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Persistence of Toluene Diisocyanate-Induced Asthma Despite Negligible Workplace Exposures*

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Six polyurethane foam workers were shown to have TDI-induced asthma by specific inhalation challenge testing. All remained in the workplace in jobs with minimal TDI exposures. Mean and time-weighted average exposure concentration for the asthmatic group was 0.64 ± 0.46 ppb, less than 5 percent of the permissible exposure limit and significantly less ($p<0.01$) than the mean TWA exposures occurring in the foam line and the finishing workers. Serial evaluation of the respiratory health of these six showed all persisted with respiratory symptoms, none had improvement in bronchial hyperresponsiveness to methacholine, and three had a greater than 15 percent decline in FEV_1 on one of the days of spirometric testing over the five-year period from 1982 to 1986. Although we could not have predicted the outcome of asthma had these workers left the workplace and ceased isocyanate exposure entirely, occupational asthma persisted despite negligible ongoing TDI exposures. *(Chest 1990; 97:121-25)*

TDI = toluene diisocyanate; TWA = time-weighted average; FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity; PD20 FEV_1 = cumulative dose provoking a 20 percent decrement in FEV_1

Toluene diisocyanate is a low molecular weight chemical used primarily in the manufacture of flexible polyurethane foams. Workplace exposures to this agent can cause asthma.[1] Among TDI workers, asthma caused by this agent has been reported to be relatively commonplace. A 1977 report showed workplace-induced asthma present in approximately 5 percent of TDI production workers.[2]

On a practical level, when a worker is found to have TDI-induced asthma, the counselling physician is called on to assess whether the worker can remain in the workplace. One strategy, without the social and financial implications of discharging the worker and the legal implications to the company, is to move the sensitized worker from his usual workplace area to a part of the workplace recognized to have no or negligible TDI exposure.

In the course of an epidemiologic survey of the respiratory health of workers using TDI to produce polyurethane foam, we performed serial assessments of six workers with challenge test-proven TDI-induced asthma transferred within the workplace where TDI exposures were thought to be negligible or absent.

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Materials and Methods

Population

A longitudinal study designed to assess the respiratory health risks associated with TDI involved 307 employees at two plants that produced polyurethane foam.[3] In 1982, six of these workers were proven TDI-sensitive by inhalation challenge testing, using a protocol reported elsewhere.[4] We reviewed the job histories of these six, and annually administered a respiratory questionnaire from 1982 to 1985. We determined work location within the plant and measured lung function and methacholine responsiveness yearly from 1982 to 1986. Personal TDI exposures also were measured during these years.

Questionnaire

A modified Medical Research Council respiratory questionnaire[5] was administered yearly to assess smoking habits and respiratory symptoms to describe: (1) lower respiratory symptoms—usual cough, usual wheeze, current attacks of dyspnea with wheeze or dyspnea while talking with other people; (2) upper respiratory symptoms—drip at the back of the nose or sinus trouble for at least three months; (3) chronic bronchitis—usual cough and phlegm for more than three months per year; and (4) dyspnea, grade 2 or higher—grade 2 = dyspnea while hurrying on level ground and grade 3 = dyspnea when walking with others one's own age. We also inquired about current medications at each yearly interview.

Pulmonary Function tests

Pre- and post-shift spirometry was performed using the Pulmolab model 5000 (Cardio-Pulmonary Instruments, Houston, TX) which includes a dry rolling-seal spirometer. An across-shift decline of 15 percent or greater in the FEV_1 was considered significant. At each testing session, subjects performed at least three satisfactory forced expiratory maneuvers, with the two largest FVC values within 5 percent of each other. From the two tests with the largest sum of FEV_1 and FVC, mean FEV_1 and FVC were expressed as percent predicted.[6]

