Pak. j. sci. ind. res. Ser. A: phy. sci. 2023 **66A**(2) 114-119

Effect of Isocyanate Exposure on Spirometry Results and Respiratory Symptoms in Toluene Di-isocyanate Foam Workers

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(received February 3, 2021; revised February 20, 2022; accepted March 18, 2022)

Abstract. Toluene di-isocyanate (TDI) is extensively used in the manufacture of flexible polyurethane foams. The present study aimed to examine pulmonary function indices and respiratory symptoms in individuals exposed to isocyanates. Spirometric indices of 136 employees, 91 (66.91%) of whom were directly exposed to isocyanates and 45 (33.08%) were not exposed. These informations regarding demographic characteristics and respiratory symptoms, including coughs and dyspnea, were collected using a questionnaire from 2013 to 2016. The mean values of all respiratory indices decreased significantly in both groups over the 4 year period. There was a significant relationship between the decline in all indices and age, work experience and smoking. In the exposed group, a decrease in FEV1 and FEV1/FVC was significantly higher in smokers than in the non-exposed group. The exposed group, although younger and with a lower smoking rate, which has lower respiratory indices than the non-exposed group at the beginning and end of the measurement.

Keywords: cough, diisocyanates, dyspnea, smoking, spirometry

Introduction

Long-term exposure to respiratory contaminants in the workplace can diminish pulmonary function and cause multiple health problems (Khaliq *et al*., 2011). In addition, a number of studies have demonstrated that smoking can decrease pulmonary function indices and have a synergistic effect on certain exposures such as dusts (Wang *et al*., 2015).

Isocyanates are highly reactive, low molecular weight compounds that have α –N=C=O functional group. These compounds are increasingly used in the manufacture of numerous products such as elastomers, paints, adhesives, coatings and resins. The high chemical reactivity of isocyanates is an important characteristic in industrial applications that also results in toxic properties (Pedata *et al*., 2017).

Toluene di-isocyanate (TDI) is extensively used in the manufacture of flexible polyurethane foams. TDIs, catalysts and other materials are present in the foaming process, which can lead to employee exposure to these substances. Di-isocyanates are respiratory stimulants and sensitizers that can cause occupational asthma (Clark *et al*., 2003). In addition to asthma as an important health problem, isocyanates are also associated with hypersensitivity pneumonitis and accelerated lung function decline (Pronk *et al*., 2009).

Numerous studies have been conducted on the ventilatory capacity of employees in the production of TDI-based polyurethane foams to investigate whether exposure to low TDI concentrations leads to lung function decline, while a number of such studies have reported TDI-related lung function decline (Omae *et al*., 1992; Diem *et al*., 1982), some have not which is reported by (Bodner *et al*., 2001).

Respiratory complications from exposure to respiratory contaminants reduce employee performance in the workplace, impose high healthcare costs and reduce the work force over time.

Pulmonary function tests, including spirometry, play an important role in the diagnosis and treatment of lung diseases. One of the most important applications of spirometry is to screen employees in workplaces. Spirometry is routinely used as a screening tool for early diagnosis of pulmonary dysfunction in employees exposed to respiratory stimuli. It is therefore, widely used in annual occupational health assessments (Mehrparvar *et al*., 2014). Spirometry is performed at the time of work initiation on employees who are going to be exposed to respiratory contaminants followed by annual tests to allow an understanding of the effect of

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exposure to these substances on the respiratory system by comparing the results with those of previous years. Spirometric indices are an important part of medical monitoring programs that, in combination with effective industrial assessments and rapid removal of sensitized employees from exposure to isocyanates, can maintain long-term lung health (Wang *et al*., 2017).

Since the majority of Iranian studies have merely addressed the presence of isocyanates in the workplace, with a limited number of studies on the relationship between respiratory symptoms and indices and exposure to isocyanates, the present paper aimed to examine pulmonary function indices and respiratory symptoms during 4 years in individuals exposed to isocyanates, compare the results with those obtained from non-exposed individuals and investigate related confounding factors.

