

Roberta Stopponi<sup>1</sup>, Cinzia Tacconi<sup>3</sup>, Ilenia Folletti<sup>2</sup>, Roberto Calisti<sup>1</sup>, Andrea Siracusa<sup>4</sup>

## Upper airway and eye involvement in polyurethane shoe sole production workers

<sup>1</sup> ASUR Marche, Area Vasta 3, Servizio PSAL, Civitanova Marche, Italia

<sup>2</sup> Sez. di Allergologia Professionale ed Ambientale, Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi di Perugia, Italia

<sup>3</sup> Medico Competente

<sup>4</sup> Dipartimento di Medicina Clinica e Sperimentale, Università degli Studi di Perugia, Italia

**ABSTRACT.** Objectives: This cross-sectional study was aimed to investigate the prevalence of work-related upper and lower airway and eye symptoms in 118 workers in polyurethane shoe soles (PSS) production. Methods: Workplace monitoring of methylene diphenyl diisocyanate (MDI) and solvents was performed. Subjects completed a study-specific questionnaire and underwent anterior rhinoscopy, skin prick tests for common aeroallergens, spirometry, nasal peak inspiratory (NPIF) and expiratory flow (NPEF). Results: MDI and solvent levels were below threshold limit value-time-weighted average (TLW-TWA) except for two measures of dichloromethane and tetrachloroethylene, respectively, and in one measure of acetonitrile, which were higher than TLW-TWA. In exposed workers the prevalence of cough ( $p < 0.05$ ) and nasal congestion at rhinoscopy ( $p = 0.05$ ) was more frequent than in non-exposed workers. Occupational exposure (OR 4.5, 95% CI 1.2-16.5) and a low FEV<sub>1</sub> (OR 2.6, 95% CI 1.1-6.3) were significant predictors of cough. Conclusions: In workers exposed to low levels of MDI and solvents in polyurethane shoe sole production there was a high prevalence of cough and nasal congestion. An improvement in the exhaust ventilation system and other preventive measures were needed.

**Key words:** polyurethane shoe soles, upper airway involvement, cough, occupation, solvents, MDI.

**RIASSUNTO.** SINTOMI DELLE VIE AEREE SUPERIORI E DELLE CONGIUNTIVE NEI LAVORATORI ADDETTI ALLA PRODUZIONE DI SUOLE IN POLIURETANO PER CALZATURE. Lo scopo di questo studio trasversale era di valutare la prevalenza dei sintomi delle vie aeree superiori e inferiori e delle congiuntive associati all'attività lavorativa in 118 lavoratori addetti alla produzione di soles in poliuretano per calzature. È stato eseguito il monitoraggio del 4,4 metilenebis(fenilisocianato) (MDI) e dei solventi. I soggetti sono stati intervistati mediante questionario e sono stati sottoposti a rinoscopia anteriore, prick test per allergeni inalanti comuni, spirometria, picco di flusso nasale inspiratorio (NPIF) ed espiratorio (NPEF). L'MDI ed i solventi sono risultati al di sotto dei valori limite di riferimento - valori medi ponderati (TLW-TWA) ad eccezione di due misure del diclorometano, due misure del tetracloroetilene e di una misura dell'acetone, che erano superiori al TLW-TWA. Nei lavoratori addetti alla produzione di soles in poliuretano abbiamo osservato una frequenza più elevata della tosse ( $p < 0,05$ ) e dell'ostruzione nasale alla rinoscopia ( $p = 0,05$ ) rispetto ai soggetti non esposti. Significativi fattori predittivi della tosse sono risultati l'esposizione lavorativa (OR 4,5, 95% CI 1,2-16,5) un basso valore del FEV<sub>1</sub> (OR 2,6, 95% CI 1,1-6,3). In conclusione, nei lavoratori addetti alla produzione di soles in poliuretano per calzature, esposti a bassi livelli di MDI e solventi, abbiamo osservato un'elevata frequenza di tosse e d'ostruzione nasale. È auspicabile un miglioramento dei sistemi d'aspirazione ed altri interventi preventivi.

**Parole chiave:** soles poliuretaniche per calzature, interessamento vie aeree superiori, tosse, attività occupazionale, solventi, MDI.

### Introduction

In the work environment exposure to occupational sensitising agents may cause occupational asthma (OA) and rhinitis (OR) while exposure to irritants may cause the reactive airways dysfunction syndrome (RADS) and upper airway and eye symptoms (8, 10, 25, 26).

For more than 30 years polyurethane foam has been used in the production of shoe soles, and is used in 6% of footwear (2). Few studies showed shoe-factory workers complained of respiratory and eye symptoms (20) and lung function impairment (22). Recently, a cross-sectional health study carried out in Thailand reported upper and lower respiratory tract and eye symptoms in footwear factory workers exposed to solvents and adhesives (32).

