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Incidence of Occupational Asthma and Exposure to Toluene Diisocyanate in the United States Toluene Diisocyanate Production Industry

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Abstract

Objective—This study examines asthma risk in facilities producing toluene diisocyanate (TDI).

Methods—A total of 197 workers were monitored from 2007 to 2012. TDI air concentrations were used to estimate exposures.

Results—The incidence of cases consistent with TDI-induced asthma was 0.009 per person-years (seven cases) or consistent with TDI-induced asthma or asthma indeterminate regarding work-relatedness was 0.012 (nine cases). Increased risk of cases consistent with TDI asthma was observed for cumulative (odds ratio [OR] = 2.08, 95% confidence interval [CI] 1.07 to 4.05) per logarithm parts per billion-years and peak TDI exposures (OR = 1.18, 95% CI 1.06 to 1.32) (logarithm parts per billion). There was a weak association with cumulative and peak exposures for decline of short-term forced expiratory volume in one second (FEV_1). Asthma symptoms were associated with workers noticing an odor of TDI (OR 6.02; 95% CI 1.36 to 26.68).

Conclusions—There is evidence that cumulative and peak exposures are associated with TDI-induced asthma.

It is estimated that up to 17% of adult-onset asthma may be the result of occupational exposure.[1–4] Diisocyanates, such as toluene diisocyanate (TDI), are a cause of occupational asthma.[1,3,5–8] Exposure to TDI can occur in primary production facilities and secondary production facilities that produce polyurethane foams and other products.[9–11] Occupational

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exposure to diisocyanates may increase a worker's risk for health outcomes including respiratory symptoms, sensitization to diisocyanates, and asthma.[12,13] There is evidence from surveillance reports of declining trends in occupational asthma during the 1990s in the United States, United Kingdom, Finland, and Canada.[7,9–12,14] Reviews of workplace studies indicate also that incidence rates of TDI-induced asthma have declined.[14,15] These favorable trends appear to be related to a reduction in workplace exposures through engineering controls and changes in work practices as well as medical surveillance practices.[14,15]

Occupational surveillance programs are often established for agents with sensitizing potential like TDI.[3,16] Historically, most high exposures to TDI resulted from accidental spills or releases.[14,17] Today, exposures in the TDI production facilities are characterized as very low.[14] We examine a TDI medical surveillance program implemented across three TDI production plants in the United States to determine the incidence rate of TDI-induced asthma over a 5-year period. We also examine the incidence of asthma indeterminate regarding work-relatedness, forced expiratory volume in one second (FEV_1) decline over any 12-month period, and symptoms of asthma among TDI workers. We estimate the association of these health outcomes with cumulative and peak exposure to TDI in these plants.

METHODS

Participants

The research methods used in this study are described elsewhere in Cassidy et al.[18] Briefly, the study participants were recruited from TDI medical surveillance programs at a BASF Corporation plant in Geismar, Louisiana, a Covestro LLC (formerly Bayer MaterialScience LLC) plant in Baytown, Texas, and a Dow Chemical Company plant in Freeport, Texas. Eligible workers included those performing tasks in areas with the potential for TDI exposure except for contract employees who were not enrolled in the plants' existing on-site medical surveillance programs. Job tasks with potential or known exposure to TDI included workers in production, maintenance, storage and transportation, housekeeping, incident response, and laboratory analysis of TDI process samples. Any worker who had experienced a TDI incident exposure during the study period was also eligible. Exposure monitoring was conducted by tasks performed in the job and more than one task with potential TDI exposure could be counted during a single shift for estimating exposures. Enrollment and data collection began in June of 2007 and ended in June of 2012. The Dow Chemical Company TDI production facility ceased operation in October of 2010, but participants were followed through the end of the study. Of 269 eligible workers, 197 volunteered to participate (185 males and 12 females). The average age at enrollment into the study was 42 years (range: 21 to 62 years). The mean and standard job tenure at the time of enrollment was 11.8 ± 10.1 years. Thirty-two participants (15.9%) had been employed for less than 1 year. The average number of person-years of observation for study participants was 3.9 person-years and ranged from 0.1 to 5.8 person-years. The Institutional Reviews Boards at NIOSH and the Dow Chemical Company approved the study protocol and monitored study progress. Informed written consent was obtained from all 197 workers before participation.

Health Outcome Classification Criteria

Some researchers have concluded that the clinical presentation of TDI-induced asthma is variable, making it difficult to diagnose and, thus, incidence rates are often unreliable.[19–22] In the present study, new cases of asthma were identified from the medical monitoring at each plant by application of standardized annual medical assessment, including spirometry and questionnaires on symptoms and exposure. In addition, workers in the study could report symptoms consistent with asthma at any time to the plant occupational health staff. If symptoms indicated possible asthma or the spirometry results indicated an FEV_1 decline of 350 mL or 10% or more in any 12-month period, further medical evaluation was to be performed. A consulting pulmonologist reviewed all the provided occupational exposure and medical information, including physiological confirmation from work-related changes, and provided a determination for each case as consistent with: asthma, other respiratory disease, or normal respiratory status. If consistent with asthma, a category was specified: (1) consistent with non-work-related asthma; (2) consistent with work-related asthma (a) consistent with TDI-induced asthma, (b) consistent with irritant-induced asthma, or (c) consistent with asthma caused by other agent(s); or (3) asthma indeterminate regarding work-relatedness indicating that TDI asthma while not definitely identified could not be ruled out.

