVC	104.2 (11.6)	100.4 (10.8)
FEV ₁ /FVC (%)	83.0 (11.2)*	89.3 (6.0)
DV in PEFR (%)	6.2 (3.6)**	4.3 (2.3)

*p = 0.01 (t test); **p = 0.02 (t test).

Table 5 Characteristics and symptoms by exposure groups

	Unexposed controls (n = 26)	Exposure < 10 y (n = 19)	Exposure ≥ 10 y (n = 7)
Age (y)	32.2 (8.9)	28.8 (7.7)	39.0 (6.4)*
Height (cm)	169.2 (5.7)	170.1 (5.6)	165.7 (4.9)
Cigarette-years	101.9 (181.0)	120.2 (166.0)	20.3 (52.8)
Eye irritation	2 (7.7)	11 (57.9)	2 (28.6)
Cough	2 (7.7)	11 (57.9)	2 (28.6)
Wheeze	0	1 (5.3)	2 (28.6)

Data are given as mean (SD) for characteristics and No (%) for symptoms.

*p < 0.01 compared with those with < 10 years of exposure (ANCOVA).

Mixers with exposure of 10 years or more had a significantly reduced FEV₁ (p < 0.001) compared with those with less than 10 years of exposure and controls (table 6). The FVC was slightly reduced (p < 0.05) and FEV₁/FVC (%) was significantly reduced (p < 0.005) compared with the controls. A total of 57.1% of the mixers with 10 years or more of exposure had FEV₁/FVC (%), of less than 70% compared with 5.3% in those with less than 10 years of exposure (p < 0.02).

Mixers with exposure of 10 years or more had a higher mean diurnal variation in PEFR compared with the controls (p < 0.05; table 6). Of the six mixers with diurnal variation in PEFR greater than 15% on any one day, three (42.9%) had 10 years or more of exposure and three (15.8%) had less than 10 years of exposure. Table 7 summarises the characteristics of these six mixers. Only two of the six had a history of wheeze and evidence of obstruction in the tests of lung function. They were also exposed the longest (21 years). The other four had normal lung function and no history of wheezing.

Discussion

Isocyanates may cause irritation of the mucous membrane as well as sensitisation of the airways.⁸ The high prevalence of symptoms such as cough and eye irritation among the mixers was not surprising, considering that the STEL of 0.02 ppm for TDI was exceeded in almost all cases. The STEL was promulgated primarily to prevent irritation in unsensitised workers.⁹ It has been reported that the minimum concentration of TDI for irritation was 0.05 to 0.1 ppm and that all subjects were irritated at 0.5 ppm.¹⁰

We found only one case of clinically overt wheezing in a mixer; he had been exposed to TDI for 21 years. His highest diurnal variation in PEFR was 25.9%, although he had no history of asthma, he was not sure whether his wheeze was related to his work. Serial PEFRs at work and away from it were

Table 6 Lung function of mixers by exposure groups

	Unexposed controls (n = 26)	Exposure < 10 y (n = 19)	Exposure ≥ 10 y (n = 7)
FEV ₁ (l)§	3.4 (0.6)	3.5 (0.6)	2.7 (0.5)****
FEV ₁ (% predicted)	102.2 (11.8)	105.3 (11.9)	83.6 (12.0)****
No (%) < 80% predicted FEV ₁	1 (3.8)	1 (5.3)	3 (42.9)†
FVC (l)§	3.7 (0.7)	4.0 (0.7)	3.5 (0.6)**
FVC (% predicted)	100.4 (10.8)	107.2 (10.8)	96.0 (10.9)**
No (%) < 80% predicted FVC	1 (3.8)	0	1 (14.3)
FEV ₁ /FVC§	90.6 (13.8)	86.3 (12.6)	78.4 (11.1)***
No (%) FEV ₁ /FVC ≤ 70%	0	1 (5.3)	4 (57.1)‡
DV in PEFR (%)¶	4.3 (3.0)	5.8 (3.2)	7.5 (3.4)*
No (%) > 15% DV in PEFR on any one day	0	3 (15.8)	3 (42.9)

Data are given as mean (SD) or No (%) as appropriate.

*p < 0.05 compared with controls; ** p < 0.05 compared with < 10 years of exposure;

*** p < 0.005 compared with controls; **** p < 0.001 (all ANCOVA).

†p < 0.05 compared with < 10 years of exposure; ‡ p < 0.02 compared with < 10 years of exposure (both Fisher's exact test).

§ adjusted for age, height, race, and cigarette-years.

|| adjusted for cigarette-years.

¶ adjusted for age and cigarette-years.

equivocal. Bronchial challenge testing to TDI up to 0.04 ppm failed to produce any significant fall in his PEFR. Although patients who are sensitive to TDI may have different thresholds of response to the agent,¹¹ there was insufficient evidence to classify this case as occupational asthma.

The absence of overt cases of occupational asthma in this group of mixers exposed to high concentrations of TDI was not unexpected. In a cross sectional study we are likely to be looking at a survivor population. Nevertheless, it is interesting that the mixers had a significantly higher diurnal variation in PEFR compared with controls matched for age, smoking, and race. The mean diurnal variation in PEFR of 6.2% was comparable with the 6.5% obtained for mixers in the PVC compounding industry.³ The method of obtaining the diurnal variation in PEFR was similar in both studies. Records of PEFR are useful in the diagnosis of occupational asthma in persons exposed to isocyanates.⁴ The higher diurnal variation in PEFR among the mixers may be interpreted as some degree of bronchial hyperreactivity induced by exposure to TDI. Non-specific bronchial hyperreactivity is often found in patients with asthma due to exposure to isocyanates.^{12,13} Subjects occupationally exposed to isocyanates but with no subjec-

tive symptoms or spirometric abnormalities had increased reactivity of small airways.¹⁴ Of the six mixers who had a diurnal variation in PEFR greater than 15% on any one day, four had no history of wheezing or abnormalities of lung function. We do not know whether they would develop asthma subsequently. This mechanism of TDI induced asthma is still unclear. It is interesting that the diurnal variation in PEFR was higher among those with 10 or more years of exposure. This relative bronchial hyperreactivity could be the direct result of longer exposure to TDI, or associated with the chronic airways obstruction seen in this group.

