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Epidemiology of Toluene Diisocyanate (TDI)-Induced Respiratory Disease

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This paper describes our experience with the respiratory effects of TDI. Five respiratory reactions attributable to TDI are described with supporting evidence. The reactions are sensitization, irritation from overexposure, acute loss of ventilatory capacity, accelerated loss of pulmonary function and induction of a general asthmatic state. Evidence is presented that suggests a safe exposure level.

In our plastic world, polyurethanes have achieved great commercial importance. The production of polyurethane involves the combination of chemicals containing two highly reactive isocyanate groups with a polyol. It is during this mixing and foaming process that the isocyanates are evolved into the workroom atmosphere. Depending on plant configuration and ventilation, few or many workers can be exposed. Other significant exposures may occur in industrial chemical laboratories and during repair or cleaning of the equipment. The products are used primarily as cushioning materials (mattresses, pillows, seat cushions, and packing materials), for insulation (thin-walled refrigerators and ovens), for soft toys, and for surface coatings (varnishes and paints).

The diisocyanates have been of concern to industrial toxicologists since the 1940's, and the first clinical report of health consequences appeared in 1951 (*1*). Since that time, cases have been reported from many parts of the world. The clinical features were admirably summarized in 1963 (*2*). Toluene diisocyanate (TDI) is the most commonly used isocyanate; unfortunately, because of its volatility it is also the most hazardous.

In many affected workers the characteristic pattern of bronchial asthma is present as the initial manifestation. Overexposures to TDI, usually as the result of accidental spills, will almost invariably produce respiratory irritation. Often eye, nose, and throat irritations are the first clinical manifestations. Dry cough with chest pain or tightness follow. The cough is characteristically worse in the evening or at night, often obscuring its occupational cause. Chest x-rays taken during the acute stage are usually interpreted as normal, although increased markings and patchy infiltrates are occasionally seen. The clinical picture can then approximate bronchitis, bronchiolitis, bronchial asthma, or pneumonitis.

After exposure stops, recovery is usually rapid. With re-exposure to even minimal amounts of TDI, workers manifesting bronchospasm may experience a worsening of symptoms, can no longer tolerate exposure and leave the industry.

We became interested in workers who did not leave the industry but who stayed and were continuously exposed to low levels of TDI. Gandevia's observation (*3*) that relatively high concentrations of TDI produced workshift loss of ventilatory capacity prompted us to look for this reaction at "safe" levels.

Of 38 workers, 34 experienced decreases in forced expiratory volume in 1 sec (FEV_1) while peak air concentrations for TDI were 0.003 ppm (0.02 ppm is considered the safe ceiling level). Workers exposed to TDI, in contrast to cotton workers, had no chest tightness or shortness of breath while sustaining

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comparable changes in FEV_1. Asymptomatic decreases of as much as 1.8 liters in FEV_1 have been observed over one workshift (*4*).

The question of whether long-term, low-level exposure to TDI produces chronic pulmonary impairment has received recent attention. McKerrow, Davies, and Jones (*5*) examined 22 men who had 2.7 yr average exposure to low levels of TDI and found that of several pulmonary function tests the FEV_1 was depressed below predicted normal. Hill (*6*) noted that bronchitis was more common among workers exposed to isocyanates than among controls. Adams (*7*) observed annual deterioration of vital capacity (FVC) and FEV_1 exceeding that expected from aging.

Our approach to determining the possible chronic effects of TDI was the following. When the data on ventilatory capacity from cross-sectional and longitudinal studies of pulmonary disease are examined, some very interesting facts are revealed. First, groups, unlike individuals, behave in a very predictable way. Table 1 summarizes and simplifies this idea. Several studies have revealed that an expected decrement for FEV_1 for a normal population is about 25 ml/yr. Whether this decline is perfectly linear over a life span is arguable, but the available data suggest that it approximates linearity. If one extrapolates this 25 ml/yr loss for 40 yr (approximately a man's working lifetime), one can see that at age 20 the FEV_1 is 4.0 liters and at age 60 the FEV_1 is 3.0 liters. The FEV_1, representing an index of the capacity of the lung, is a potentially powerful tool for determining the chronic disease potential of a given occupational exposure. This is particularly so for diseases which are largely dose-dependent and/or those in which host variability is relatively unimportant and for which no other special diagnostic characteristic appears early in the course of the disease.

Table 1. Expected decrement in ventilatory capacity.

	Decrement in FEV_1, l./yr	FEV, liters	
		Age 20	Age 60
Normal[a]	0.025	4.0	3.0
Chronic obstructive lung disease[b]	0.080	4.0	0.8

[a] Data of Kory (*8*), Ferris (*9*), Rosenzweig (*10*), Fletcher (*11*), Higgins (*12*), Morris (*13*).
[b] Data of Medical Research Council (*14*), Howard (*15*), and Burrows (*16*).