Until 15-20 years ago toluene diisocyanate (TDI), a very strong sensitizer, was used for the manufacture of polyurethane but was then replaced by methylene diphenyl diisocyanate (MDI), a compound with a lower vapour pressure and volatility. Even though MDI has less potential for inducing OA and OR, it has still been associated with work-related asthma, upper airway involvement and conjunctival symptoms (11, 14, 37). Besides MDI several other chemicals, such as chlorinated solvents (trichloroethylene, tetrachloroethylene, dichloromethane), dimethylformamide, N-methyl-2-pyrrolidone, aliphatic hydrocarbons C7-C10, and phthalates, have been used in the production of polyurethane shoe soles (PSS) and several are still in use at a technical grade of purity. Hazardous agents, such as acetonitrile, toluene, and methyl ethyl ketone, were sometimes found in environmental monitoring of PSS factories (23).

The objectives of the present study, which was carried out in 2004-2005 as part of the Marches (central Italy) regional project on "Chemical risk in the work environment", were to determine whether workers exposed to MDI and solvents in the production of PSS had a high prevalence of work-related upper and lower airway and eye symptoms and to establish whether factors such as exposure, atopy and smoking were predictors of work-related symptoms in this setting.

## Methods

### Factories

In 2004-2005 a health survey was conducted at five factories in the Macerata province, Italy, which produced PSS for medium quality shoes. *The technological process of molding the soles in polyurethane, from 2004 to now, has not been subjected to innovation.* The five factories (A, B, C, D, and E) are a sample of firms in the area with a workforce of more than 15 which had started production more than ten years before the present study was initiated. At each factory members of the study team spent one day on a walk-through survey to obtain information about the use of chemicals, job tasks, and departments. We interviewed 51 workers in factory C, and between 15 and 20 workers in each of the other factories. The health survey included environmental measures (MDI and solvents in the casting wheel sector and solvents in the spray painting area) and a cross-sectional study (questionnaires and diagnostic procedures). MDI replaced TDI more than ten years before this study started.

PSS are produced on a rotational casting wheel in six stages (23):

1. Polyol and prepolymer MDI are mixed together in a closed circuit at a temperature of 40-50 °C.
2. The reaction mixture is poured into 40-60 aluminium moulds. They close and rotate around the central axis of the casting wheel, which has a local ventilation system. The infusion pump, which is washed with dichloromethane, is also provided with a local ventilation system.
3. The mixture polymerises in 3-7 minutes i.e. within  $\frac{3}{4}$  of one casting wheel rotation.
4. After polymerisation the aluminium mould opens automatically and the sole is extracted manually or automatically.
5. Aluminium moulds are cleaned using brushes and rags soaked in heptane (use of dimethylformamide was stopped a year or more before the study started).
6. Moulds are automatically sprayed with aliphatic hydrocarbons C7-C10 or heptane, which carries a silicone detachant and the PSS production cycle, begins again. This workplace is provided with a local emission abatement system.

PSS are then washed in a closed circuit with tetrachloroethylene or soap detergents. After moulding, several PSS models are varnished with water- or solvent- based paints. Solvents include acetone, methyl acetate, ethyl acetate, methyl ethyl ketone, heptane, toluene, butyl acetate, xylene, and cyclohexanone. Painting was sprayed in a separate department in a varnish booth with local ventilation and water abatement systems.

### Environmental measurements of workplace exposure to MDI and solvents

Workplace monitoring of MDI was performed in 4/5 factories. Factory B went bankrupt before MDI monitoring could be performed. The results of MDI monitoring have already been reported (30). Briefly, 8-9 active per-

sonal or area samples were collected on one single day by means of a flow/volume pump at a flux of 0.5 l/min. Each sample had a minimum duration of four hours. Three factories (A, C, and D) were selected for solvent measurements. Factory E was excluded for budget restraints and Factory B went bankrupt before monitoring.

In the factories A C and D we used a radial passive sampler (radiello®) (6) to monitoring the following airborne solvents: acetone, n-hexane, methyl ethyl ketone, dichloromethane, tetrachloroethylene, acetonitrile, toluene, isomer xlenes, aliphatics hydrocarbons C7-C10. Solvents were chosen on the basis of knowledge of factories obtained in routine surveillance in previous years, the walk-through survey, and consultation of technical sheets. Sampling duration was one hour or more and was carried out on one single day.

MDI and solvent levels were compared with threshold limit values (TLVs) (31). Environmental conditions appeared stable according to routine surveillance reports over previous years and the walk-through survey.