Material and Methods

This cross-sectional study was conducted between 2013 and 2016 on the employees of a polyurethane foam manufacturing plant. All employees with complete medical records and at least one year of work experience were included and those with underlying cardiovascular diseases, respiratory diseases, second or previous jobs affecting spirometry results and incomplete medical records were excluded.

Spirometric indices of the employees were extracted from 2013-2016 and information regarding their age, work experience, smoking, BMI and respiratory symptoms, including coughs and dyspnea, which was collected using a questionnaire. Spirometric indices examined in this study were the forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC and forced expiratory flow at 25-75% (FEF_{25-75}). The data of all the employees whose spirometric results were available in their records in the first year of the study were examined. Over the course of four years, a number of employees were dismissed from work for such reasons as displaying symptoms, diminished spirometric indices, inability to carry out the work or unwillingness of the employer to continue collaborating with them. Data analysis for these individuals was conducted until dismissal. Spirometry was performed by a trained in-house technician using the MIR Spirolab III spirometer. All tests were performed by a single device and a single technician over the course of 4 years.

Environmental monitoring. The concentration of toluene diisocyanate was measured through substance monitoring in ambient air. During this time, contaminants were sampled and measured in the plant's HSE (Health, Safety and Environment Unit). The average concentration of contaminants in the workplace ambient air was lower than occupational exposure levels when the workplace ventilation system was switched on (TWA <0.005 ppm). The employees were placed into two general groups, with the first group being those directly exposed to contaminants and the second group, the non-exposed employees (performing administrative work). Employees in the exposed group were all working in a collaborative work environment.

All participants signed an informed written consent form and the study was approved by the Ethics Committee of Iran University of Medical Sciences (Code: IR.IUMS.FMD.REC. 1399.458).

Statistical analysis. Data were analyzed in SPSS 20. The normal distribution of data was examined using the Kolmogorov-Smirnov test, revealing the non-normal distribution of data ($P < 0.005$). The data analysis was performed using nonparametric tests, including the Mann-Whitney U test for comparing quantitative variables in the two groups as well as the Friedman test for examining changes in spirometric indices over the course of 4 years.

Results and Discussion

In this study, 136 employees working in a polyurethane foam manufacturing plant were included, 91 (66.91%) of whom were directly exposed to isocyanate compounds and 45 (33.08%) were not. In the second year of the four-year study period and the data about the respiratory indices of 15 individuals, 9 and 6 of whom belonged to the exposed and non-exposed groups, respectively, this is unavailable due to them leaving the workplace. Data on 8 employees in the third year and 2 in the fourth year, all of whom belonged to the exposed group, could not be gathered because they left the workplace. The mean population age was 30.19±10.19 years. 29.7% of employees were smokers with a mean pack-year of 3.9±3.73.

Study of symptoms revealed that 14.4% of individuals reported dyspnea and 2.5% coughs together with dyspnea. Demographic characteristics and spirometric indices at the beginning and end of the study are listed in Table 1.

Table 1. Demographic characteristics and spirometric indices at the initial and final test

	Exposure group	Non exposure group	P value
Age (mean ±SD)	29.85 ± 11.05	31.33 ± 6.60	0.092
Work history (mean ±SD)	6.93 ± 6.59	4.83 ± 5.14	0.086
BMI (mean ±SD)	23.34 ± 3.74	24.11 ± 2.98	0.185
Smoking N (%)	23 (25.3)	12 (44.4)	0.091
Symptoms N (%)	14 (82.4)	3 (17.6)	0.759
Initial test			
FEV_1 (mean ±SD)	3.99 ± 0.43	4.06 ± 0.49	0.356
FVC (mean ±SD)	4.80 ± 0.46	4.82 ± 0.57	0.679
FEV_1% (mean ±SD)	82.31 ± 8.29	82.06 ± 6.90	0.931
FEF_{25-75} (mean ±SD)	81.81 ± 15.83	81.77 ± 22.48	0.545
Final test			
FEV1 (mean ±SD)	3.89 ± 0.42	4.03 ± 0.44	0.150
FVC (mean ±SD)	4.69 ± 0.41	4.76 ± 0.55	0.286
FEV_1% (mean ±SD)	82.04 ± 6.08	82.00 ± 5.74	0.639
FEF_{25-75} (mean ±SD)	83.86 ± 12.93	88.71 ± 12.62	0.070

Examination of the course of changes in employees' pulmonary indices over four years. Among those whose spirometry indices were available for 4 years, 68 (64.8%) had a decline in FEV_1 of more than 30 cc per year and 64 (61%) had a decline in FVC of more than 25 cc per year (*i.e.*, an excess annual expected decline).

