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Accelerated Loss of FEV-1 in Polyurethane Production Workers: A Four-Year Prospective Study

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A four-year longitudinal study of ventilatory function in polyurethane-foam production workers exposed to toluene diisocyanate (TDI) revealed a dose-response relationship between average exposure to TDI and change in forced expiratory volume per second (FEV-1). Workers with mean exposure in excess of 0.0035 ppm showed a greater rate of decline of FEV-1 over the four-year period than that expected from aging. Factors other than TDI exposure (sex, smoking history, history of atopy) do not account for the loss. The current threshold limit value (TLV) for exposure to TDI in industry (0.02 ppm) does not protect workers from accelerated impairment of ventilatory capacity.

Key words: TDI, forced expiratory volume, prospective study

INTRODUCTION

Over 400 million pounds of toluene diisocyanate (TDI) are consumed annually in the USA in producing flexible polyurethane foams for cushions and material for insulation and surface coatings. Workers exposed to this chemical include those employed in the manufacture of adhesives, urethane insulation, diisocyanate resins, lacquers, and wire coating as well as paint sprayers, plastic workers, ship builders, and textile processors.

Health effects of TDI were noted as early as World War II and the first scientific report was made in 1951 [Fuchs and Valade, 1951]. Since then a number of populations have been studied and effects on the respiratory system, both acute and chronic, have been noted [Peters et al, 1968, 1970; Wegman et al, 1974, 1977; Butcher et al, 1977; Smith et al, 1980].

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The current study was carried out over a four-year period in a population employed in manufacturing automobile seat cushions. In these subjects a relationship was previously shown between TDI exposure and one day loss of FEV-1 [Wegman et al, 1974], as well as two year decrement in FEV-1 [Wegman et al, 1977]. This report completes a four-year evaluation of the same subjects.

METHODS

Workplace Description

The manufacturing facility included a production area with one room containing two parallel mold lines 9 m apart and 42 m long; also included were rooms for finishing, supplies, storage, quality control laboratories, and clerical work. Production begins between the two lines in a compounding area where the TDI, polyols, a fire retardant, and a catalyst are mixed and directed immediately through hoses toward the pouring area. This mixture is poured into open waxed molds on a conveyor. A cover is locked on and the closed mold passes through an oven tunnel where temperature is controlled in a graduated fashion between 107°C and 149°C. When the mold emerges from the oven the cover is removed ("take off"), the foam extracted and both cover and mold are cycled back on either side of the ovens to the start. The foam is conveyed automatically to an adjacent room for finishing, where removal of the flashing and repair of small defects with scrap foam and glue takes place. The finished product is bagged in polyethylene and shipped or stored in a nearby warehouse.

Subjects

All 111 first-shift workers were seen in 1972 on the first Monday of November. Those of this group who were still employed and at work on the day of the 1974 study (63 subjects) were seen again on the first Monday of November 1974. The current population (48 subjects) were all those who were still at work on the first Monday of November 1976. On all three occasions each worker was evaluated before entering the plant and as many as possible were seen again 6–10 hours later.

The questionnaire elicited symptoms primarily of the upper and lower respiratory tract. Upper respiratory symptoms included sneezing (which occurred most days in the preceding year), sinus trouble or postnasal drip, and hay fever. Lower respiratory symptoms included coughing (which occurred most days or nights for periods greater than three months), wheezing (apart from colds), and shortness of breath (walking slower on the level than others of the same age). Chronic bronchitis was classified as cough and phlegm on most days for periods of three months or more in the previous two years. Atopy was considered if a subject admitted to suffering from hay fever, asthma, or hives.

Pulmonary Function

Ventilatory capacity was recorded using a water-filled spirometer.* FEV-1 was calculated for each individual by extrapolating from maximum slope of the spirogram to indicate zero time and using the mean of the best three FEV-1 measurements from five technically satisfactory forced expiratory spirograms (corrected to BTPS). Curves were judged to be acceptable when the forced vital capacities of three curves varied by less than 100 ml or 5% of each other. Using these criteria, spirograms from four of the

*Stead-Wells Spirometer, Warren E. Collins, Braintree, Massachusetts.

48 individuals were judged unsatisfactory and were not included in the analysis. The pulmonary function tests were administered with the same technique and used the same equipment for each survey.

For each worker, the difference between FEV-1 at the beginning and end of a workshift was calculated to provide a measure of "acute" change in FEV-1. Chronic change in FEV-1 was calculated as the difference between FEV-1 obtained Monday morning in 1972 and FEV-1 obtained Monday morning in 1976 (four-year Δ FEV-1).

Environmental Monitoring

Environmental sampling was done at selected work sites (mixing and pouring, "take-off", and finishing) on the same day as pulmonary function testing on each occasion. Sampling was additionally performed periodically during the first two years of the study. Personal sampling was used in the production area, and area samples were taken in the warehouse and in other nonproduction sites having little direct contact with TDI. No tests were taken in the interval between 1974 and 1976, so the average of the values taken in November of those years was used to represent the interim exposure. Experience from the first two years of the study indicated that this was reasonable. Samples were collected in Marcali solution at the rate of 2 l/min for periods ranging from 20 to 90 minutes [Marcali, 1957]. The long sampling times were necessary for monitoring low levels of TDI. The sensitivity of the technique allowed the measurement of TDI to the nearest 0.0005 ppm.

