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Chronic pulmonary function loss from exposure to toluene diisocyanate[1]

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ABSTRACT In 1972 a total of 112 workers exposed to toluene diisocyanate (TDI) were examined for acute pulmonary function changes during a work shift on the first day of the working week. A dose-response relationship was demonstrated for the acute effects of TDI in this population. The cohort was restudied in 1974 to determine whether there was excessive loss of pulmonary function, and if so, whether there was an exposure level below which this did not occur. The original cohort was reduced to 63 workers available for re-survey of which 57 could be assigned reliable personal exposure levels for the two-year study period. Pulmonary function measurements were made again before and after work on the first day of the working week. A total of 132 environmental samples were collected on this and previous occasions during the study period. The 57 workers were divided into three exposure subgroups ($\leqslant 0{\cdot}0015$; $0{\cdot}0020 - 0{\cdot}0030$; $\geqslant 0{\cdot}0035$ ppm). Using the $FEV_{1.0}$ as a measure of response, a dose-response relationship was observed. Only those in the lowest exposure subgroup showed normal two-year declines. The $FEV_{1.0}$ of those in the highest exposure group fell 206 ml in two years (103 ml/year) which exceeds the expected value by three- to fourfold. The decrement of $FEV_{1.0}$ in the middle exposure group was borderline (42 ml/year). These differences in $FEV_{1.0}$ by exposure subgroup were not explained by age, months employed, smoking habits, or variables related to lung size. A significant association ($r = 0{\cdot}35$, $P < 0{\cdot}005$) between acute and chronic decrement in $FEV_{1.0}$ was shown again. We conclude that chronic occupational exposure to TDI at 0·003 ppm or higher is unsafe.

Polyurethane plastics have gained great popularity since the second world war for cushioning materials (mattresses, pillows, seat cushions and packing materials), insulation (thin-walled refrigerators and ovens) for soft toys, and surface coatings (varnishes and paints). Unfortunately, the increased use has been accompanied by pulmonary disease associated with exposure to the volatile isocyanate groups used to manufacture polyurethane.

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The production of polyurethane involves combining a polyol with a chemical containing two highly reactive isocyanate groups. It is during this mixing and foaming process that the isocyanates are released into the workroom atmosphere. Toluene diisocyanate (TDI) is the most commonly used isocyanate, and because of its volatility it is also the most hazardous.

The clinical features of isocyanate-associated illness were summarised by Brugsch and Elkins (1963). Eye, nose and throat irritation are usually the first clinical manifestations. Dry cough with chest pain or tightness often follow. Because the cough or wheeze are characteristically worse in the evening or at night, the patient or doctor may not recognise its occupational aetiology. Rhonchi or coarse rales are frequently present. In some workers the characteristic pattern of bronchial asthma is the initial manifestation; in others it develops late. Chest radiographs taken during the acute stage are usually

interpreted as normal, although increased markings and patchy infiltration are occasionally seen. The clinical picture can then approximate to acute or chronic bronchitis, bronchial asthma, or rarely, pneumonitis.

This study comprises a two-year follow-up of a cohort of workers exposed to TDI in polyurethane cushion manufacture. A dose-response relationship was demonstrated for acute effects of TDI in this population in 1972 (Wegman *et al.*, 1974). We re-examined this cohort to determine whether accelerated loss of pulmonary function was observable and whether an exposure level could be found below which excessive loss of forced expiratory volume was not seen.

Previous studies of other working populations exposed to TDI have shown that:

1. Acute pulmonary effects occur when workers are measured before and after a workshift on the first day of the week (Gandevia, 1963; Peters *et al.*, 1968). These effects are, for the most part, asymptomatic.

2. Excess chronic loss of pulmonary function occurs over periods of up to three years (Peters *et al.*, 1969; Peters, 1970; Peters *et al.*, 1970; Peters and Wegman, 1975).

3. The acute and chronic effects are correlated, that is, those showing the largest acute responses are likely to show the greatest chronic changes (Peters *et al.*, 1969; Peters, 1970).

4. The acute and chronic changes are seen in subjects exposed to levels of TDI below the existing permissible exposure level of 0·02 ppm (Peters *et al.*, 1969; Peters, 1970).