Given the non-normal distribution of data, the Friedman test was used to examine changes in the respiratory indices over 4 years. P value < 0.001 was calculated for all 4 respiratory indices in both exposed and non-exposed groups. Considering the significance of the test results, it can be concluded that the mean values of all respiratory indices were different over the 4 year period, which is showing a significant decrease. Since, the beginning of the study, FEV_1, FVC, and FEF_{25-75} indices were in a lower range in the exposed group compared with the non-exposed group (Fig. 1).

The mean age was 29.85±11.05 years in the exposed group and 31.33±6.60 years in the non-exposed group. In addition, 25.3% and 44.4% of individuals were smokers in the exposed and non-exposed groups, respectively. Although younger and with a lower smoking rate, the exposed group has lower respiratory indices than the non-exposed group.

Examination of the relationship between different variables and decline in respiratory indices over the 4 year period using the Mann-Whitney U test pointed to a significant relationship between a decline in all indices and age, work experience and smoking. There was no significant relationship between a decline in indices and display of symptom and exposure to toluene diisocyanate. Further, examination that indices has a significantly greater decline in smokers who also has respiratory exposures compared to each category on its own (Table 2).

Another finding of the study was the significantly greater mean work experience of symptomatic individuals compared with asymptomatic ones (14 *vs* 5 years).

In regression analysis to adjust the effect of contextual variables including age and work experience, the relationship between simultaneous exposure to cigarettes and isocyanates with a decline in FVC index was still significant (P value = 0.046).

Table 3 shows the concomitant effect of smoking and exposure to isocyanates on the decline of respiratory indices. Smokers in the exposed group experienced a significantly greater decline in the FEV_1 and FEV_1/FVC than the non-exposed group (P < 0.001).

Longitudinal study and comparison of spirometric indices over time contributes to the early diagnosis of occupational and non-occupational pulmonary diseases as well as to occupational fitness assessment. From a general health perspective in a working population, a diagnosis based on longitudinal data (periodic spirometry) may prove more effective than a non-normal test (Hnizdo *et al*., 2011; Townsend *et al*., 2011; Enright, 2003).