### Subjects

118 of a total of 121 workers (97.5%) agreed to participate in this study and signed informed consent forms. 82 subjects (69.5%) worked at the rotational casting machine on four job tasks: mixing, moulding, maintenance, and mould cleaning. They were exposed to MDI and solvents. Seven (5.9%) were spray painters who were exposed to solvents. 29 (24.6%) were not directly exposed to MDI or solvents as they worked in separate departments as PSS trimmers, washers in a closed circuit, packers, or storekeepers. Therefore, they were classified as non-exposed. All exposed workers used personal respiratory and skin protection (nitrile rubber gloves and work clothes). 90% of workers were male. Median age was 40 years (range 22-62) and median duration of work in PSS production was 5 years (range 0.4-29). 39% were smokers, 38% never smokers, and 23% ex-smokers. In the three years before the study started none of the workers had been transferred to jobs with lower exposure or had left work because of work-related symptoms.

All 118 subjects completed a physician-administered study-specific questionnaire. Questions focussed on job, exposure (duration, type and degree), use of personal protective equipment (mask, gloves, work clothes, etc.) smoking habits, personal history of atopy, work-related and non work-related upper and lower respiratory symptoms, eye involvement and systemic symptoms (fever, chill, muscle pain) in the previous 12 months.

### Definitions

Symptoms during last 12 months were defined as *work-related* if they improved or disappeared at weekends or during holiday periods. *Asthma*: at least two of three lower respiratory symptoms (cough, breathlessness, and wheezing) (3). *Rhinitis*: at least one of three nasal symptoms (runny nose, stuffy nose, and sneezing) (3). *Conjunctivitis*: at least one of two conjunctival symptoms (itching and/or red eye with or without tearing) (13). *Upper airway/eye irritative symptoms*: affirmative answer

to the question “Do you feel burning or pain in your nose/throat/eye?” *Symptoms*: at least one upper or lower respiratory or eye symptom. *Work-related symptoms*: at least one work-related upper or lower respiratory or eye symptom. *Atopy*: at least one positive skin prick test (SPT) to common allergens. *Airway obstruction*: Forced expiratory volume in 1 second (FEV<sub>1</sub>)/forced vital capacity (FVC) < 70% (9). *Smoker*: anyone who smoked as much as one cigarette per day for one year or more, *ex-smoker*: a smoker who had not smoked for six months or more, *never smokers*: the others.

**Subjects with a questionnaire based diagnosis of work related asthma have been reported to the occupational physician to manage work related symptoms.**

### Diagnostic procedures

112 subjects provided informed consent and underwent SPT for 11 common aeroallergens (orchard, rye, Bermuda, velvet, *Parietaria*, olive, cypress, *Dermatophagoides pteronyssinus*, cat, dog, and *Alternaria tenuis*), positive (histamine 10 mg/mL) and negative (normal saline) control solutions. A test was regarded as positive if after 15 minutes it had produced a wheal with a diameter at least 3 mm greater than the one produced by the negative control. Six subjects did not undergo SPT because one refused and five were on antihistamine treatment.

FEV<sub>1</sub> and FVC were measured in all subjects in the sitting position with a digital turbine spirometer Spirolab (MIR, Rome, Italy) in accordance with the recommendations of the American Thoracic Society (1). Values are expressed as percentage of predictive values.

118 subjects underwent anterior rhinoscopy by an ear, nose, and throat (ENT) specialist. Nasal peak inspiratory (NPIF) and expiratory flow (NPEF) were measured in 116 subjects using an In-Check portable nasal inspiratory flow meter (Clement Clarke, Harlow, UK) and a Mini-Wright Peak Flow Meter (Clement Clarke, Harlow, UK), both equipped with a facial mask. Subjects received appropriate instructions on how to use NPIF and NPEF meters and were supervised by an ENT specialist while readings

were obtained. Three measurements were recorded for each subject and the highest value was used in the data analysis.

### Statistical analysis

Data were analyzed using the Statistical Analysis System (SAS) package for PC (Version 8, SAS Institute, Cary, NC, USA). Values for continuous variables are expressed as median and range. Differences in continuous variables were tested by the two-tailed paired *t* test. Differences in proportions were tested by the  $\chi^2$  or the Fisher exact test, when appropriate. Differences were considered significant at *p* < 0.05. Logistic regression models were used to analyze the effect of exposure to MDI and solvents, atopy, smoking status, FEV<sub>1</sub>, NPIF, and NPEF (predictors) on symptoms or work-related symptoms (dependent variables). Symptoms were analyzed in groups and one by one (see definitions). The results are given in terms of odds ratio (OR) with 95% confidence intervals (95% CI). Dependent and independent variables were binary (0= absence, 1= presence of the condition). Continuous variables (FEV<sub>1</sub>, NPIF, and NPEF) were transformed into categorical variables using the distribution above or below the median i.e. values below the median were equal to 1; values above were equal to 0. To assess the significance of the effects of different predictors, the (asymptotic)  $\chi^2$  distribution of the log-likelihood test (*G*<sup>2</sup>) and the normal distribution of the parameter estimates were used.

