

Occupational Asthma, Lung Function Decrement, and Toluene Diisocyanate (TDI) Exposure: A Critical Review of Exposure-Response Relationships

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An extensive amount of clinical/epidemiological literature exists regarding the effects of toluene diisocyanate (TDI) exposure on respiratory health. This review presents an evaluation and synthesis of that literature with an emphasis on assessing exposure-response relationships in the workplace. The key respiratory disorders examined are bronchial asthma and an accelerated decline in lung function. In the early years of the industry, annual incidence rates of TDI-induced occupational asthma (OA) were as high as 5–6 percent. In settings where mean TDI concentrations have been maintained below 5 ppb based on 8-hr personal samples, OA incidence rates have declined to <1 percent annually. Recent data also suggest that overexposure incidents may play an important role in inducing OA, particularly in work environments engineered to minimize routine ambient air concentrations. Fourteen studies were reviewed that examined lung function decrement. Early studies from the 1960s and 1970s provided evidence of transient or fixed lung function loss (measured as a decline in forced expiratory volume in one second [FEV1]) during periods of ongoing exposure among employees experiencing high rates of work-related symptoms of OA. Such findings would not be unexpected in that modest FEV1 declines have been demonstrated in general population studies of persons with bronchial hyperresponsiveness or persistent non-occupational asthma. More recent workplace studies have provided no consistent evidence of accelerated FEV1 loss among employees exposed up to 5 ppb TDI (8-hr TWA) even with documented routine short-term TDI concentrations exceeding 20 ppb TDI.

Keywords Toluene Diisocyanate, Occupational Asthma, Dose-Response Assessment, Lung Function Decrement

Toluene diisocyanate (TDI) is an important chemical intermediate used in producing flexible polyurethane (PUR) foams

and other products such as surface coatings, cast elastomers, sealants, and adhesives.⁽¹⁾ The dominant commercial product is an 80:20 mixture of the 2,4- and 2,6-isomers, respectively. Over the years, numerous reports have been published regarding adverse respiratory health effects due to TDI exposure in the workplace. These have ranged from reports of case histories to those of analytical epidemiological studies. In this review, studies contributing to an understanding of exposure-response relationships between TDI and both occupational asthma and lung function decrement will be examined with the aim of narrowing uncertainties regarding those relationships.

OVERALL APPROACH

Selection of studies for consideration in this review was based on criteria discussed below, use of Medline searches including toluene diisocyanate and occupational asthma as key search terms, and review of earlier literature including National Institute for Occupational Safety and Health (NIOSH) Criteria Documents for Toluene Diisocyanate and Diisocyanates^(2,3) and other governmental review documents. In addition, NIOSH Health Hazard Evaluations for the years 1981–1996 were reviewed to identify exposure assessment studies regarding TDI. Five key criteria were used in screening and weighting studies to be included in this discussion. These were 1) adequacy of the assessment of TDI concentrations in the workplace, 2) quality of the health outcome data, 3) use of a longitudinal rather than cross-sectional study design, 4) size of the study and duration of longitudinal follow-up, and 5) inclusion of a non-exposed referent group for assessing internal and external validity. In addition, it was decided to assess studies conducted in the TDI manufacturing and using industries separately. This was done because of considerable differences in the respective work settings. These included distinct sets of possible confounding exposures, open-air construction of TDI production units versus enclosed construction of TDI-using facilities, and differing job tasks and exposure circumstances associated with the respective industries.

Exposure Assessment Considerations

There have been marked improvements in both sample collection and analysis procedures for measuring TDI concentrations over the years. During the 1950s and 1960s, sampling was mostly carried out using fixed area monitors, and analyses were performed by colorimetric methods subject to interference and underestimation of the 2,6-isomer.^(4,5) It has been estimated, for example, that the Marcali colorimetric method may underestimate the 2,6-isomer by nearly 50 percent.⁽⁴⁾ In the flexible foam industry, underestimation of total TDI concentrations could have been considerable, as the 2,6-isomer predominates in ambient air of finishing areas of these facilities.^(4,6) This occurs because the 2,4-isomer is more apt to be consumed in chemical reactions during foam production.

Since the mid-1970s, there has been increased use of 1) personal sampling to assess workplace TDI exposures, 2) continuous paper-tape monitoring to evaluate short-term as well as long-term average TDI concentrations,⁽⁷⁾ and 3) high performance liquid chromatographic (HPLC) methods that increased the analytical precision of the measurements and enabled separate determination of TDI isomers.⁽⁸⁾ These developments led to more reliable estimates of both short-term and 8-hr time-weighted average (TWA) concentrations and more consistency in the reporting of personal exposure concentrations across studies. For these reasons, the most relevant health studies for the purposes of this review are those conducted since the mid-1970s.