Methods

STUDY POPULATION

Because of recent labour turnover and cutbacks in the work force, only 63 of the 112 workers studied two years previously were still employed and available for restudy. We have collected the following data on these workers:

1. A past occupational history to identify subjects with significant exposure to pulmonary irritants other than TDI.

2. A current occupational history to determine duration of employment by job type.

3. A detailed smoking history.

4. A standardised questionnaire on respiratory symptoms (cough, phlegm, wheezing and shortness of breath).

5. Date of birth.

6. Height in stockinged feet to nearest centimetre.

7. Ventilatory capacity was assessed by recording at least three technically satisfactory forced vital capacity manoeuvres on a water-filled spirometer with a fast kymograph speed.

The tests were performed before and after the work shift on the first day of the work week (Monday) and the mean of the best three efforts was called the true value. This value was then temperature corrected. The $FEV_{1.0}$ was used as the principal index of ventilatory capacity. Because of the acute effects seen on Monday, this population was tested on Monday morning following a three-day weekend.

ENVIRONMENT

Sampling was performed throughout the workday in different seasons, and included both area and personal sampling. Personal samples were used to characterise exposure except where area sampling was equivalent, for example in rooms away from direct exposure to either TDI or the polyurethane production line. Breathing zones were sampled at all job locations so that actual exposure values could be assigned to each job. Air samples were collected in Marcali solution at the rate of two litres/minute for periods ranging from 20 to 90 minutes. The long sampling periods were necessary to identify low exposures. The sensitivity of our method (Marcali, 1957) allowed the detection of TDI at 0.0005 ppm.

Results and discussion

A relatively large number of dropouts is a particular problem in isocyanate-exposed populations. In this study 45% of the original population was not available for restudy. Of these 80% had voluntarily terminated employment. Before analysis of lung function the retested and lost populations were compared to identify any selection bias in the re-studied population. Tables 1 and 2 show that the two populations are similar. Those not restudied had on average worked 12 months less than those restudied. This was expected because lay-offs are based on seniority and because voluntary resignation usually occurs in the first year of employment. The small differences in age and years of smoking also reflect this. The difference in mean acute change in $FEV_{1.0}$ measured in 1972 is not statistically significant. The sex distribution is similar in the two groups. The only notable difference in the two populations is a larger proportion of non-smokers in the lost group.

We have found that, in TDI-exposed populations, individuals who have the larger acute responses tend to drop out. The lost group was examined to evaluate this possibility. Of the 49, nine had been laid off and had an average decrease in $FEV_{1.0}$ of 81 ml. The 40 who had resigned had an average decrease in $FEV_{1.0}$ of 126 ml. These differences are

Table 1 *Comparisons of restudied and non-restudied populations (1972)*

	Restudied N = 63		*Non-restudied N = 49*		*Total N = 112*	
	No	*%*	*No*	*%*	*No*	*%*
Sex						
Male	46	73	33	67	79	70
Female	17	27	16	33	33	30
Smoking history						
Non-smokers	17	27	19	39	36	32
Current smokers	39	61	25	51	64	57
Ex-smokers	7	11	5	10	12	11

Table 2 *Comparisons of restudied and non-restudied populations (1972)*

	Restudied N = 63		*Non-restudied N = 49*		*Total N = 112*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age	30·9	10·6	28·3	9·7	29·8	10·2
Height	168·0	8·5	168·2	9·2	168·1	8·8
Years smoking	13·5	9·2	11·8	8·9	12·8	9·1
Months employed	28·7	25·0	16·5	16·0	23·4	22·3
Acute change in $FEV_{1.0}$ (ml)	96	188	118	139	106	171

not statistically significant, but the trend is consistent with our experience. In comparison, the retested group had an average decrease in $FEV_{1.0}$ of 96 ml.

The exposure variables considered were both duration of employment and TDI exposure at each work station. Job-specific exposure was determined on five occasions during the course of the two-year study. These were used to assign a usual value to each work station. A total of 118 personal and 14 area samples were taken to characterise 20 work stations. The average exposure values for these stations ranged from 0·0005 to 0·0090 ppm TDI. These results were compared with the 45 samples used to characterise major exposure areas during the two years prior to this study. The results were similar, indicating stable exposure levels.

When the work stations had been categorised by TDI exposure level, each individual was classified by work station. The group had been very stable in work assignments during the last two years, but in some instances job changes had occurred. None of the 63 individuals had worked for less than 12 months at one station; 30 had not changed jobs during the two years, and average length of usual job assignments was 20 months. Because of this general job stability, each individual was classed according to his or her usual work station held during the two years and to its exposure level.