## Results

### Environmental measures of airborne exposure to MDI and solvents

MDI was used as prepolymer. Table I shows the results of MDI monitoring. Personal MDI measures were < 0.002 mg/m<sup>3</sup> in 29 samples. Area measures were ≤ 0.001 mg/m<sup>3</sup> in 14 samples. All these levels were markedly below threshold limit value-time-weighted average (TLV-TWA = 0.051 mg/m<sup>3</sup>) (31).

**Table I. Results of air sampling for MDI (mg/m<sup>3</sup>)**

<b>Personal samples</b>			
<b>Job</b>	<b>N. of samples</b>	<b>Median</b>	<b>Range</b>
Insert charge	5	<0.001	<0.001-0.002
Sole extraction	14	<0.001	<0.001-0.001
Various jobs	3	<0.001	<0.001-0.001
Rotational casting foreman	6	0.0005	<0.001-0.001
MDI handling/mixing	1	0.001	/
<b>Area samples</b>			
<b>Location</b>	<b>N. of samples</b>	<b>Median</b>	<b>Range</b>
Control panel of rotational casting	6	<0.001	<0.001-0.001
MDI handling/mixing	6	<0.001	<0.001-0.001
MDI loading	2	0.0005	<0.001-0.001

MDI, 4,4'-methylene diphenyl diisocyanate.

**Table II. Monitoring of selected solvents in the work environment in three factories**

Factory	Chemical	Personal samples			Area samples			TLW-TWA <sup>a</sup> (mg/m <sup>3</sup> )
		n	median	range	n	median	range	
A	dichloromethane	5	84	51-503	3	50	48-65	174
C	dichloromethane	8	2	1-25	12	2	0.5-10	174
	tetrachloroethylene	10	28	4-231	19	93	7-3737	170
D	acetonitrile	6	1	<0.1-151	2	87	5-168	34
	dichloromethane	2	9	6-11	2	10	6-14	174

<sup>a</sup> Threshold limit values (31)

Table II shows solvent levels were occasionally above the TLV-TWA threshold in three companies. In company A two personal measurements of dichloromethane were 190.8 and 502.9 mg/m<sup>3</sup>, respectively (TLW-TWA= 174 mg/m<sup>3</sup>). In company C one personal measurement of tetrachloroethylene was 230.6 mg/m<sup>3</sup> and an area measurement was 3737.0 mg/m<sup>3</sup> (TLW-TWA= 170 mg/m<sup>3</sup>). In company D one area measurement of acetonitrile was 168.5 mg/m<sup>3</sup> (TLW-TWA= 34 mg/m<sup>3</sup>). All the other measurements of acetone, n-hexane, methyl ethyl ketone, toluene, isomer xilenes, aliphatic hydrocarbons C7-C10 were more than 90 times lower than threshold limit values (TLVs) in companies A and D, and more than 9 times lower in company C (data not reported).

#### Prevalence of symptoms

The prevalence of work-related and non work-related symptoms was not different in 82 rotational casting wheel workers who were exposed to solvents

and MDI and seven spray painters who were exposed only to solvents. Therefore, the two groups were combined in the analysis.

Table III shows the prevalence of symptoms in 89 exposed and 29 non-exposed workers. The prevalence of asthma and eye irritation was not different in the two groups. All other symptoms were more frequent in exposed workers, although the difference was significant only for cough, which was three times more frequent in exposed than in nonexposed workers ( $p < 0.05$ ). No systemic symptoms were reported.

There was one case of work-related asthma, one of concomitant work-related asthma and rhinitis and three of work-related rhinitis. Only one out of four subjects with work-related rhinitis had positive SPT to grass. One case of work-related rhinitis worked in Factory A, the others were employed in Factory C. All were exposed to low levels of MDI and solvents in the casting wheel and used protective respiratory equipment, nitrile rubber gloves and

**Table III. Prevalence of symptoms and signs, skin prick tests, FEV<sub>1</sub>, and nasal peak flows in exposed and non-exposed workers**