Respiratory Health Outcomes

The two main respiratory conditions linked to repeated TDI exposure are bronchial asthma (a disease of the bronchi and smaller airways characterized by inflammation, bronchial hyperresponsiveness [BHR], and reversible airway obstruction) and accelerated loss of lung function (considered to be a consequence of chronic airway inflammation and individual susceptibility). Hypersensitivity pneumonitis (an allergic disease of the terminal airways and lung) is a third respiratory condition linked to diisocyanate exposures that will not be reviewed as it has only occasionally been noted in connection with TDI exposure.⁽⁹⁻¹⁷⁾

In the workplace, asthma is induced mainly by allergic mechanisms, but can also be caused by severe irritant exposures. Occupational asthma (OA) due to TDI may be defined as a condition of airway inflammation and BHR caused by TDI exposure and manifesting itself as reversible air flow obstruction upon re-exposure to very low TDI concentrations. A bronchial provocation challenge to known sub-irritant TDI concentrations is regarded as the "gold standard" in diagnosing the condition. Even so, Malo has shown that multiple day exposure protocols may be required to elicit a response in some individuals.⁽¹⁸⁾ Bronchial responses may be early (occurring within minutes of exposure to a threshold dose), late (measured in hours after exposure to a threshold dose), dual, or atypical, with late responses being more frequent with TDI. OA due to TDI may develop after a la-

tent period during which sensitization is acquired or after single exposures to highly irritating concentrations.

Case definitions of OA have varied widely across epidemiology studies and have often relied on subjective criteria such as self-reported symptom histories. However, the same can be said of asthma studies in general.⁽¹⁹⁾ Malo pointed out that, whereas 88 percent of subjects with proven OA reported symptoms improved during holidays, 76 percent of subjects without OA reported a similar improvement in symptoms during holidays.⁽²⁰⁾ In two large series of patients referred for OA evaluation because of suspect symptom profiles, between 30 and 41 percent could be confirmed by TDI challenge.^(21,22) Objective criteria for confirming an OA case due to TDI would include serial monitoring of peak expiratory flow during and after a workplace challenge, bronchial provocation challenge in a medical setting, and immunological tests to identify TDI-specific antibody responses. Given the range of case definitions used in various studies and differing efforts to confirm cases through objective tests, it is not surprising that considerable variability in the incidence of TDI-induced OA may be reported across studies.

The most common measure of air flow limitation employed in epidemiological studies is the forced expiratory volume in one second (FEV1).⁽²³⁾ Because this measure has been consistently reported across lung function studies of TDI-exposed employees and because well-defined criteria have been developed for assuring the quality of these measurements, this was the measure relied upon in this review. Air flow limitation may occur as a result of increased thickness of airway walls, subepithelial fibrosis, obstruction of airway lumen by exudate or mucus, changes in elastic properties of the airway walls, or loss of interdependence between the airways and surrounding parenchyma. The air flow limitation seen in cigarette smokers appears to be mostly related to increased thickness of the airway walls and obstruction of airway lumen by exudate and mucus. An accelerated decline in FEV1 is frequently seen among patients with persistent or severe asthma, regardless of the cause of the asthma.⁽²⁴⁻²⁶⁾ With respect to TDI exposure, accelerated declines in FEV1 could be postulated to occur as a secondary consequence of persistent or severe OA, or as a result of daily exposure sufficient to cause chronic lower airway inflammation.

Other Study Design Considerations

In general, longitudinal studies are regarded as superior to cross-sectional studies because exposure can be linked to change in health outcome during a relevant time period. With a longitudinal study, the incidence of new onset OA may be estimated as a function of the person years of observation. With cross-sectional studies, the prevalence of OA cases can be estimated at a point in time, but to obtain incidence estimates would require further information or assumptions about employee turnover and dates of OA onset. Similar issues arise in assessing lung function decline over time. For these reasons, preference has been given to longitudinal studies in this review.

Greater precision in effect estimates is associated with either larger sample size or increased length of follow-up or both. Although no formal analytical procedures were used to combine effect estimates across studies, again higher weightings have been accorded the larger studies with longer follow-up. These same studies were more likely to be supported by detailed exposure assessments and to have been conducted in more recent years.

Use of a control group with no exposure to TDI can provide both an internal and external benchmark for judging the quality of a study. Several of the earlier TDI studies lacked internal controls, which contributed to a downgrading of these studies. Studies were judged in the context of how potential confounding issues were handled such as exposure to other agents in the workplace (e.g., phosgene in TDI manufacturing and amine catalysts in flexible foam facilities) or other factors influencing respiratory health such as cigarette smoking.

DISCUSSION OF STUDIES

TDI Manufacturing Units

Commercial production of TDI began in 1956 in the United States, lagging a number of years behind its commercial development in Europe.⁽²⁷⁾ The U.S. industry expanded rapidly during the first several decades with production increasing by over tenfold between 1960 and 1980.^(27,28) Growth slowed in the last several decades with only a doubling of production between 1980 and 2000.⁽²⁹⁾ There has also been physical consolidation in the industry with production currently limited to 6 active sites within the United States, whereas 10 sites were operating in 1979. Such consolidation should result in fewer employees with potential exposures in these larger automated production units.

TDI Concentrations in Manufacturing Units

Because of the open-air construction of TDI manufacturing units, the potential for exposure generally occurs during the performance of specific job tasks. Tasks associated with high potential exposure include line opening (e.g., that required during transfer of product to tank car, equipment maintenance, or process sample collection), handling of process residues, and laboratory analysis of process samples. Control room operators monitoring the process operation at remote computer terminals would have minimal potential for exposure during normal operating conditions. In characterizing employee exposure, it can be critical to assess short-term TDI concentrations during the performance of specific tasks as well as to collect long-term (4- to 8-hr) samples for TWA determinations. This is particularly the case where adverse health effects may be dependent upon reaching a threshold concentration as opposed to being determined by cumulative dose.