Exposure Assessment

The development of exposure estimates is described in Middendorf et al[23] and is briefly summarized here. Exposure assessment was conducted at the three plant locations. Participants who performed similar tasks that had the potential to produce similar time-weighted average (TWA) TDI exposures, based on detailed discussions of job descriptions, were grouped into plant-level similar exposure groups subsequently referred to as Plant SEG. Air samples representing shift length duration TWA exposures and exposures during the defined short-term high potential exposure tasks were collected. Air samples were collected and analyzed using the Covestro Industrial Hygiene Laboratory Method. All workers in a Plant SEG were eligible for sampling whether or not they participated in the study. Workers were asked through questionnaires if, during the past 12 months they noticed an odor of TDI in their work area.[23]

TWA Exposures

A method was developed to combine Plant SEGs, which had been determined using job titles and other relevant factors based on professional judgment, into data-derived cross-facility SEGs subsequently referred to as SuperSEGs. To develop the SuperSEGs, the TWA exposure results, without regard to the use of respirators for each Plant SEG, were categorized into one of the following five categories: <0.1 parts per billion (ppb); 0.1 to <0.5 ppb; 0.5 to <2 ppb; 2 to <5 ppb; and ≥5 ppb. The bounding categories (<0.1 and ≥5 ppb) were chosen because 0.1 ppb is approximately the limit of quantification (LOQ), and 5 ppb was the 8-hour TWA-threshold limit value at the time of this study.

Peak Exposures

Because the high potential exposure tasks were not collected in sufficient numbers to allow estimates of peak exposures, we used 95th percentiles of the TWA exposures. The 95th percentile for the TWA was determined for each worker by assigning that worker's highest estimate of the 95th percentile among the Plant SEGs in which the worker was employed. The range for the estimated 95th percentiles was 0.01 to 19.2 ppb unadjusted for respirator use.

Cumulative Exposures

Cumulative TWA exposure estimates for individuals were developed based on the log means for the TWA exposure clusters and the length of exposure. The range for the estimated cumulative TWA exposure was 0.04 to 21.6 ppb-years unadjusted for respirator use. Because detailed work-histories were not available, the length of exposure was based on worker reports collected from questionnaires. About one-quarter of the workers stated their first TDI exposure date. For the other workers, the potential exposure was assumed to commence with the beginning of study when the hire-date preceded the start of the study, or was assumed to begin at their hire-date when this occurred after the start of the study.

Analysis

Incidence rates and 95% confidence intervals (95% CIs) for four health outcomes were calculated for the entire study period: (1) consistent with TDI-induced asthma, (2) consistent with TDI-induced asthma or asthma indeterminate regarding work-relatedness, (3) short-term FEV_1 decline, and (4) symptoms of asthma that met criteria for clinical evaluation. Cases of asthma were not formally diagnosed by the consulting pulmonologist and therefore they were categorized as "consistent with TDI-induced asthma." The number of type of asthma cases classified by the consulting pulmonologist was the numerator for the first two rates. For those in the asthma category, person-years were calculated from the date of first completed questionnaire to the date of symptom onset. For participants not classified in an asthma category, person-years were calculated from date of the first completed questionnaire to date of last questionnaire. The number of workers with a 350-mL or 10% or more decline in FEV_1 over any 12-month period was the numerator for the incidence of short-term FEV_1 decline.[24] The denominator was the number of person-years before the decline in FEV_1. The number of workers reporting respiratory symptoms that met criteria for further clinical evaluation of work-related asthma was the final numerator. Such symptoms include reporting any one of the following symptoms at least four times during the past 12 months: (1) had wheezing or whistling in the chest; (2) had an attack of chest tightness or shortness of breath with wheezing or whistling in the chest; (3) been awakened by coughing, wheezing, or chest tightness; (4) felt tightness in the chest for longer than a minute; or (5) had chills, fever, cough, and muscle aches. All had at least one of the first four sets of symptoms. The number of person-years before symptom onset was the denominator.

A series of logistic regression models examined each of the four health outcomes as the dependent variable and independent variables of age, cumulative exposure to TDI, and peak exposures. Cumulative and peak TDI exposure were modeled separately. Odds ratios (OR) and 95% CIs were calculated for each predictive variable and represent the change in the

odds per unit increase in the natural-logarithm. We also provide the predicted probability of being a case based on median age of the study workers for various levels of cumulative and peak exposures to assess the impact of dose. Both cumulative and logged transformed TDI exposures were used in separate models. Parallel analyses were carried out for consistent with TDI-induced asthma, asthma indeterminate regarding work-relatedness, short-term FEV_1 decline, and symptoms of asthma. All analyses were done using SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

The incidence rates for asthma are presented in Table 1. There were nine cases consistent with asthma and they were identified as consistent with TDI-induced asthma (seven cases) or asthma indeterminate regarding work-relatedness (two cases). These classifications reflect a determination based on the study protocol, not clinical diagnoses. The rate of consistent with TDI-induced asthma was 0.009 per person-years, and the rate of combined consistent with TDI-induced asthma or asthma indeterminate regarding work-relatedness was 0.012 per person-years. The rate of FEV_1 decline of 350 mL or 10% or more in any 12-month period was 0.026 per person-years. Seventeen of the 19 workers with FEV_1 decline did not have findings consistent with asthma. The rate of respiratory symptoms qualifying for clinical examination among 23 workers for possible work-related asthma was 0.030 per person-years.