	Exposed workers (n=89)	Non-exposed workers (n=29)	P
Breathlessness, n (%)	10 (11)	1 (3)	NS
Wheezing, n (%)	9 (10)	2 (7)	NS
Cough, n (%)	28 (31)	3 (10)	<0.05
Asthma, n (%)	6 (7)	2 (7)	NS
Sneezing, n (%)	18 (20)	7 (24)	NS
Runny nose, n (%)	17 (19)	4 (14)	NS
Stuffy nose, n (%)	18 (20)	3 (10)	NS
Rhinitis, n (%)	18 (20)	4 (14)	NS
Nasal congestion at rhinoscopy, n (%)	43 (48)	8 (28)	0.05
Upper airway irritation, n (%)	27 (30)	5 (17)	NS
Eye irritation, n (%)	23 (26)	7 (24)	NS
Conjunctivitis, n (%)	26 (29)	6 (21)	NS
Positive skin prick tests, n (%)	20 (24)	8 (29)	NS
FEV <sub>1</sub> , % predicted, median (range)	98 (70-125)	96 (65-121)	NS
NPIF, l/min, median (range)	100 (30-300)	95 (50-180)	NS
NPEF, l/min, median (range)	250 (60-450)	250 (100-450)	NS

NS, not significant; NPIF, nasal peak inspiratory flow; NPEF, nasal peak expiratory flow.

work clothes. One of the two workers with work-related asthma showed airway obstruction ( $FEV_1$  was 65% predicted) while spirometry was normal in the other.

33 subjects had at least one non work-related upper or lower respiratory or eye symptom and 39 workers reported at least one work-related symptom.

Table IV shows potential predictors in symptomatic and asymptomatic subjects. Symptomatic subjects included more smokers (47%) than asymptomatic subjects (28%,  $p=0.009$ ). Degree and duration of occupational exposure and atopy were not predictors of symptoms.

### Results of anterior rhinoscopy, skin prick tests, spirometry, NPIF, and NPEF

Anterior rhinoscopy showed nasal septum deviation in 59.3% of workers, mild lower turbinate congestion/mild hypertrophy in 43.2%, mild hyperaemia of pharynx in 62.7% and larynx in 40.5%, with no differences among exposed and non-exposed workers. There was a trend towards a significant difference ( $p=0.05$ ) for nasal congestion, which was 1.75 times more frequent in exposed workers (Table III).

28 subjects (25%) had positive skin prick tests (SPT) to common allergens. Atopy, estimated by positive SPT, was significantly more frequent in non work-related asthmatics than in work-related asthmatics ( $p < 0.0003$ ). Positive SPT tended to be more frequent in workers with non work-related symptoms (17% vs. 9%,  $p < 0.06$ ). No significant difference emerged in the distribution of positive SPT for any other work-related or non work-related symptom.

Spirometry showed seven subjects (5 smokers, 1 ex-smoker and 1 non-smoker) had  $FEV_1/FVC < 70\%$ , indicating airway obstruction (9). Baseline median  $FEV_1$  was 97% of predicted

(range 65-125).  $FEV_1$  below the median value of 97% was associated with a higher prevalence of cough ( $p < 0.05$ ).  $FEV_1$  was not associated with occupational exposure (Table III) or any other work-related or non work-related respiratory symptom.

Baseline median NPIF was 100 l/min. (range 30-300) with NPEF at 250 l/min. (range 60-450). NPIF and

NPEF measurements were not significantly different in exposed and non-exposed workers (Table III), in subjects with or without nasal obstruction, other nasal symptoms, or in subjects with or without airway obstruction.

### Predictors of symptoms

Logistic regression analysis yielded the predictive values of risk factors for work-related and non work-related symptoms. Table V shows only significant results. Current and former smoking but not occupational exposures were predictors of symptoms (work-related and non work-related), after adjusting for atopy. Current smoking and positive skin prick tests were inversely associated with work-related symptoms when analysed against non work-related symptoms, after adjusting for exposure to MDI and solvents. Occupational exposure and a low  $FEV_1$  were predictors of cough, after adjusting for atopy and smoking. No other symptoms were associated with work at rotational casting wheel/spray painting after adjusting for atopy and smoking.

**Table V. Predictors of symptoms, simultaneously adjusted for exposure to MDI and solvents, atopy and smoking status<sup>a</sup>**

	OR	95% CI
<i>Dependent variable: symptoms (work-related and non work-related)</i>		
No symptoms	1.0	
Current smoker	4.2	1.7-10.0
Ex-smoker	2.7	1.0-7.3
<i>Dependent variable: work-related symptoms</i>		
Non work-related symptoms	1.0	
Positive skin prick tests	0.3	0.1-0.93
Current smoker	0.3	0.1-0.98
<i>Dependent variable: cough</i>		
No cough	1.0	
Rotational casting machine worker/spray painter	4.5	1.2-16.5
$FEV_1 < 97\%$ predicted <sup>b</sup>	2.6	1.1-6.3

<sup>a</sup> As determined by logistic regression analysis.

<sup>b</sup> 97 is the median value of  $FEV_1$ , % predicted.