Long-term trends in workplace TDI concentrations have been assessed in five TDI unit studies.^(7,30-33) The two early studies

evaluated TDI concentrations spanning a period from 1956 to 1974 using area monitoring and colorimetric analysis.^(30,31) In both studies, measured TDI concentrations were reported to have declined over the years. In the Adams study, this was reflected by lower percentages of sample readings above 20 ppb,⁽³⁰⁾ whereas in the Porter study, mean TDI concentrations declined from about 60 ppb to <5 ppb over a 16-year period.⁽³¹⁾ No estimates of 8-hr TWA concentrations were available for these studies. However, it is likely that sampling was mostly performed in areas of high potential exposure. The three more recent studies included both short-term and 8-hr TWA exposure estimates and utilized personal sampling with analysis by paper-tape or HPLC.^(7,32,33) During the 1970s, TWAs for unit field operators, loaders, and maintenance personnel averaged between 5 and 10 ppb TDI. TWA estimates were generally below 5 ppb for other jobs. From 1980 forward, mean TWA concentrations were consistently below 5 ppb for all job categories. There was a sharp downward trend in TDI concentrations between the 1970s and early 1980s followed by a slower downward trend after 1980. In one unit that reported data separately by isomer, between 60 and 70 percent of the TDI measured in ambient air was comprised of the 2,4 isomer.⁽³²⁾

The relationship between short-term and 8-hr TWA concentrations was examined in two of the TDI unit studies based on continuous paper-tape monitoring.^(7,32) The number of samples with short-term (9-12 minute averaging time) TDI concentrations >20 ppb per work shift varied by job category and time period in parallel with changes in the corresponding 8-hr TWA estimates. In one unit, the percent of work time spent above 20 ppb was estimated at 3 percent across all jobs and more than 10 percent in jobs with an arithmetic mean exposure of 6.8 ppb TWA.⁽⁷⁾ In this study, more than 50 percent of the time in which short-term concentrations exceeded 20 ppb, they also exceeded 40 ppb TDI. In the other TDI unit, the percent of 8-hr work shifts with short-term concentrations >20 ppb was 0 percent, 36 percent, and 59 percent, in low, moderate, and high potential exposure jobs, respectively.⁽³²⁾ In both of these studies, paper-tape tracings demonstrated the importance of specific job tasks in accounting for total exposure over an 8-hr shift. Utilizing acute exposure incidents reported to the occupational medical clinic, the frequency of non-routine acute exposure incidents was also found to parallel changes in mean 8-hr TWA estimates in the only unit providing such data.⁽³²⁾

Health Outcomes in TDI Production Units

Four longitudinal studies of TDI-induced OA occurrence have been conducted in TDI production units.^(7,30-32) Estimates of TDI concentrations and annual OA incidence rates derived from these studies are summarized in Table I. The study by Adams used a somewhat more ambiguous case definition, and included a higher percentage of cases arising within two months of first employment than the remaining studies. Case documentation was strongest in the Weill study, which utilized inhalation

TABLE I

Estimated TDI concentrations and annual incidence of TDI-induced OA in four longitudinal studies of TDI production units

Study (case criteria)	IH sampling/analysis	Time period	Annual incidence		Sampling results TDI concentrations
			Nbr.	%	
Adams, 1975, N = 565 (removal due to symptoms)	Area samples 1962-70, colorimetric method	1961-70	124	5.6	1962-64 58%-72% of samples >20 ppb 1965-66 4%-21% of samples >20 ppb 1967-70 1%-2% of samples >20 ppb
Porter, 1975, N = 300 (MD assessment)	Area samples 1957-74, colorimetric method	1956-59	11	1.6	1956-57 60 ppb mean area conc.
		1960-69	16	0.8	1960-69 steady decline in area conc.
		1970-74	3	0.3	1974 <4 ppb mean area conc.
Weill, 1981, N = 277 (MD assessment)	Area samples 1973-75, paper-tape;	1973-78	12	1.0	1.6-6.8 ppb TWA (range by job) (STCs >20 ppb 5%-11% of time in moderate to high exposure jobs)
	Personal 1975-78, paper-tape				
Ott, 2000, N = 297 (MD assessment)	Area samples 1967-75, colorimetric method;	1967-79	11	1.8	3.4-10.1 ppb TWA (range by job)
	Personal 1976-96, paper-tape, HPLC	1980-96	8	0.7	0.3-2.7 ppb TWA (range by job) (STCs >20 ppb 0.5-0.9 times/shift in moderate to high-exposure jobs)

STC: short-term concentration (9-12 minutes) measured by paper-tape method.

challenge tests to confirm a number of the OA cases.⁽⁷⁾ The two studies with the longest observation periods reported declining OA rates over time that paralleled decreases in TDI concentrations as well.^(31,32) The annual incidence of OA in the only study reporting observations beyond 1979 was 0.7 percent between 1980-1996.⁽³²⁾ TWA concentrations averaged below 5 ppb TDI for all jobs during this time period. Annual incidence rates above 1 percent appear to be associated with settings in which TWA estimates would have routinely exceeded 5 ppb TDI for employees in high potential exposure jobs.