Isocyanate Exposure

Occupational histories were abstracted from personnel records. Cumulative exposure of each worker was calculated from the sum of the products of the time spent at the usual job (in months) during each of the two time intervals of the study, ie, 1972–1974 and 1974–1976, and from the measured exposure level for each job site (ppm) during that time interval. The exposure accumulated in this manner was then divided by the sum of the months spent in the two usual jobs to establish a usual exposure level (in ppm) for each worker during the study period. Seven of the workers were in maintenance jobs that required work in all areas of the plant, so no assignment for exposure could be made. These workers were excluded from analyses dealing with TDI exposure levels. The remainder of the workers had an average of 20.3 months in the usual job during the first 24 months, and 19.8 months in the usual job during the second 24 months. The mean usual exposure level was therefore treated as the mean exposure level for the study period. The population was divided into three exposure categories so that each group would include approximately one third of the workers. The categories were low (<0.0020 ppm), medium (0.0020–0.0034, and high (>0.0033 ppm).

In the follow-up group of 48, accurate information was obtained on exposure history and acceptable spirograms for 37 workers. This group comprises the population under study for the relationship of TDI exposure to pulmonary function status.

RESULTS

Isocyante Exposure

The time periods, number of samples collected and exposure levels in the three major work areas are presented in Table I. With the exception of the mixing and pouring areas median exposure was lower after 1974.

Respiratory Symptoms

The prevalence of workers with upper and lower respiratory symptoms was unrelated to exposure category. However, the six workers who remained asymptomatic throughout the four-year period of the study demonstrated a decline in FEV-1 of 46 ml. This compared with a 138 ml decline for the 10 subjects originally asymptomatic who developed one or more symptoms by the end of the four years. Mean TDI exposure for the former was 0.0015 ppm and for the latter 0.0030 ppm. Pack-years of cigarettes averaged 5.7 for the former and 11.2 for the latter, indicating that the relationship between symptoms and exposure may have been confounded by smoking.

Pulmonary Function

The 37 subjects with acceptable spirograms and definable exposure history demonstrated an overall mean decline in FEV-1 of 119 ml during the four years. Of the 119 ml decline, 92 ml occured during the first two years and 19 ml during the second two years of study. The high-exposure group contained no females and fewer smokers than the medium- and low-exposure groups. The frequency of atopy in the medium-exposure group was less than in the low- or high-exposure group. But the other variables measured were similar for workers in each group. The four-year change in FEV-1 was significantly directly related to the exposure category (Table II). It is also consistent within each smoking category (Table III).

Change in FEV-1 (Δ FEV-1) was standardized for lung size by expressing the value as a ratio of initial FEV-1. This size-standardized Δ FEV-1 increased with exposure and was significantly different among the exposure groups (Table II). When men were examined separately the difference between the low- and high-exposure groups (258 ml) was significant by t test ($p = 0.003$). Thus, when differences in lung size as a result of uneven distribution in women are considered, there is still a clear relationship between accelerated loss of FEV-1 and increased TDI exposure.

The four-year change in FEV-1 was studied by a stepwise multiple regression procedure. In this method, the independent variables are added sequentially to a model selected in the order of their strength of association with the outcome variable (four-year Δ FEV-1). The independent variables selected for study were: initial FEV-1, years smoked, mean exposure to TDI and length of time employed. The results of this analysis are shown in Table IV. The "F" value associated with each variable in Table IV is an indication of the relative importance of each category in predicting the four-year Δ FEV-1, while accounting for the other variables in the model. The R-square can be interpreted as the percent of the variability in the dependent variable (four-year Δ FEV-1), which is explained by the model.

The results were particularly interesting in that mean exposure to TDI was the best predictor of four-year Δ FEV-1. Mean exposure to TDI was the first independent variable to enter the equation and was the only variable that contributed significantly to the prediction ($p < 0.025$) as each new variable was added. Mean exposure to TDI was able to account for 13% of the variation in Δ FEV-1 among the workers ($R^2 = 0.128$). Age in 1972 was the second best variable added to the model. The positive coefficient for age and the substantial increase in R-square ($R^2 = 0.137$) probably reflects the fact that 38% of the study group were younger than 25 years at the start of the study. Had all the study group been 25 years or older their lungs would have been mature and age would probably have contributed much less, if at all, to the model. In contrast to age

TABLE I. Environmental Sampling Results

Work process[a] group	1972–1974 Number of samples	1972–1974 Range (ppm)	1972–1974 Median (ppm)	1974–1976 Number of samples	1974–1976 Range (ppm)	1974–1976 Median (ppm)
Mixing and pouring	17	0.001–0.017	0.004	8	0.005–0.040	0.007
Take off	35	0.000–0.010	0.005	16	0.001–0.004	0.002
Finishing	14	0.002–0.014	0.003	26	0.000–0.006	0.002
Miscellaneous	30	0.000–0.007	0.002	19	0.000–0.004	0.001
All areas	96	0.000–0.007	0.004	69	0.000–0.040	0.003

[a]See "Methods" for description of processes.