Longitudinal studies of workers exposed to TDI have shown progressive loss of FEV₁.^{15,16} This is reflected in the negative correlation of FEV₁ and FEV₁/FVC (%) with duration of exposure to TDI in this cross sectional study. The lower cigarette-years among those with 10 years or more of exposure was unexpected. All four workers from one factory owned by a paternalistic employer had worked for him for more than 16 years. He had insisted that his workers did not smoke from the time they joined the factory for reasons of health and safety (fire hazard). This may explain the lower cigarette-years in this category.

Table 7 Characteristics and lung function of mixers with diurnal variation in PEFR greater than 15% on any one day

Mixer	Age (y)	Exposure duration (y)	Highest DV in PEFR (%)	Mean DV in PEFR (%)	FEV ₁ (%) predicted	FEV ₁ /FVC (%)	History of wheeze	Cigarette- years
1	40	21.0	15.6	11.0	69.4	70.1	+	0
2	38	21.0	25.9	11.2	76.4	61.7	+	0
3	42	16.0	18.8	14.8	100.7	76.4	—	2
4	27	7.0	19.6	12.5	110.7	88.1	—	70
5	32	3.6	15.7	9.5	102.9	91.1	—	260
6	22	1.8	17.7	12.8	105.9	98.3	—	0

The study has shown that mixers in the polyurethane foam industry may still be exposed to high concentrations of TDI. Besides an increased prevalence of irritative symptoms, they also have an increased diurnal variation in PEFR. Those with 10 or more years of exposure showed evidence of chronic airways obstruction on spirometry.

- 1 Lander F, Gravesen S. Respiratory disorders among tobacco workers. *Br J Ind Med* 1988;45:500-2.
- 2 Revsbech P, Anderson G. Diurnal variation in peak expiratory flow rate among grain elevator workers. *Br J Ind Med* 1989;46:566-9.
- 3 Lee HS, Ng TP, Ng YL, Phoon WH. Diurnal variation in peak expiratory flow rate among polyvinylchloride compounding workers. *Br J Ind Med* 1991;48:275-8.
- 4 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.
- 5 Zee KO. Ventilatory function in normal industrial workers in Singapore. *Proceedings of the XII Singapore-Malaysia Congress of Medicine*. The Academy of Medicine, 1977; 587-95.
- 6 US Department of Health Education and Welfare. 2,4-Toluene diisocyanate (TDI) in air. Method: P and CAM 141. In: *National Institute for Occupational Safety and Health, manual of analytical methods*. 2nd ed. Vol 1. Washington: US Department of Health Education and Welfare, 1977; 141.1-141.8. (DHEW (NIOSH) publ No 77-157-A).
- 7 American Conference of Governmental Industrial Hygienists. *Threshold limit values for chemical substances and physical agents and biological exposure indices*. Cincinnati: 1990-1991; 35.
- 8 National Occupational Health and Safety Commission. *Iso-cyanates*. Canberra: Australian Government Publishing Service, July 1990.
- 9 American Conference of Governmental Industrial Hygienists. Toluene-2,4-diisocyanate (TDI). In: *Documentation of the threshold limit values*. 4th ed. Cincinnati: ACGIH, 1980; 401-2.
- 10 Brugsch HG, Elkins HB. Toluene di-isocyanate toxicity. *New Engl J Med* 1963;268:353-7.
- 11 Paggiaro PL, Lastrucci L, Pardi F, Rossi O, Bacci E, Talini D. Specific bronchial reactivity to toluene di-isocyanate: dose-response relationship. *Respiration* 1986;50:167-73.
- 12 Butcher BT, Karr RM, O'Neil CE, et al. Inhalation challenge and pharmacologic studies of toluene diisocyanate sensitive workers. *J Allergy Clin Immunol* 1979;64:655-7.
- 13 Banks DE, Sastre J, Butcher BT, et al. Role of inhalational challenge testing in the diagnosis of isocyanate-induced asthma. *Chest* 1989;95:414-23.
- 14 Hjortsberg U, Orback P, Arborelius Jr M. Small airway hyperreactivity among lifelong non-atopic non-smokers exposed to isocyanates. *Br J Ind Med* 1987;44:824-8.
- 15 Wegman DH, Musk W, David MM, Pagnotto LD. Accelerated loss of FEV₁ in polyurethane production workers: a four-year prospective study. *Am J Ind Med* 1982;3:209-15.
- 16 Peters JM, Murphy RLH, Pagnotto LD, Whittenberger JL. Respiratory impairment in workers exposed to "safe" levels of toluene diisocyanate. *Arch Environ Health* 1970;20:364-7.

Accepted 16 September 1991

Destruction of manuscripts

From 1 July 1985 articles submitted for publication will not be returned. Authors whose papers are rejected will be advised of the decision and the manuscripts will be kept under security for three months to deal with any inquiries and then destroyed.