The relationship between short-term concentrations and OA occurrence was evaluated in two of the studies that utilized paper-tape monitoring to assess TDI concentrations and reported acute exposure events in relation to OA case status as well.^(7,32)

In the Weill study, half the cases were associated with prior documented major exposure episodes, and in the Ott study, both prior acute phosgene and TDI exposures were associated with increased risk of later OA case onset. Also, 9 of the 12 cases in the Weill study⁽⁷⁾ were assigned to jobs in which short-term TDI concentrations would have been expected to exceed 20 ppb from 7-24 minutes/day. One of the remaining three cases had been involved in a major spill episode.

Five longitudinal pulmonary function studies have been conducted in TDI units including three U.S. studies.^(7,30,32-34) Brief descriptions (design and numbers of pulmonary function tests [PFTs] performed and subjects tested) and FEV1 findings are summarized in Table II for each study. The maximum interval between initial determination and most recent FEV1

TABLE II
Reported FEV1 findings among employees assigned to TDI manufacturing units

Study	Design	No. of PFTs/subjects	FEV1 findings
Adams, 1975	Surveillance 1964-73	1,100/180 asymptomatic 61/61 symptomatic no controls	No excess FEV1 loss among asymptomatic employees, lower FEV1 among men removed from unit due to respiratory symptoms
Weill, 1981	Longitudinal 1973-78	669+/223 exposed no controls	No significant relationship of FEV1 to cumulative dose treated as a continuous variable, relative FEV1 decrease in high- vs. low-dose never cigarette smokers
Omae, 1984	Longitudinal 1980-82	170/115 exposed 60/39 controls	No TDI-related effect on FEV1, annual loss in FEV1, or cross-shift change in FEV1
Ott, 2000	Longitudinal 1980-96	1,954/219 exposed 687/77 controls	No relationship of annual FEV1 loss to TDI dose, final FEV1/FVC% reduced among TDI-induced asthma subgroup
Bodner, 2001	Longitudinal 1971-97	1,878/305 exposed 3,014/581 controls	No relationship of FEV1 to cumulative TDI dose

determination varied from 2 to 22 years across studies. More than 1000 pulmonary function tests were performed among exposed employees in three of the studies. Trends in TDI concentrations in the three U.S. units were discussed earlier, and short-term TDI concentrations were described relative to two of the three U.S. TDI units. Relatively high TDI concentrations, based on area samples, were reported for the two TDI manufacturing units included in Adams' study.⁽³⁰⁾ These units had been constructed in 1961 and 1965, respectively.

In the Adams study, no relationship was observed between FEV1 decrement and prior duration of TDI exposure among asymptomatic employees, and age-related FEV1 changes were comparable to those seen in a referent population.⁽³⁰⁾ Among 61 employees reassigned to other production units after developing respiratory symptoms, there was a greater than expected loss in FEV1 of about 270 ml compared to normal predictive values. No data were presented regarding years of symptomatic exposure, and of 20 individuals with both pre-employment and post-sensitization spirometry data, 11 showed no loss in FEV1, 6 showed a decline of up to 10 percent, and 2 showed a decline of 10–20 percent in FEV1.

The study by Weill began with the start-up of a new TDI unit in 1973 and continued for 5.5 years.^(7,35) In this study, the investigators combined extensive industrial hygiene (IH) monitoring data with comprehensive medical examinations offered on a semi-annual basis, but did not include an unexposed referent group. Regression analyses that treated cumulative TDI dose as a continuous variable did not identify a significant association between annual FEV1 decrement and TDI dose. However, separate analyses using a dichotomous variable (TDI dose: ≤ 68.2 vs. > 68.2 ppb-months) did identify a statistical difference in annual FEV1 decline between 21 high-dose and 36 low-dose employees who never smoked cigarettes. No statistical difference was observed in a corresponding comparison among former cigarette smokers.

In a study of another TDI unit that was quite similar to the one studied by Weill, annual decline in FEV1 was not related to cumulative TDI dose treated as a continuous variable.⁽³²⁾ In addition, there were no significant differences in annual FEV1 decrement between exposed versus unexposed employees overall or among employees who never smoked cigarettes. This study reported longitudinal pulmonary function data over a 17-year period. Among 15 individuals diagnosed with OA due to TDI, the annual rate of FEV1 decline was unremarkable after transfer to other work areas. However, these subjects had statistically lower final FEV1/FVC ratios than did other employees in the study. Lower FEV1/FVC ratios were also observed for employees in this study with a history of nonoccupational asthma. The median time between onset of asthmatic symptoms and reassignment to another area was < 6 months, and the longest time was two years.

The most recent and largest longitudinal study (1971–1997) of pulmonary function in TDI manufacturing employees also found no relationship between mean annual FEV1 decrement

and cumulative TDI dose.⁽³³⁾ This study included 305 exposed and 581 referent employees. The mean length of longitudinal follow-up per employee was 7.8 years with a maximum of 22 years.