In contrast to normal losses the annual decrement for patients with chronic obstructive lung disease is much greater as seen in several studies conducted in Great Britain and the United States (see Table 1). It would appear from these studies that the development of chronic obstructive lung disease is a slow, insidious process taking many years to develop, especially when observed in a population of affected persons. The FEV_1 decrements in these groups of sick persons range from 0.079 to 0.084 l./yr. If one extrapolates again from age 20, at which time the FEV_1 is approximately 4.0 liters, to age 60, the FEV_1 has fallen to 0.8 liters.

With these facts in mind we followed a cohort of workers exposed to low levels of TDI for 3 yr. We measured their ventilatory capacity annually on a Monday morning after a weekend of no exposure and before exposure had begun on that day.

At one year we found a fall of 0.12 liters in the FEV_1. A similar decrement was approximated in the second year, and by the end of the third year it was clear that the decrement was a persistent 120 ml/yr.

It is clear that this rate of decrement is excessive and strongly suggests that TDI has a chronic disease potential. In addition the acute reaction seen over one shift correlates highly with subsequent long-term decrement ($r = 0.71$). This has important implications for the screening, control, and surveillance of exposed workers. It is also a large enough correlation for a safe level of continued exposure to be estimated on the basis of acute reactions to TDI.

The correlation between acute, workshift decreases in FEV_1 and cumulative decrements over 3 yr led to a study designed to examine the possible dose–response relationship for acute effects.

A total of 111 workers exposed to TDI were examined during a work shift. Their ventilatory capacity was measured before and after the shift on a Monday. Their exposures ranged from 0.002 ppm to 0.013 ppm. Workers were divided into four groups over this exposure range. All four groups demonstrated significant declines in FEV_1 with the magnitude of de-

crease correlating with level of exposure (Table 2).

Table 2. Levels of TDI exposure.

Mean TDI concentration, ppm	Group	n	Mean change in FEV_1, liters	SD	p
0.002	A	51	0.078	0.173	0.01
0.003					
0.004	B	24	0.112	0.155	0.01
0.005	C	19	0.106	0.165	00.2
0.006					
0.007					
0.009	D	17	0.180	0.185	0.01

To verify this, a stepwise regression analysis was performed which revealed one independent variable to contribute significantly to the explanation of variance. That factor was magnitude of exposure (Table 3).

Table 3. Stepwise regression analysis for determinants of mean change in FEV_1.

Independent variable	Magnitude of exposure[a]	(Constant)
B[b]	0.014	0.048
SE of B	0.066	
r^2	0.04	
F value	4.70	
p	0.05	
Analysis of variance		
$D=1$		
Sum of squares	1,331.5	
Mean square	1,331.5	
F	4.70	
$D=109$		
Sum of squares	30,883.6	
Mean square	283.3	

[a] No other variable was significant determinant.
[b] Positive value denotes negative mean change in FEV_1.

In an attempt to gain some insight into the mechanism and possibly to determine which workers would be most likely affected by exposure to TDI, we measured circulating eosinophil levels Monday morning prior to exposure and again on Wednesday morning. On the same workers, FEV_1 was measured before and after their Monday shift. There was a statistically significant rise in absolute eosinophil count and a statistically significant fall in FEV_1. The two were correlated (Table 4).

Unfortunately, knowledge of the eosinophil level prior to exposure to TDI was not predictive of the magnitude of decrease in FEV_1.

Table 4. Relationship of eosinophilic response to change in ventilatory capacity (FEV_1), males only.[a]

	Eosinophils		
	Decrease	Increase	
FEV_1 increase	8	3	11
FEV_1 decrease	5	14	19
	13	17	30

[a] $\chi^2 = 4.37$, $p < 0.05$

We conclude that while eosinophils may be involved in the mechanism of pulmonary response leading to change in ventilatory capacity, the use of eosinophil counts in surveillance of workers exposed to TDI does not appear useful.

Another important observation concerns what appears to be the induction of a general asthmatic state by TDI. Some workers "sensitized" to TDI appear to be specifically reactive only to TDI such that cessation of exposure solves their bronchospastic problem. On the other hand, we have seen several workers "sensitized" to TDI in whom a general asthmatic state exists. Following the induction of this state the individuals behave as ordinary asthmatics being affected by pollens, smoke, cold, anxiety etc. These cases frequently occur in persons with no personal or family history of atopy. The "natural" incidence of adult-onset asthma is not known but it seems clear that excessive numbers come from populations exposed to TDI.

Summary

It appears that there are at least five describable patterns of respiratory reaction to TDI. They are not necessarily mutually exclusive.

The first and most widely recognized is that of TDI sensitization. In our experience approximately 2.5% of workers exposed to "safe" levels will develop asthmatic symptoms each year. Following development of this state, no further exposure to TDI is tolerable.

Another respiratory reaction is that of chemical bronchitis following overexposure usually as a result of an accident. Sensitization as described above does not necessarily follow.

The fall in ventilatory capacity seen over a workshift constitutes another reaction to TDI and because of its correlation with accelerated

loss of pulmonary function described below, is important for screening and surveillance of workers.

TDI appears to accelerate loss of pulmonary function. Prolonged exposure could thus result in the indidious development of chronic obstructive lung disease.

The incidence of adult-onset asthma appears to be excessive from populations exposed to TDI.

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