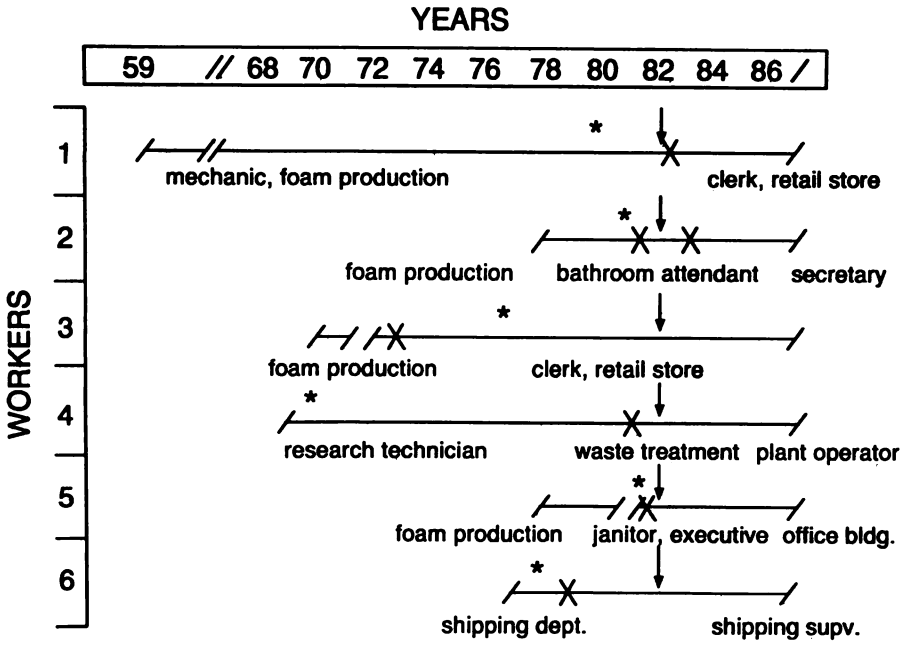

FIGURE 1. This figure reports a summary of job histories within the polyurethane foam manufacturing plants for the six asthmatic subjects. The *asterisk* notes the year of developing respiratory symptoms; the *arrow* reflects the date of TDI challenge testing; and the *X* marks the date of job change in the workplace.

Measurement of Bronchial Responsiveness to Methacholine

Using a modification of the French-Rosenthal dosimeter method,[3] nebulized methacholine dilutions were administered. The FEV_1 was measured using a Pulmonaire bellows spirometer (Jones Medical Instruments Co., Oak Brook, IL). Following baseline FEV_1 measurements, the maximal FEV_1 was determined from three expiratory maneuvers, five minutes after each incremental dose of methacholine. The initial methacholine dose was 0.3 cumulative methacholine inhalation units (five breaths of 0.6 mg/ml solution), with doubling concentrations to a maximum of 640 cumulative methacholine inhalation units or until a 20 percent decline in the FEV_1 compared with baseline occurred. The PD20 FEV_1 was used to describe the degree of bronchial responsiveness to methacholine.

Personal TDI Measurements

The TDI exposures were measured using the model MCM continuous paper tape monitor (MDA Scientific, Lincolnshire, IL). In order to improve response and resolution of the monitor, it was altered to collect sequential samples.[7,8] As modified, the MCM monitor collected samples of 12-minute duration every 36 minutes. Exposures were measured from the start to approximately 30 minutes prior to the end of the work shift. Monitors were worn at the worker's waist and inspected occasionally to be certain the instrument was positioned appropriately and functioned properly. At the completion of sampling, the tape was removed and examined for contamination by interfering materials. Stains thought to represent contamination were not used in calculating TDI exposure. The TDI samples were quantitated by passing the paper tape through a Model 4100 Reflectance meter (MDA Scientific, Lincolnshire, IL). For 1982, the average lower limit of detection was 1.0 ppb for the 12-minute sampling period. In subsequent years, this meter was modified and the average lower limit of detection decreased to 0.5 ppb. For calculation of the TWA concentration, 12-minute samples without detectable TDI were assigned values one half the lower limit of detection.

We compared TDI exposures of the six asthmatic subjects with two other groups of workers. The first group was the foam line workers (n = 49), employees involved in foam production and likely to have the highest exposures. The second group was the finishing workers (n = 132), employees who work away from foam production with exposures typically arising from general background levels of TDI. Mean and standard deviation TWA concentrations for these three groups were compared using Tukey's multiple comparison test.[9] A p value of 0.05 or less was considered statistically significant.