TDI-Using Industries

Since nearly the inception of the diisocyanate industry, TDI monomer has been used predominantly to produce flexible PUR foam. Chemically, the process involves the reaction of TDI with polyols in the presence of catalysts including tertiary amines. The first commercial production of flexible foam in the United States occurred in 1953.⁽³⁶⁾ In 1965, approximately 62 percent of all available TDI was consumed in flexible PUR foam production, with the remainder used in manufacturing rigid foams (23%), surface coatings (9%), adhesives and sealants (3%), and other end products (3%).⁽³⁷⁾ By 2000, the corresponding percentages were flexible foam (88%), rigid foam (4%), surface coatings (3%), adhesives and sealants (3%), and other products (3%).⁽²⁹⁾ Use of TDI to produce non-flexible foam products has been, and continues to be, more common in Asia and Europe than in the United States. Flexible foam operations include slabstock and molded foam production. Currently, production of slabstock accounts for about three-quarters of all TDI consumed in flexible foam operations.⁽²⁹⁾

TDI Concentrations in PUR Foam Facilities

Key work areas in PUR flexible foam facilities are the slabstock area, the molded foam process area, and finishing areas where foam is further processed or warehoused. Slabstock foam equipment is typically run for several hours per day with the rest of the workday spent in finishing activities, whereas molded foam processes may be run on a continuous basis throughout the day. In past years, tasks linked to high potential TDI exposure included operating the slab foam equipment, transfer, handling, and maintenance activities, pouring mix into molds, stripping molds when these were manual operations, foam cutting operations, and scrap recovery.

In recent years, increased use of robotics and personal respiratory protection has reduced the potential for TDI exposure. Small amounts of unreacted TDI may be emitted from fresh foam. However, Hugo and colleagues have shown in a chamber study that no quantifiable amount of TDI is extractable from 3-day post-production PUR foam.⁽³⁸⁾ These authors indicated that past studies had not detected "free" TDI, even in foam samples aged for only 24 hours.

Early accounts of TDI exposure in the PUR foam industry described many manual operations and TDI concentrations (analysis by colorimetric methods) ranging up to 100 ppb in some work areas.^(39–46)

Long-term trends in TDI concentrations have been assessed in six U.S. and 12 U.K. PUR foam production facilities using paper-tape and HPLC data beginning in the late 1970s.^(6,47–51) On an 8-hr TWA basis, TDI concentrations in slab foam

production averaged 3.8 ppb in 1979, and declined to 2.6 ppb during the 1980s.^(6,49,51) In molded foam operations, TDI concentrations averaged 1.3 ppb in 1979 and 1.8 ppb during the 1980s.^(6,47,49,50) In finishing work areas, TDI concentrations were generally lower, averaging 1.5 ppb in slab finish and 1.2 ppb in mold finish operations.^(6,49,51) However, relatively higher exposures were associated with operations where scrap foam is recovered and rebonded by adding TDI, and in applications where fresh foam is cut or seared.^(6,52) Exposures to aliphatic amines, respirable dusts, and other chemicals used in flexible foam production have been characterized in several comprehensive IH surveys of the industry.^(48,53)

Short-term concentration patterns were studied in PUR foam production facilities during the 1980s based on paper-tape monitoring methods. In the study of 12 U.K. facilities, it was found that 33 percent of the 8-hr personal samples collected for slab foam process operators contained one or more short-term concentrations above 20 ppb TDI, where the overall mean TWA was 2.6 ppb.⁽⁴⁹⁾ In molded foam processes with an overall mean TWA of 1.6 ppb, 4 percent of all 8-hr samples included short-term concentrations above 20 ppb. Interestingly, about 46 percent of the time when the short-term concentration exceeded 20 ppb, it also exceeded 40 ppb TDI.

Similar results were obtained from two U.S. slab foam facilities. In the older facility with a mean 8-hr TWA of 4.5 ppb TDI, 4 percent of all 12-minute samples exceeded 20 ppb TDI.⁽⁵¹⁾ Given the number of 12-minute samples possible during an 8-hr shift, the probability is rather high of having at least one short-term concentration above 20 ppb per shift. In the newer facility with an 8-hr TWA of 2.9 ppb TDI, 1.2 percent of all 12-minute samples exceeded 20 ppb TDI. Also, in a Japanese slab foam plant, 16 of 129 (12%) paper-tape samples included at least one short-term concentration > 20 ppb TDI.⁽⁵⁴⁾

Finally, in a study of a molded foam facility, employees were asked to complete a questionnaire concerning prior exposures and symptoms resulting from TDI spills.⁽⁵⁰⁾ Current 8-hr TWA estimates averaged 1.4 ppb TDI in this facility. The facility had been in operation for about 13 years at the time of the most recent survey in 1983. Among current production employees, 75 percent reported experiencing at least one prior spill episode and nearly 50 percent reported experiencing 4+ prior spill episodes. These results are similar to those reported in a clinical record survey of one TDI production facility.⁽³²⁾

TDI Concentrations in Other Using Industries

Additional activities with potential for TDI exposure include spray and brush painting with TDI-based coatings, use of TDI-based adhesives, and activities such as flame lamination of PUR products. In past years, TDI had been used in indoor spray foaming applications and in coatings for sheet steel.^(55,56) During the 1950s and 1960s, TDI-based coatings were employed in the furniture finishing industry in the United States with TDI concentrations (colorimetric analysis) measured at about 10 ppb (areas means) ranging from 80–120 ppb.^(40,57) During

the 1980s, area concentrations averaged 15, 44, and 112 ppb TDI (colorimetric analysis) in three Asian furniture finishing facilities, respectively.⁽⁵⁸⁾ TDI concentrations in three work areas of a TDI-based adhesives facility averaged 12, 21, and 47 ppb, respectively.⁽⁵⁹⁾ In the latter facility replacement of TDI with the less volatile methylene diphenylmethane diisocyanate (MDI), resulted in an elimination of complaints of asthmatic symptoms.