**Table IV. Potential predictors of symptoms (work-related and non work-related) in symptomatic and asymptomatic workers**

	Symptomatic subjects (n=72)	Asymptomatic subjects (n=46)	p
Exposure to MDI and solvents, n (%)	57 (79)	32 (70)	NS
Positive skin prick tests, n (%) <sup>a</sup>	18 (26)	10 (23)	NS
Duration of exposure (years), median (range)	6 (0.4-29)	5 (0.5-20)	NS
Smoking, n (%)			0.009
no	19 (26)	25 (54)	
yes	34 (47)	13 (28)	
ex	19 (26)	8(17)	
$FEV_1$ , % predicted, median (range)	98 (65-125)	96 (68-122)	NS
NPIF, l/min, median (range)	100 (30-300)	100 (50-200)	NS
NPEF, l/min, median (range)	240 (60-400)	250 (100-450)	NS

<sup>a</sup> Skin prick tests carried out in 68 symptomatic and 44 asymptomatic workers. NS, not significant; NPIF, nasal peak inspiratory flow; NPEF, nasal peak expiratory flow.

---

## Discussion

In the present study workers producing PSS, who were exposed to low level of solvents and MDI, had a higher prevalence of cough than non-exposed workers. Moreover, workers in the casting wheel occasionally had work-related asthma and rhinitis. Although exposure to solvents and isocyanates and adverse health effects in footwear factory workers have already been described, work-related symptoms in PSS production have seldom been reported (20, 21, 32, 33). Our results concur with other studies on footwear factory workers, which detected work-related upper and lower respiratory and eye complaints (20, 32).

Adverse health effects were described in workers exposed to solvents and MDI in other jobs. Findings in the present study provide evidence in support of observations on the effects of exposure to solvents on the nasal mucosa and/or conjunctiva. e.g. exposure to 200 ppm methyl ethyl ketone in 19 healthy volunteers caused sub-clinical rhinitis (19). Mixed solvents in video tape manufacturing factory were associated with a 21% prevalence of eye and nose irritation in 19 exposed workers (5). A high prevalence of irritative eye symptoms was observed in 28 car painters exposed to organic solvents far below the limit values (17). A 22% prevalence of eye irritation was detected in 255 house painters exposed to low concentrations of ammonia, formaldehyde, and volatile organic compounds (34).

Worldwide, exposure to diisocyanates, particularly to TDI, underlies much OA (15, 36). Although MDI, a diisocyanate with a low vapour pressure and less OA-inducing potential than TDI, is increasingly used in manufacture of several products including PSS (4), it can still cause OA, OR, irritative eye and nose symptoms (3, 11, 13, 14, 24). Moreover, a high prevalence of work-related irritative symptoms were reported at exposure far below TLVs (28).

Although most of these reports described eye symptoms in exposed workers as work-related, findings in the present study observed no differences in eye involvement in exposed and non-exposed workers. Several factors may account for this discrepancy. There was a slightly higher prevalence of atopy in non-exposed workers and in subjects with non work-related symptoms. Non-exposed workers may have been indirectly exposed to low levels of MDI and solvents. These factors may explain, at least partially, the high prevalence of eye symptoms and lack of differences in exposed workers and those not directly exposed to MDI or solvents (Table III).

In the present study, even when we used the TLV for mixtures, which is calculated according to the formula for additive effects, the exposure concentration was below the TLV (31). The PSS production workers had, however, a high prevalence of eye and upper airway irritative symptoms in the 12 months before the study started, suggesting a multiplicative effect may have determined chronic sub-clinical symptoms and exerted a priming effect. Moreover,

environmental monitoring is relatively short in comparisons to lifetime worker exposure.

Environmental measures of MDI and solvents were below TLVs. Skin exposure to isocyanates was described in footwear factories with inadequate skin protection (33). In our study as workers used an effective hand and skin protection, we believe skin absorption was unlikely.

Non work-related symptoms were predicted by smoking while work-related symptoms were inversely associated with smoking and atopic status (Table V). In the present study, as in all cross-sectional studies on working populations, the prevalence of work-related symptoms may be overestimated (information bias) or underestimated (healthy worker effect) and it is always difficult to determine whether one or both counteracting biases prevails or whether they are balanced. The healthy worker effect seems possible because subjects with work-related symptoms tend to be non-smokers or ex-smokers and nonatopics. Moreover, in the three years before our study began no workers had been transferred to less exposed jobs or had retired because of work-related symptoms. Thus when the study started selection bias in this cohort was not very likely, even though workers who had left the workplace for reasons other than work-related symptoms may have had more symptoms than those who remained and formed the study population.

Using anterior rhinoscopy we found a high prevalence of nasal septum deviation, mild nasal congestion, hypertrophy of lower turbinates, and hyperaemia of the pharynx and larynx confirming observations in an international study on 2589 adult ENT patients in 14 countries which showed a 90% prevalence of septal deformities without differences among countries (16).