TABLE II. Population Parameters by Exposure Categories

Mean (ppm) exposure	No. of Subjects Males	No. of Subjects Females	Average age	Average height	No. with atopy[a]	Average months worked	Average smoking (pack-years)	4-Year Δ FEV(SD)[b]	Standardized[c] Δ FEV
<0.0020	10	3	30	166.3	4	82.5	9.5	−2 (168)	0
0.0020–0.0034	6	7	33	163.6	2	81.1	10.7	133 (184)	48
>0.0035	11	0	32	168.0	3	67.0	6.1	242 (174)	65

[a]See "Subjects" for definition.
[b]Anova F, $p = 0.007$; t test low vs high, $p = 0.002$.
[c]Anova F, $p = 0.013$; t test low vs high, $p = 0.003$.

TABLE III. Four-Year Change in FEV-1 by Smoking History and Exposure Category*

Exposure category	Nonsmokers	Exsmokers	Current smokers
Low	−52 (4)	−23 (4)	56 (5)
Medium	−18 (2)	−16 (2)	199 (9)
High	336 (3)	175 (1)	189 (6)

*Figures in parentheses are number of subjects.

TABLE IV. Stepwise Regression Analysis for Determinants of Four-Year Decrement in FEV-1

Dependent variable: Δ FEV independent variable	B	Standard error of B	R-square (change)	F	p
Mean exposure (ppm × 10^4)	4.94	2.03	0.128	5.92	<0.025
Age in 1972 (year)	7.82	4.61	0.137	2.88	<0.100
Months employed	−1.54	1.60	0.028	0.93	>0.25
Height in 1972 (cm)	−2.82	3.80	0.011	0.55	>0.25
Years smoked	1.14	4.44	0.002	0.07	>0.25
(Constant)	302.5				

Analysis of variance	DF	Sum of squares	Mean square	F	p
Regression	5	495904	99180.8	2.729	<0.05
Residual	31	1126496	36338.5		

TABLE V. Characteristics of Restudied and Nonrestudied Groups

Years tested	N[a]	% Women	Mean age in 1972	Height (cm)	Pack-years cigarettes	TDI exposure in 1972 (ppm)	Acute Δ FEV-1 (ml) (1972)
1972	111	30	29	168	8.3	0.0035	106
1972 and 1974	63	27	29	168	9.0	0.0035	83
1972 and 1976	37	27	32	166	8.9	0.0040	116

[a]Number of subjects tested.

and exposure, the variable years smoked was not a significant variable and the R-square change was negligible. This regression analysis, then, is further confirmation that the accelerated decrement in FEV-1 in this study population is associated primarily with exposure to TDI.

The acute change in FEV-1 over a workshift observed at the beginning of this study was weakly associated with long-term change in FEV-1: when controlling for age, the partial correlation coefficient of one-day change in FEV-1 with the 2-year change in FEV-1 was 0.45 ($p = 0.04$), and with the 4-year change was 0.25 ($p = 0.06$).

DISCUSSION

We have demonstrated a relationship between TDI exposure and impairment of pulmonary function over four years. This relationship is not explained by differences between the groups in age, sex, or smoking history. The decline in FEV-1 (60 ml/year) observed in the high-exposure group exceeds the annual decrement observed in cross-sectional and longitudinal studies of normal populations that have demonstrated expected annual declines of 32–47 ml FEV-1 [Ferris et al, 1976, 1979; Berry et al, 1973; Kauffman et al, 1979; Van der Lende, 1981].

The major potential problem with this study, as with most longitudinal studies of morbidity, is selection bias introduced by loss of subjects from the study. The analysis is directed only at the survivors of the original population. However, comparison of the survivor group with the initial cohort suggests that the restudied subjects are representative of the original group (Table V).

TDI exposure has previously been associated with respiratory symptoms in populations exposed at levels generally higher than those reported here. Hama reported that

respiratory symptoms occurred when TDI concentrations in an automobile plant were 0.010–0.030 ppm but not when they were below 0.010 ppm [Hama, 1957]. Elkins found respiratory illness at concentrations above 0.010 ppm but not below that level [Elkins et al, 1959]. In a prospective study of exposed subjects (mean exposure 0.002–0.006 ppm), Butcher and co-workers [1977] showed a greater prevalence of bronchitis (chronic cough and phlegm) in the exposed than in controls. The absence of symptoms associated with exposure level in this study, therefore, is not surprising.

The study indicates that chronic exposure to levels of TDI greater than 0.0035 ppm results in pulmonary function loss that is greater than predicted. This corroborates the experience of the same cohort after 2 years of follow up [Wegman et al, 1977], and the work of Weill [Weill et al, 1981]. It suggests that the current TLV is not sufficient to protect workers from continued deterioration of respiratory function which, if sustained for a 30 or 40 year working life would result in symptomatic chronic airflow obstruction.

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