Health Outcomes in TDI-Using Industries

In contrast to the situation with TDI production unit studies, many OA studies in the using industries were cross-sectional in design and thus provided mostly findings on OA prevalence. Prevalence estimates across nine cross-sectional studies ranged from 0 percent to 41 percent.^(53,56,58–64) In the study with the highest prevalence rate (case definition: cough for >1 month or wheezing for 1 month), the authors indicated that symptoms reported by many of the 14 cases might have been due to the irritant rather than sensitizing effects of TDI.⁽⁵⁹⁾ Case rates were reported to be 85 percent among employees working with TDI-based adhesives in an area with mean TDI concentrations (colorimetric analysis) of 47 ppb and 0 percent in a work area with mean TDI concentrations of 12 ppb.

In another Asian study with very high reported TDI concentrations associated with spray painting operations (7 cases among 48 employees), a positive gradient of OA prevalence was again seen with higher mean TDI concentration.⁽⁵⁸⁾ The OA prevalence was reported to be 27 percent (4 cases) in a factory with a mean TDI concentration (colorimetric analysis) of 112 ppb and decreased to 0 percent in a factory with a mean TDI concentration of 15 ppb. The overall prevalence of OA was also relatively high (10%, 8 cases) in a second Asian study of spray painters using a TDI-based varnish.⁽⁶⁴⁾

A 10 percent OA prevalence rate was reported as well among employees assigned to a process in which steel was coated with a plastic finish that was later found to have included a TDI-based component (21 cases determined mostly based on questionnaire responses among 221 employees).⁽⁵⁶⁾ The coated steel was oven-cured, apparently releasing fumes containing TDI at concentrations (HPLC analysis) of up to 26 ppb. After excluding the TDI-based component in 1979, no new OA cases were identified in a subsequent survey about nine months later.

In the study by White, 3 of 4 reported OA cases (prevalence rate of 3%) reacted to a challenge test based on cutting and sewing PUR-backed fabric in an enclosed room rather than to a TDI challenge per se.⁽⁶²⁾ Thus, it could be that exposure to other materials including fabric fibers contributed to the respiratory conditions observed in this work population.

IH sampling for TDI was more extensive in two of the cross-sectional studies.^(60,61) In a study of a U.S. R&D facility, where 550 breathing zone samples were collected over a 10-year period beginning in 1957, all five OA cases were reported to have encountered diisocyanate exposures above 20 ppb.⁽⁶⁰⁾ Among the 185 area samples reported in the Franzinelli study of a European facility producing refrigerators insulated by PUR

foam, 52 percent were in the 7–49 ppb range and 13 percent ranged from 50 to 500 ppb TDI.⁽⁶¹⁾ In this study, cases were established by provocation challenge tests. Although the OA prevalence rate was only 3 percent (2 cases), it was indicated that 14 cases had been identified among 81 transferred employees in past years. Of a total work force of 1150, about 66 were considered directly exposed to TDI. Assuming a 4-year period of operation and that all cases arose among directly exposed employees, the annual OA incidence rate would have been 6 percent. In another European PUR foam facility, current TDI concentrations determined by HPLC analysis were in the 1–2 ppb range.⁽⁵³⁾ There were no current cases of OA identified, but an annual incidence rate of 1 percent could be estimated based on three prior cases reported over a 6-year period. These latter two studies taken together indicate a declining rate of OA with decreased TDI concentrations comparable to that seen in TDI manufacturing units.^(53,61)

Four longitudinal OA studies have been conducted in TDI-using facilities; by far the largest being a study by Bugler in 12 British PUR foam facilities.^(49,65) TDI concentrations and OA incidence rates for these studies are summarized in Table III.^(49,51,66,67) The two smaller and earlier studies were based on inception cohorts; that is, follow-up began at the start of production, whereas the two larger studies were initiated in existing facilities.^(66,67)

In the Woodbury study, a number of spill incidents were described over the 18-month surveillance period with TDI concentrations being sufficient to produce acute irritant effects.⁽⁶⁶⁾ Two probable and five possible cases of TDI-induced asthma were identified among the 25 employees for an overall annual OA rate of 5–19 percent. Four OA cases were identified over an 18-month period in the Williamson study among 99 employees who worked for 1+ months during the time period.⁽⁶⁷⁾ TDI and MDI concentrations were described as normally below 20 ppb, but as high as 200 ppb during spills.

The overall incidence of OA over a 6-year period between 1981 and 1986 in the U.K. study of 12 PUR foam production facilities was 0.8 percent based on 41 observed new onset cases.^(49,65) This count does not include eight cases regarded as prevalent cases because they were symptomatic before the start of the surveillance period, but does include 10 cases categorized as having only upper airway symptoms. These cases would probably not have met a more rigorous definition of OA. TDI concentrations ranged from 0.9–2.6 ppb on an 8-hr TWA basis and may have been higher in earlier years as at least one facility dated back to 1957. In this study, the annual OA incidence rate for work in production areas was 1.0 percent and for work in handling or office areas of 0.3 percent. Six of 18 cases among new hires after the start of surveillance also reported only upper airway symptoms. Fourteen of these cases occurred among employees assigned to jobs with routine short-term TDI concentrations above 20 ppb (11 above 40 ppb), and three others had been assigned to jobs with routine short-term concentrations of 10–19 ppb, which was determined based on only three 8-hr samples per job. The one person, whose current job had short-term concentrations below 10 ppb, had previously been assigned to a job with short-term TDI concentrations >20 ppb.