The relationship between nasal symptoms or signs and NPIF or NPEF is controversial. Several investigations showed an association between the subjective sensation of nasal obstruction, as assessed by questionnaire, and NPIF (7, 29, 35), while others did not (12, 18, 27). In the present study we showed no association between nasal symptoms or signs and NPIF or NPEF. However, NPIF measurements were lower (median 100 l/min.) in our workers than in the general population. where a NPIF cut-off of 115 l/min. or lower was indicative of a negative predictive value for moderate/severe signs of rhinitis (29).

In conclusion, in workers exposed to low level of MDI and solvents in polyurethane shoe sole production we observed a high prevalence of cough and nasal congestion. Peak nasal inspiratory and expiratory flow measurements had a low sensitivity in detecting work-related nasal symptoms. Thus, an improvement in the exhaust ventilation system and other preventive measures in the workplace were needed.

---

## Acknowledgements

The authors would like to thank Dr. A. Marabini and Dr. G.A. Boyd for their help in reviewing the manuscript.

### Funding

This study was supported by grants from the project of Marches region on "Chemical risk in the work environment" and from the University of Perugia.

### Ethical Committee

The study was not presented to the Marches Ethical Committee as it was part of the Italian National Health Service programme for Workplace Surveillance and Health, which the Marches Regional Administration, employers and trade unions had previously agreed upon.