RESULTS

Job histories within the polyurethane plant for the six asthmatic subjects are reported in Figure 1. The primary occupation in the plant was foam manufacturing. The retail foam store was approximately one hundred yards from the foam plant. The office building was adjacent to this store. Secretarial employment was on the second floor of a small administrative building attached to the foam production facility. The waste treatment facility was off-site. Finally, the shipping supervisor worked on the loading dock in the shipping department but with less direct interaction with manufactured foam than those who loaded trucks and rail cars. At least since 1982, all six asthmatic subjects worked in areas thought to have negligible or no TDI exposure.

None of these six workers had respiratory or asthmatic complaints prior to employment in this workplace. Workers 1, 3, 4 and 5 were never smokers or had not smoked in 15 years. Worker 2 smoked one-half package and worker 6 smoked one-third package of cigarettes daily. No worker changed smoking habits during the four years the questionnaire was administered.

Resolution of respiratory complaints did not occur during this time (Table 1). Worker 1 required beta agonist inhalation therapy and theophylline for the first two years and then cromolyn sodium was added to the regimen. Worker 2 required treatment with theophylline and beta agonist inhalers when first tested, but discontinued theophylline in the latter

Table 1—*Lower Respiratory Symptoms, Upper Respiratory Symptoms, Bronchitis and Dyspnea**

Worker	1	2	3	4	5	6
1982	+/−/−/−	+/+/−/−	+/−/−/+	+/−/−/−	+/−/+/+	+/+/+/−
1983	+/+/−/−	+/+/−/−	+/−/−/+	+/+/−/−	+/−/+/+	+/+/−/−
1984	+/+/−/+	+/+/−/−	+/−/−/+	−/+/−/−	ND†	+/+/−/−
1985	+/+/−/−	+/+/−/+	+/−/−/−	+/+/−/−	+/+/+/+	+/+/−/−

*The presence (+) or absence (−) of lower respiratory symptoms, upper respiratory symptoms, bronchitis and dyspnea are serially reported for the four years the questionnaire was administered.
†ND = not done.

years of the study. Workers 3, 4 and 6 used only a beta agonist inhaler on an as-needed basis during this period. Finally, worker 5, when first evaluated, required inhaled beclomethasone, beta agonist inhalations and theophylline to control his asthma. Later, the addition of oral prednisone therapy was necessary due to continuing respiratory complaints.

Pre- and post-shift lung function tests are reported in Table 2. Three of the six workers had a greater than 15 percent FEV_1 decline on one of the days of testing during this five-year period.

Changes in bronchial responsiveness over time are plotted in Figure 2. All six had bronchial hyperresponsiveness to methacholine with PD20 FEV_1 less than 30 cumulative methacholine units. Resolution of bronchial hyperresponsiveness to methacholine was not measured in any of these six workers.

Eleven TDI personal samples were obtained in these six asthmatic subjects from 1982 to 1986. Three shifts were monitored for two workers, two shifts for one worker and one shift was monitored for the remaining three workers. For the 94 12-minute increments of exposure, 84 (88 percent) were 1.0 ppb or less and detectable only 35 percent of the time. Mean and SD for the 11 TWA concentrations was 0.64 ± 0.46 ppb, with the TWA of only one of the 11 shifts sampled exceeding 1.0 ppb. In that case, exposure exceeded 5 ppb for 13 percent of the sampling period (an exposure of 6.4 ppb).

For 49 foam line workers, TDI exposures during 89 shift-long samples (920 12-minute samples) were measured. Mean ± SD TWA was 3.82 ± 5.51 ppb. For 132 finishing workers, mean ± SD TWA was 1.35 ± 1.03 ppb for 236 shift-long measurements (2,308 12-minute samples). Mean exposures for the foam line and finishing workers differed significantly ($p<0.01$) from those of the six asthmatic subjects.

Figure 3 illustrates the distribution of the short-term (12-minute) TDI exposure samples by group of workers. These samples were categorized by percentage above the lower limit of detection, greater than 5 ppb and greater than 20 ppb, and show differences in exposure in these groups by these categories.