The study of two U.S. slab foam production units by Jones included extensive personal sampling for TDI and utilized provocation challenge tests to confirm at least six of the 12 reported OA cases.^(51,68) TDI concentrations ranged from 1.4 to 4.5 ppb TWA depending on job and unit. Both of these facilities were constructed well before surveillance began in 1982, and six of the cases had been symptomatic before the start of the surveillance period, and should be recorded as prevalent cases rather than new onset cases.

Taken together, these four studies provide further evidence of OA incidence rates being 1 percent or below, provided mean TWA concentrations are maintained below 5 ppb TDI. The findings from the Bugler study also indicate that repeated high

TABLE III
Estimated TDI concentrations and reported incidence of TDI-induced OA in 4 PUR foam production facilities

Study (case criteria)	IH sampling/analysis	Time period	Annual incidence		Sampling results TDI concentrations
			Nbr.	%	
Woodbury, 1956, N = 25 (MD assessment)	No IH sampling data	1954–55	2	5.0	Multiple TDI spill episodes described in 18-month period
Williamson, 1964, N = 99 (MD assessment)	Area samples colorimetric analysis	1962–63	4	>2.7	Samples mostly <20 ppb (up to 200 ppb detected during spills)
Bugler, 1991, N = 1,462 (self-report)	Personal 1979–86, paper-tape	1981–86	41	0.8	0.9–2.6 ppb TWA (range by job) 22% of 8-hr samples with STCs >20 ppb and 10% with STCs >40 ppb
Jones, 1992, N = 386 (MD assessment)	Personal 1982–86, paper-tape	1982–86	12	0.7	1.4–4.5 ppb TWA (range by job) (STCs >20 ppb 3% time in production and 0.1% of time in finishing jobs)

STC: short-term concentration (9–12 minutes) measured by paper-tape method.

TABLE IV
Reported FEV1 findings among employees assigned to PUR foam and other TDI-using operations

Study	Design	No. of PFTs/subjects	FEV1 findings
Peters, 1968	Longitudinal 1966-69	~400/38 exposed, no controls	Mean FEV1 loss 120 ml/yr; cross-shift FEV1 loss averaged 220 ml, and 350-450 ml in symptomatic employees
Wegman, 1974	Longitudinal 1972-76	~420/111 exposed no controls	Mean FEV1 loss 60 ml/yr in 11 subjects at TDI concentrations >3.5 ppb, (no adjustment for aging or smoking)
Musk, 1982	Longitudinal 1971-81	~760/(47 exposed + 37 controls)	No evidence of cross-shift, cross-week, or long-term change in FEV1 related to TDI or MDI exposure
Holness, 1984	Cross-sectional 1982	285/95 exposed 111/37 controls	No FEV1 effect in exposed vs. controls; 50 ml mean cross-shift loss in exposed, no correlation with TDI concentration per se
Alexandersson, 1985	Cross-sectional 1979	134/67 exposed 22/11 controls	No evidence of cross-shift or long-term effects on FEV1 not explainable by smoking
Huang, 1991	Cross-sectional 1988-89	48/48 exposed 18/18 controls	Decreased FEV1 at average TDI concentrations of 44 and 112 ppb (all subjects reported eye, nose, and throat irritation)
Omae, 1992	Longitudinal 1981-85	171/57 exposed 72/24 controls	No FEV1 effect in exposed vs. control employees; higher annual FEV1 loss in 15 employees with peak exposures of 30 to >80 ppb (8.5 ppb TWA)
Jones, 1992	Longitudinal 1982-86	1,222/294 exposed	Initial FEV1 not associated with prior TDI exposure. Annual FEV1 loss higher than expected, but unrelated to TDI concentration
Clark, 1998	Longitudinal 1981-86	~3,200/780 exposed	Initial FEV1 not associated with prior TDI exposure. Annual FEV1 loss unrelated to mean TDI concentration overall and comparable to general population data, no cross-shift effects

short-term TDI concentrations may play an important role in initiating respiratory sensitization. In an injection molding facility using MDI and engineered to minimize routine diisocyanate exposure, three OA cases were identified over a 6-year period in a work force of over 200 employees.⁽⁶⁹⁾ The authors concluded that all three cases appeared to have been induced as a result of intermittent high exposures during non-routine work activities.

Results of nine lung function studies conducted in TDI-using units are summarized in Table IV.^(42-46,49,51,52,54,58,65,70-73) An early longitudinal study in a molded PUR foam facility (1966-1969) included relatively few subjects, with only 15 followed for a full 3 years, no referent group, and provided limited area sampling data.⁽⁴²⁻⁴⁴⁾ Highest measured TDI concentrations (colorimetric analysis) were 30 ppb in the pour area. Prior duration of TDI exposure as of the initial examination date ranged from a few weeks to about 10 years. The annual FEV1 loss of 120 ml/yr over the 3-year period was clearly larger than would be expected, but no referent group was available to provide an internal validity check on spirometry performance over time. Based on the mean cross-shift loss in FEV1 of 220 ml overall and 350-450 ml in symptomatic employees, many of these subjects had probably already developed OA.