### References

- American Thoracic Society. Standardization of spirometry, 1987 update. *Am Rev Respir Dis* 1987; 136: 1285-1298.
- Andrew G, Tobias J, Stehley P. Surfactant technology for low density molded microcellular and flexible polyurethane systems. *PU Latin America* 2001; Technical Update 4, Footwear and CASE Paper 8, 2001: 1-6.
- Bernstein DI, Korbee L, Stauder T et al. The low prevalence of occupational asthma and antibody-dependent sensitization to diphenylmethane diisocyanate in a plant engineered for minimal exposure to diisocyanates. *J Allergy Clin Immunol* 1993; 92: 387-396.
- Bernstein JA. Overview of diisocyanate occupational asthma. *Toxicology* 1996; 111: 181-189.
- Chia SE, Ong CN, Phoon WH, et al. Neurobehavioural effects on workers in a video tape manufacturing factory in Singapore. *Neurotoxicology* 1993; 4: 51-56.
- Cocheo V, Boaretto C, Sacco P. High uptake rate radial diffusive sampler suitable for both solvents and thermal desorption. *Am Ind Hyg Assoc J* 1996; 57: 897-904.
- Farley JW, Durham LH, Ell SR. Correlation of subjective sensation of nasal patency with nasal inspiratory peak flow rate. *Clin Otolaryngol* 1993; 18: 19-22.
- Gautrin D, Bernstein IL, Brooks SM, Henneberger PK. Reactive airways dysfunction syndrome and irritant-induced asthma. In Bernstein IL, Chan-Yeung M, Malo J-L, Bernstein DI (eds) *Asthma in the Workplace*. 3rd edn. Taylor & Francis, New York, pp 581-629, 2006.
- Global Initiative for Chronic Obstructive Lung Disease: National Institutes of Health. National Heart, Lung, and Blood Institute. Publication Number 2701, 2001.
- Hempel-Jørgensen A, Kjærgaard SK, Mølhave L. Cytological changes and conjunctival hyperemia in relation to sensory eye irritation. *Int Arch Occup Environ Health* 1998; 71: 225-235.
- Jacobsson K, Kronholm-Diab K, Rylander L, Hagmar L. Airway symptoms and lung function in pipelayers exposed to thermal degradation products from MDI-based polyurethane. *Occup Environ Med* 1997; 54: 873-879.
- Jones AS, Willatt DJ, Durham LM. Nasal airflow: resistance and sensation. *J Laryngol Otol* 1989; 103: 909-911.
- Littorin M, Rylander L, Skarping G et al. Exposure biomarkers and risk at gluing and heating of polyurethane - a cross-sectional study of respiratory symptoms. *Occup Environ Med* 2000; 57: 396-405.
- Littorin M, Truedsson L, Welinder H et al. Acute respiratory disorder, rhinoconjunctivitis and fever associated with pyrolysis of polyurethane derived from diphenylmethane diisocyanate. *Scand J Work Environ Health* 1994; 20: 216-222.
- Meredith SK, Taylor VM, McDonald JC. Occupational respiratory disease in United Kingdom 1989: a report to the British Thoracic Society and the Society of Occupational Medicine in the SWORD project group. *Br J Ind Med* 1991; 48: 292-298.
- Mladina R, Čujić E, Šubarić M, Vuković K. Nasal septal deformities in ear, nose, and throat patients: an international study. *Am J Otolaryngol* 2008; 29: 75-82.
- Moen BE, Hollund BE. Exposure to organic solvents among car painters in Bergen, Norway. *Ann Occup Hyg* 2000; 44: 185-189.
- Morrissey MS, Alun-Jones T, Hill J. The relationship of peak inspiratory airflow to subjective airflow in the nose. *Clin Otolaryngol* 1990; 15: 447-451.
- Muttray A, Jung D, Klimek L, Kreiner C. Effect of an external exposure to 200 ppm methyl ethyl ketone on nasal mucosa in healthy volunteers. *Int Arch Occup Environ Health* 2002; 75: 197-200.
- Nijem K, Kristensen P, Al-Khatib A et al. Prevalence of neuropsychiatric and mucous membrane irritation complaints among Palestinian shoe factory workers exposed to organic solvents and plastic compounds. *Am J Ind Med* 2001; 40: 192-198.
- Nijem K, Kristensen P, Thorud S et al. Solvent exposure at shoe factories and workshops in Hebron City, West bank. *Int J Occup Environ Health* 2001; 7: 182-188.
- Oleru UG, Onyekwere C. Exposure to polyvinyl chloride, methyl ketone and other chemicals. The pulmonary and non-pulmonary effect. *Int Arch Occup Environ Health* 1992; 63: 503-507.
- Orfei G, Astuti MC, Minnetti L et al. Esperienza di misura dell'esposizione a solventi in aziende marchigiane della produzione di soles in poliuretano per calzature (Solvent exposure measures in Marches factories producing polyurethane shoe soles). *Giornale degli Igienisti Industriali* 2004; 29: 250-257.
- Sari-Minodier I, Charpin D, Signouret M et al. Prevalence of self-reported respiratory symptoms in workers exposed to isocyanates. *J Occup Environ Med* 1999; 41: 582-588.
- Shusterman D. Toxicology of nasal irritants. *Curr Allergy Asthma Rep* 2003; 3: 258-265.
- Siracusa A, Desrosiers M, Marabini A. Epidemiology of occupational rhinitis: prevalence, aetiology and determinants. *Clin Exp Allergy* 2000; 30: 1519-1534.
- Siracusa A, Pace M, Tacconi C et al. Prevalence of upper and lower respiratory symptoms in workers exposed to colophony and MBTS. *J Allergy Clin Immunol* 2004; 113: S61.
- Skarping G, Dalene M, Svensson B-G et al. Biomarkers of exposure, antibodies, and respiratory symptoms in workers heating polyurethane glue. *Occup Environ Med* 1996; 53: 180-187.
- Starling-Schwanz R, Peake HL, Salome CM et al. Repeatability of peak nasal inspiratory flow measurements and utility for assessing the severity of rhinitis. *Allergy* 2005; 60: 795-800.
- Stopponi R, Quaglio F, Cocheo L et al. Monitoraggio ambientale di isocianati in aziende marchigiane produttrici di soles in poliuretano per calzature (Workplace monitoring of polyisocyanates in Marches factories producing polyurethane shoe soles). *Giornale degli Igienisti Industriali* 2006; 31: 231-235.
- TLVs and BEIs based on the documentation of the Threshold Limit Values for chemical substances and physical agents & Biological Exposure Indices. ACGIH, Cincinnati, 2007.
- Todd L, Puangthongthub ST, Mottus K et al. Health survey of workers exposed to mixed solvent and ergonomic hazards in footwear and equipment factory workers in Thailand. *Ann Occup Hyg* 2008; 52: 195-205.
- Todd L, Mottus K, Mihan G. A survey of airborne and skin exposures to chemicals in footwear and equipment factories in Thailand. *J Occup Environ Hyg* 2008; 5: 169-181.
- Wieslander G, Norbäck D, Edling C. Occupational exposure to water based paint and symptoms from the skin and eyes. *Occup Environ Med* 1994; 51: 181-186.
- Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ. Subjective and objective markers of treatment response in patients with seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2000; 85: 111-114.
- Wisnewski AV, Mapp CE, Bernstein DI. Polyisocyanates and their prepolymers. In Bernstein IL, Chan-Yeung M, Malo J-L, Bernstein DI (eds) *Asthma in the Workplace*. 3rd edn. Taylor & Francis, New York, pp 481-495, 2006.
- Zeiss CR, Kanellakes TM, Bellone JD et al. Immunoglobulin E-mediated asthma and hypersensitivity pneumonitis with precipitating anti-hapten antibodies due to diphenylmethane diisocyanate (MDI) exposure. *J Allergy Clin Immunol* 1980; 65: 347-352.