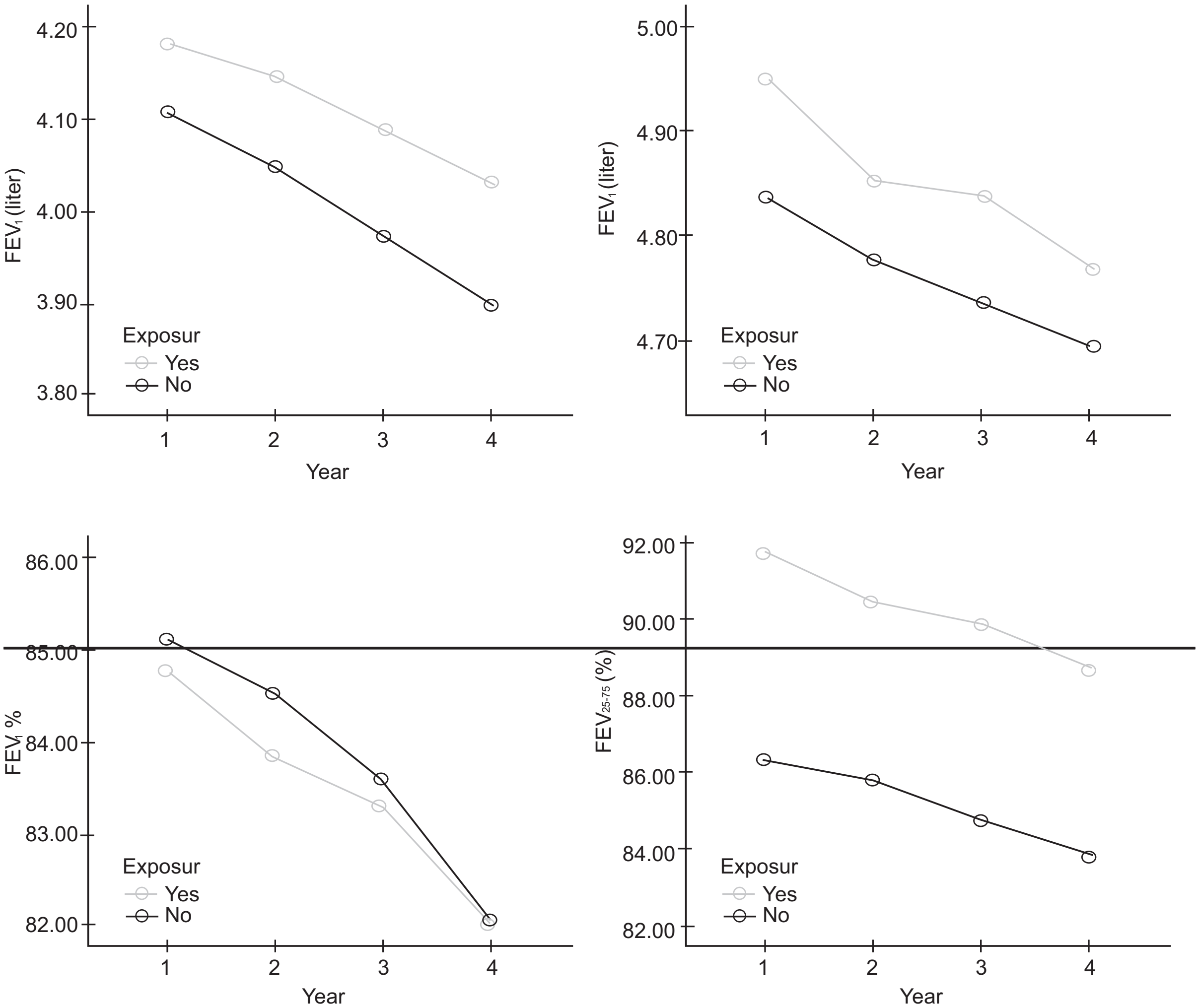

Fig. 1. Changes in employees' pulmonary indices over the course of four years.

Table 2. The relationship between different variables and decline in respiratory indices over the four years

Variable		FEV_1 Decline		FVC Decline		FEV_1 Decline		FEF_{25-75} Decline	
		Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value	Mean ± SD	P-value
Age	<30y	0.12±0.13	<0.001	0.09±0.11	<0.001	1.97±2.71	<0.001	1.93±3.24	0.001
	≥30y	0.33±0.26		0.26±0.20		4.91±3.93		3.81±3.92	
Work history	<6y	0.13±0.18	<0.001	0.09±0.12	<0.001	2.15±3.03	<0.001	2.29±3.65	0.021
	≥6y	0.33±0.22	0.29±0.19		4.91±3.66		3.25±3.39		
Smoking	Yes	0.43±0.25	<0.001	0.30±0.21	<0.001	6.47±3.91	<0.001	5.71±4.00	<0.001
	No	0.12±0.14		0.10±0.12		1.96±2.56		1.66±2.90	
Symptoms	Yes	0.23±0.04	0.307	0.33±0.09	0.04	2.14±0.99	0.878	1.33±1.15	0.766
	No	0.19±0.21		0.14±0.16		3.01±3.51		2.62±3.63	
Exposure	Yes	0.20±0.22	0.282	0.14±0.14	0.771	3.05±3.64	0.967	2.45±3.42	0.841
	No	0.15±0.16		0.18±0.24		2.75±2.79		3.00±4.17	
Smoking and exposure	Yes	0.14±0.15	<0.001	0.14±0.16	0.026	2.35±2.73	<0.001	2.14±3.41	<0.001
	No	0.53±0.27		0.23±0.17		7.25±4.77		5.50±3.47	

Table 3. Comparison of respiratory indices in the two groups of exposure and non-exposure based on smoking Status