In a second study of a facility with one slab and two molded foam lines, an initial group of 111 employees was examined and reassessed two and four years later, with 37 employees still available at the 4-year assessment.^(45,46) TDI concentrations in mixing and pouring areas ranged from 1-40 ppb based on personal samples analyzed by a colorimetric method. Duration of

prior TDI exposure did not correlate with mean annual FEV1 decrement; however, an annual FEV1 loss of 60 ml/yr was observed among 11 employees reported to be exposed to TDI concentrations >3.5 ppb.⁽⁴⁶⁾

A third study by the same research group was begun in 1971 and included a 5-year and 10-year reassessment of pulmonary function.⁽⁷⁰⁻⁷²⁾ In this study, there was no evidence of cross-shift, cross-week, or accelerated annual decrement in FEV1 related to TDI or MDI exposure. Mean TDI concentrations were lower in this study with breathing zone concentrations averaging about 3 ppb. This study did include a control group.

Three cross-sectional lung function studies were carried out, two in flexible foam production facilities and one in three spray painting factories.^(52,58,73) TDI concentrations in the flexible foam facilities averaged below 5 ppb TWA, and were assessed based on personal samples analyzed by colorimetric methods in one study⁽⁵²⁾ and by HPLC methods in the second study.⁽⁷³⁾ No evidence of FEV1 effect was observed between exposed and control subjects in the Canadian study of four companies in which employees had worked for an average of 6.5 years at the time of the study.⁽⁵²⁾ A decrease in mean cross-shift FEV1 of about 50 ml was observed among foam line operators and personnel assigned to finishing operations in these facilities. No indication of cross-shift or long-term effects on FEV1 not explainable by cigarette smoking was seen in the other study of two slab foam and five molded foam production operations.⁽⁷³⁾

In the cross-sectional study of three spray painting facilities, a statistical decrease in FEV1 was reported among employees

assigned to the two facilities with mean TDI area concentrations (colorimetric analysis) of 44 and 112 ppb, respectively.⁽⁵⁸⁾ Employees had worked in these facilities for an average of 7 to 8 years prior to the study. Exposures were quite high as all employees reported experiencing eye, nose, and throat irritation.

In a 4-year longitudinal study by Omae, no overall FEV1 effect was observed between exposed and referent employees in a study of Japanese flexible foam production facilities.⁽⁵⁴⁾ Mean prior years of TDI exposure in these facilities was 13.3 years. A statistically higher mean annual FEV1 loss was observed, however, among 15 employees exposed to short-term TDI concentrations (paper-tape monitoring) ranging from 30–80 ppb and whose 8-hr TWA concentration was estimated to be 8.5 ppb.

In a 5-year longitudinal study by Jones of two slab foam facilities (mean TDI concentrations of 2.9–4.5 ppb TWA in the foaming areas and 1.4–1.5 ppb TWA in the finishing areas), a TDI-related dose effect in initial FEV1 was found, but only among current cigarette smokers.⁽⁵¹⁾ At baseline, employees had worked for an average of 9.4 years in the facilities. The effect among current cigarette smokers may have been secondary to a correlation between cumulative dose (a function of years of prior employment) and cumulative pack years smoked. In this study, the annual FEV1 loss (67 ml/yr in current smokers and 53 ml/yr in those who never smoked) was higher than would be expected; however, neither concurrent nor cumulative TDI exposure was correlated with annual FEV1 loss.

In the largest lung function study conducted in 12 British PUR foam plants with both slab and molded foam operations, initial FEV1 was not associated with prior TDI exposure group.^(49,65) Annual FEV1 loss was unrelated to mean TDI concentration overall and was comparable to general population norms. Among 24 employees classified as having OA, the annual FEV1 decrement was 49 ml/yr, which is about 10 ml/yr greater than for non-sensitized employees. This is consistent with other studies suggesting an accelerated FEV1 decrement among employees with OA who continue to work in exposure areas.

CONCLUSIONS

Annual OA incidence rates due to TDI were as high as 5–6 percent in the early years of the industry in both TDI manufacturing units and in the using industry. With reduction of mean TDI concentrations to below 5 ppb as measured by 8-hr personal samples, rates have declined to below 1 percent annually in both the producing and using industries. Empirical data from studies with more extensive IH monitoring indicate that the majority of TDI-induced asthma cases may arise as a secondary consequence of short-term TDI concentrations considerably in excess of 20 ppb.^(7,32,49,60) These exposures are typically associated with specific tasks such as line opening or with non-routine overexposure events.

Decrements in FEV1 had been demonstrated in several early studies of employees where work-related symptoms were also reported for a high percentage of the work force. Similar findings were observed in follow-up studies of employees who contin-

ued to work with diisocyanates long after a diagnosis of OA was made. These results are in agreement with the modestly accelerated FEV1 declines seen in studies of adults with persistent asthma or BHR regardless of the cause of the condition. No consistent evidence of accelerated FEV1 loss has been seen in more recent studies of employees exposed up to 5 ppb TDI (8-hr TWA), even with documented routine short-term TDI concentrations exceeding 20 ppb TDI.

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