The average two-year loss in $FEV_{1.0}$ was calculated for the 63 individuals. One individual was eliminated from the analysis because of unreliable pulmonary function test results.

Five of the 63 persons restudied had job classifications as utility workers, who filled in at a variety of jobs on the production lines. The two lines involved had jobs where exposure levels varied over most of the exposure range (from 0·0020 to 0·0080 ppm). It was therefore not possible to assign these workers to an exposure group and they were removed before examination of the two-year $FEV_{1.0}$ differences.

To examine our results for a dose-effect relationship we divided the population into three exposure groupings with approximately 20 subjects/group. The three exposure categories for the 57 subjects available for final analysis were $\leqslant$ 0·0015 ppm, 0·0020-0·0030 ppm, and $\leqslant$0·0035 ppm TDI.

Reports of symptoms collected on the standard questionnaire were compared according to the three exposure categories. The questions concerned four groups of symptoms: cough, phlegm, wheezing, and shortness of breath. The prevalence of cough and phlegm (presence, occurrence in the morning, and occurrence all day) increased proportionately with increase in exposure. The same was true for phlegm (presence, and occurrence in the morning). In both symptom groups more than 70% of the responses were negative. Approximately 15% had responses consistent with chronic bronchitis (cough or phlegm for most days for three months of the year), but the positive answers were no greater in the high exposure group. Thirty per cent reported wheezing occasionally or most of the time, apart from colds and 10% reported dyspnoea equal to or greater than that from climbing one flight of stairs. Neither of these were associated with exposure.

The objective findings associated with the three exposure groupings are shown in Table 3. The

Table 3 *Summary of possible confounding variables (1974) according to exposure category*

Exposure†	*n*	*Age (yr)*	*Months employed*	*Nonsmokers Number (%)*	*Yr Smoking for smokers*	*Height (cm)*	*Women Number (%)*	*Two-year change in $FEV_{1.0}$ in ml (SD)**
Low	20	33·5	51·5	4 (25)	15·8	166·7	4 (25)	−12 (204)
Medium	17	33·6	55·8	2 (12)	15·9	170·4	3 (18)	−85 (177)
High	20	33·0	55·1	4 (25)	13·8	168·0	7 (35)	−205 (185)
Total	57	33·3	54·0	10 (18)	15·2	168·2	14 (25)	−102 (204)

†Low = $\leqslant$ 0·0015 ppm; Medium = 0·0020-0·0030 ppm; High = $\geqslant$ 0·0035 ppm
*f = 5·2539; P < 0·01

Table 4 *Size-standardised loss in $FEV_{1.0}$ by exposure groupings**

Exposure	*n*	*2-year Δ in $FEV_{1.0}$*	*2-year Δ in standardised $FEV_{1.0}$ (SD)***
Low	20	− 12	−4·3 (72·6)
Medium	17	− 85	−26·1 (49·5)
High	20	−205	−59·3 (50·5)

*Standardised $FEV_{1.0} = \frac{\text{2-year } \Delta \text{ in } FEV_{1.0}}{FEV_{1.0} \text{ at start of study}} \times 1000$

**f = 4·41, P < 0·03

two-year change in $FEV_{1.0}$ increases with increasing exposure. Analysis of variance (Nie *et al.*, 1975) showed that the differences in loss of $FEV_{1.0}$ according to exposure groupings is significant (f = 5·2539, P < 0·01). There was no significant deviation from linearity. The decrement in the low exposure groups (−12 ml) is clearly within expected limits for normal populations while that in the high exposure groups (−205 ml) is clearly excessive (Kory *et al.*, 1961; Ferris *et al.*, 1965; Rosenzweig *et al.*, 1966; Fletcher, 1967; Higgins *et al.*, 1968; Morris *et al.*, 1971).

The five subjects who had been excluded because of mixed exposure levels were also evaluated. They were all males and were on average slightly younger (29·6 years) and shorter (164·4 cm) than the remainder. They had worked for less time (41·0 months) and although all were cigarette smokers, they had smoked for fewer years (11·4 years). The mean annual change in $FEV_{1.0}$ over the two-year period was a small and statistically insignificant increase (24 ml).