Variables	Exposure group			Non-exposure group		
	Smoker	Non Smoker	P-value	Smoker	Non Smoker	P-value
	Mean ±SD	Mean ±SD		Mean ±SD	Mean ±SD	
FEV_1 Decline	0.53±0.27	0.14±0.14	<0.001	0.29±0.14	0.04±0.06	<0.001
FVC Decline	0.23±0.17	0.12±0.13	0.020	0.40±0.24	0.02±0.02	<0.001
FEV_1% Decline	7.25±4.77	2.21±2.72	<0.001	5.43±2.17	0.75±0.69	<0.001
FEF_{25-75} Decline	5.50±3.47	1.85±3.09	<0.001	6.00±4.82	0.75±1.35	0.001

This study was performed to examine the effects of isocyanate exposure on pulmonary function in employees working in the production of polyurethane foams. Moreover, the potential interaction between smoking and exposure to isocyanates was investigated.

There was no significant difference between the exposed and non-exposed groups in terms of decline in respiratory indices; even though FEV_1 and FEV_1/FVC has a greater decline in the exposed group. A study by (Clark *et al*., 2003) on the decline in respiratory indices in employees exposed to TDI showed no significant relationship between the annual decline in respiratory indices and exposure to TDI. In a review by (Ott *et al*., 2002) no evidence was found on the decline of FEV_1 in studies conducted on employees exposed to low levels of TDI (upto 5 ppb).

FEV_1 and FEV_1/FVC has a significantly greater decline in smokers of the exposed group than the non-exposed group. Similar results were found in a study of workers exposed to the thermal degradation products of polyurethane (Aziz and Saad, 2005). Airflow limitation, characterized by a decline in FEV_1, may result from increased thickness of the airway wall, sub epithelial fibrosis, obstruction of the airway lumen by exudate or mucus and changes of elastic properties of the airway walls. Increased thickness of the airway walls and obstruction of the airway lumen by exudate or mucus are the potential reasons for a decreased pulmonary function in relation to smoking (Ott *et al*., 2003).

Although younger and with a lower smoking rate, the exposed group scored lower mean values of FEV_1 and FVC indices compared with the non-exposed group at the beginning and end of the measurement. In contrast, the mean FEV_1/FVC was higher in the exposed group; albeit without any statistically significant difference. In a study conducted by (Wang *et al*., 2017) concerning the longitudinal and cross-sectional analyses of the pulmonary function of TDI production-line employees in the United States, the mean FEV_1 and FVC were lower in the study population ??at the beginning and end of the measurement than in the general population. However, the mean FEV_1/FVC was significantly higher than that in the comparison group, which is consistent with the findings of our study.

The incidence of symptoms including dyspnea and coughs was higher in the exposed group than in the non-exposed group, albeit without any statistically significant difference. In addition, the mean work experience was significantly higher in symptomatic individuals than in asymptomatic ones. In a study examining the cardiovascular effects of occupational exposure to the thermal degradation products of polyurethane, the incidence of cough and wheeze was not significantly different in the exposed and control groups; however, the exposed group experienced shortness of breath significantly more than the control group (Aziz and Saad, 2005).

Our study is among the few that examine the effects of TDI-exposure on respiratory indices and symptom display in employees in Iran. Although all spirometric tests were performed by a single device and a single technician over the course of 4 years, it is not free of limitations. First, isocyanate exposure monitoring was only performed in workplace ambient air, without individual exposures being available. Given that all employees worked in a single saloon with similar working conditions, exposure levels may be considered roughly equal in all exposed individuals, regardless of individual factors. Second, this was a cross-sectional study comparing exposed individuals with those engaged in non-exposed administrative works. However, con-founding factors such as age and smoking could not be homogenized in the two groups.

Based on the results of this study, smokers in the exposed group experienced a significantly greater decline in the FEV_1 and FEV_1/FVC than the non-exposed group. The mean FEV_1 and FVC indices at the beginning and end of the measurement were lower in the exposed group than in the non-exposed group. Symptomatic individuals exposed to isocyanate had more work experience than asymptomatic individuals.

Acknowledgment

This study was conducted with support from the Deputy for Research at Iran University of Medical Sciences.

Conflict of Interest. The authors declare they have no conflict of interest.

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