Discussion

Five of the six workers with TDI-induced asthma were moved to areas with negligible TDI exposures. Worker 3 developed asthma while working in an area thought to have negligible or no exposure. The need for less or additional asthma therapy in these six workers was not predictable. Although bronchial responsiveness persisted in these six subjects, there was no clear trend toward increasing or decreasing responsiveness during this study. The lung function changes of these asthmatic subjects showed changes similar to the bronchial responsiveness measurements. The TDI exposures for the asthmatic group were minimal and significantly less than exposures in the rest of the workplace, implying that these workers were segregated from the main work force. Mean TWA for the asthmatic group was less than 5 percent of the Occupational Safety and Health Administration permissible exposure limit of 20 ppb, yet chest symptoms and bronchial hyperresponsiveness persisted.

The natural history of TDI-induced asthma is not clearly defined. Two case reports have shown resolu-

Table 2—*Pre- and Post-shift FEV_1 Values**

Worker	1	2	3	4	5	6
1982	113/115	123/111	83/84	82/81	70/ND	118/110
1983	111/109	120/112	84/75	76/75	81/82	109/83‡
1984	119/109	110/111	77/76	82/86	ND	101/97
1985	122/119	105/112	83/83	84/81	77/71	110/112
1986	ND†	102/110	86/46‡	ND	85/71‡	104/109

*FEV_1 expressed as percent of predicted.
†ND = not done.
‡FEV_1 decline greater than 15 percent of pre-shift value.

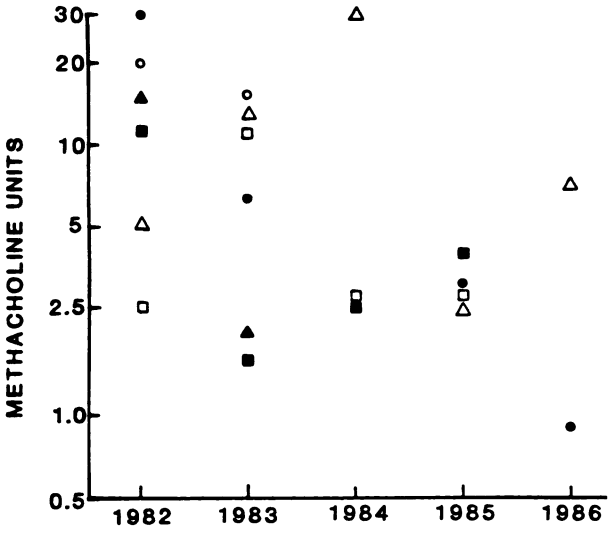

FIGURE 2. This figure plots bronchial hyperresponsiveness (PD20 FEV_1) by year for each of the six asthmatic subjects. Worker 1 is denoted by an *open circle*; worker 2 by an *open triangle*; worker 3 by an *open square*; worker 4 by a *solid square*; worker 5 by a *solid triangle*; and worker 6 by a *solid circle*. Not all workers performed methacholine testing each year.

tion of airway hyperresponsiveness to TDI by specific inhalation challenge tests. Butcher et al[10] reported a worker with TDI-induced asthma who lost bronchial hyperresponsiveness to methacholine 11 months after leaving the workplace and TDI reactivity within two years after ceasing TDI exposure. Banks and Rando[11] reported a worker who had recovered from the symptoms of TDI-induced asthma after five years and was specific challenge-test-negative after 11 years.