Possible confounding variables were explored to determine whether some factor besides exposure level could explain this observed difference. The variables considered were age, months employed, smoking habits, and variables related to lung size (sex, height, and race). These variables, with the exception of race, are shown in Table 3. There are no significant differences in these variables by exposure groupings. The differences in the first three groups of variables (age, months employed, and smoking habits) are too small to explain the differences in $FEV_{1.0}$.

The final group of variables were placed together because they all relate to lung size. Women on average have smaller lungs than men. Lung size also varies according to height and racial origin. The absolute amount of decrement in $FEV_{1.0}$ may be dependent upon the size of the lungs. If so, and if these variables were selectively distributed by exposure groupings either individually or in combination, they might account for the differences ascribed to exposure. A review of sex and height distribution (Table 3) shows that there are some differences. The variability in racial origin in this population was described in an earlier publication (Wegman *et al.*, 1974).

To standardise for lung size the loss in $FEV_{1.0}$ over two years was divided by the absolute $FEV_{1.0}$ measured on Monday morning in 1972. The differences in the standardised $FEV_{1.0}$ in the three exposure groups shown in Table 4, was still significant at P < 0·03. Therefore lung size has only a minor effect, if any, and does not account for the greater decrement in $FEV_{1.0}$ with higher exposures.

As none of the possible confounding variables explain the differences, we conclude that the excessive loss of pulmonary function is a result of exposure to TDI at levels at least as low as 0·0035 ppm and possibly as low as 0·002 ppm.

The findings in the longest prospective study of TDI workers to date (Adams, 1975) are not consistent with those presented here. Adams concluded that long-term exposure to low levels of TDI did not affect lung function. Although exposure values are not reported, it is suggested that most exposures during the majority of the nine-year study period were below 0·02 ppm. There are several possible reasons for the different results.

The assessment of chronic loss in lung function, specifically decrease in $FEV_{1.0}$ and its association with the workplace, has to be approached with care. In some studies of occupational lung disease we have found that the ascertainment of duration of employment or the presence or absence of possible exposure together with a measurement of lung function are sufficient to evaluate the effect of expo-

sure on loss of lung function. These, however, have not proved to be sufficient in our TDI studies.

The careful use of environmental measurements, even those well below the current TLV of 0·02 ppm has proved essential in analysis of TDI-exposed populations. In this study, no difference in loss of $FEV_{1.0}$ was found when months employed was used as the index of exposure. However, when subjects were classified by usual TDI exposure level, a dose-related effect became evident at a level below the current TLV. Furthermore, acute losses in $FEV_{1.0}$ up to 1·81 litres have been noted in TDI-exposed populations (Peters *et al.*, 1969). At high exposures significant acute losses occur every day (Gandevia, 1963). At lower exposures (0·02 ppm) acute losses occur at least on the first day of the work week (Peters *et al.*, 1969). As some recovery occurs overnight we have found it necessary to make the interval between last exposure and pulmonary function testing as long as possible (at least a weekend) to best approximate baseline function.

In the light of this experience we compared Adams' methodology to our own. First, we observed that area and not personal monitoring was performed and that no exposure level groupings were established. Secondly, he performed his lung function examinations in the afternoon so that measurement of lung function was not baseline and does not account for the possible contribution of the varying acute response occurring during the nine-year period. Finally, his evaluation of lung function loss used regression analysis and not paired differences. The latter is more sensitive for comparing an individual's change over time in contrast to considering each measurement independently as in regression analysis. With these differences in methodology we do not believe that his findings can reliably be interpreted as showing no effect.

Finally, another study population (Peters, 1970), showed a highly significant correlation between measurement of acute decrease in $FEV_{1.0}$ and subsequent chronic loss. In this two-year study, the correlation coefficient (r) for the restudied population was 0·35. This value, although highly significant ($P < 0·005$), is smaller than that found in our first population. The finding of a significant correlation between acute and chronic loss suggests that careful monitoring of acute change in $FEV_{1.0}$, on a day following at least two days' non-exposure, deserves consideration as a medical screening test. Any person who shows a large acute decrement should be re-examined at six-month intervals to detect any early excessive chronic loss. However, if exposure levels are kept continuously below 0·0030 ppm, the finding of significant acute or chronic loss in $FEV_{1.0}$ should be rare.

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