Numerous investigators have studied workers to

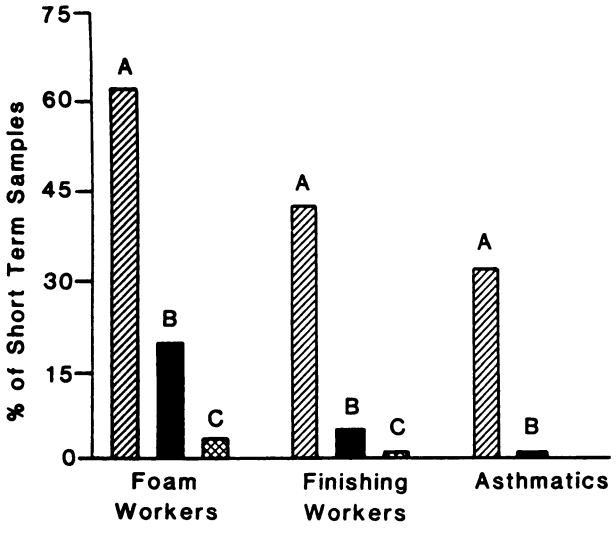

FIGURE 3. Distribution of short-term (12-minute) exposures to TDI among the foam line workers, finishing workers, and asthmatic subjects. *A* reflects the percentage of samples with a TDI concentration above the lower limit of detection. *B* reflects the percentage of samples with a TDI concentration greater than 5 ppb. *C* reflects the percentage of samples with a TDI concentration greater than 20 ppb.

assess the outcome of occupationally induced asthma. The results have not been uniform. A study by Hudson et al[12] showed a reasonably good outcome for TDI-induced asthma. This group reported 63 workers with occupational asthma caused by numerous agents for at least six months after ceasing exposure.[12] Resolution of symptoms appeared to depend on the causative agent. In general, those with snow crab- and TDI-induced asthma did better (only two of ten with isocyanate-induced asthma had persistent symptoms), while those with Western red cedar-induced asthma did poorly. A later study done by this group specifically addressed the outcome of snow crab-induced asthma approximately five years post-diagnosis.[13] At follow-up, 10 of 31 workers sensitized to snow crab required asthma medication (primarily beta agonist inhalers); only two of 31 had an FEV_1 less than 80 percent predicted; yet bronchial hyperresponsiveness persisted, but declined, in the majority of participants. Since outcome of occupational asthma may be related to the agent causing asthma or the mechanism by which it occurs, it may be difficult to extrapolate the work of Chan-Yeung et al[14] showing the relatively poor outcome of asthma due to Western red cedar and that of Burge[15] regarding the poor respiratory fate of asthma induced by colophony to the outcome associated with isocyanate-induced asthma.

Yet, most studies reflect the poor outcome of isocyanate-induced asthma. Paggiaro et al[16] studied 27 workers with TDI-induced asthma approximately two years after diagnosis. Although symptoms of dyspnea and wheeze were less frequent in the 12 that had left the industry, only four were without respiratory symptoms. In just one of 15 who remained in the workplace did resolution of respiratory complaints occur. More than half who remained developed chronic cough with phlegm. No data stating whether those who remained in the workplace were moved to jobs associated with lesser TDI exposures was provided.

Moller et al[17] reported seven workers with TDI-induced asthma. In six, asthma persisted for as long as 12 years (mean, 4.5 years) despite leaving the workplace. Lozewicz et al[18] suggested many with isocyanate-induced asthma persist with respiratory complaints. Forty-one of 50 workers away from isocyanate exposure for at least four years continued with respiratory complaints and 22 required respiratory medication at least once weekly. In these workers, the frequency of complaints was similar among workers who had left the workplace and in those who had relocated in their original workplace to jobs without recognized direct isocyanate exposures.

Only one study measuring TDI sensitivity both at diagnosis and follow-up has been reported. Mapp et al[19] reported repeat testing of 35 workers with TDI-induced asthma at a mean follow-up of ten months.

Eight of 30 who had left the workplace lost TDI reactivity at follow-up testing.[19] Five who remained in the same jobs had persistent asthma. Those who recovered from TDI sensitization were younger, had a shorter duration of exposure and symptoms prior to diagnosis and were more likely to have either an immediate or dual asthmatic response. At follow-up, those who recovered had significantly less bronchial responsiveness to methacholine and a significant increase in FEV_1.

We recognize the outcome of isocyanate-induced asthma to be variable. It is possible that respiratory symptoms of these six subjects would have persisted despite ceasing exposure. Although we could not have predicted asthma outcome had these workers left the workplace and ceased isocyanate exposure entirely, occupational asthma persisted despite negligible TDI exposures. It appears that the best chance for altering the outcome of isocyanate-induced asthma is avoidance of further workplace exposure to this sensitizing agent.

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