Of the seven with findings consistent with TDI-induced asthma, four had less than 1 year of job tenure (range 1 to 7 months), one had worked for 2 years when beginning participation, and the other two had worked at the job for 7 and 8 years. Tenure at the time of an event that met criteria for further evaluation for asthma ranged from 3 months to 8 years. Two of the seven had less than 1 year tenure at the time of event and one less than 2 years. Of the two participants with more than 7 years of job tenure, one had a triggering event at the time of intake and the other 4 months from the start of the study.

Table 2 presents the logistic regression results for two models based on either cumulative or peak exposures for cases consistent with TDI-induced asthma, consistent with TDI-induced asthma or asthma indeterminate regarding work-relatedness, short-term FEV_1 decline, and symptoms of asthma. We present the models for logged cumulative TDI exposure as these models fit these data slightly better than the non-logged cumulative TDI exposure models. However, the non-logged cumulative exposures yielded similar results. For cases consistent with TDI-induced asthma, the OR for cumulative exposure was 2.08 (95% CI 1.07 to 4.05) per logarithm ppb-years and for peak exposures was 1.18 (95% CI 1.06 to 1.32) logarithm ppb. For cases consistent with TDI-induced asthma or asthma indeterminate regarding work-relatedness, the cumulative OR was 1.55 (95% CI 0.92 to 2.64) and the peak OR was 1.13 (95% CI 1.04 to 1.23). For short-term FEV_1 decline, the OR for cumulative exposures was 1.40 (95% CI 0.99 to 1.97) and the OR for peak exposures was 1.06 (95% CI 1.00 to 1.13). Neither cumulative (OR = 1.20, 95% CI 0.87 to 1.66) nor peak (OR = 1.04, 95% CI 0.99 to 1.11) exposures appear associated with symptoms of asthma. However, we did find that workers who reported an odor of TDI while working were much more likely to report symptoms of asthma (OR = 6.02, 95% CI 1.36 to 26.68) and have findings consistent with

TDI-induced asthma (OR = 3.21, 95% CI 0.38 to 27.32), although the asthma OR is imprecise. However, workers who reported an odor of TDI were not more likely to have a decline in FEV_1 (OR = 0.87, 95% CI 0.33 to 2.35).

Six of the seven participants with findings consistent with TDI-induced asthma reported detecting an odor of TDI from 1 to 3 times to weekly in the previous 12 months. Five of the seven reported having been in the area of a release of TDI, three 1 to 3 times, one 4 to 11 times, and one weekly in the previous 12 months. All seven reported either detecting TDI odor or having been in the area of a release. For the overall cohort, 85 (43%) ever reported detecting an odor of TDI: 36 (18%) 1 to 3 times, 27 (14%) 4 to 11 times, 16 (8%) monthly and 6 (3%) weekly in the previous 12 months. Being in the area of a release was ever reported by 69 (35%) participants: 1 to 3 times by 49 (24%) participants, 4 to 11 times by 16 (8%), and monthly by 4 (2%) in the previous 12 months. These responses were collected annually during the study.

Tables 3 and 4 present the predicted strength of the effect of cumulative and peak exposures respectively. For cumulative exposures in Table 3, comparing the cases consistent with TDI-induced asthma for cumulative exposure from 5 to 20 ppb-years, results in a 153% predicted increase [(0.134 to 0.053)/0.053]. Performing the same calculation for peak exposure in Table 4 results in a 962% [(0.138 to 0.013)/0.013] predicted increase of being a case.

DISCUSSION

This study has some important strengths. First, the study was longitudinal in design, which allowed us to follow workers for an extended period to simultaneously monitor their workplace exposures and potential development of asthma. The study design also allowed for estimation of cases consistent with TDI-induced asthma incidence among TDI production workers that are more recent than the prior longitudinal studies, which were completed before 1975 when exposure to TDI was higher.[25–28] Second, the study had an extensive exposure monitoring protocol, which allowed us to estimate cumulative exposure and potential for peak exposures for all study participants. Third, each of the plants in this study had an onsite staffed medical facility that not only collected much of the data for the study, but also monitored the health of the study participants helping to ensure accurate and timely recording of respiratory symptoms.

There are some limitations to this study. First, the risk of work-related asthma is highest within six to 24 months after initial exposure, and the latency period may be much longer.[3] Cassidy et al[18] reported that this workforce was employed for a mean of 11.8 years and only 32 (15.6%) participants had worked for less than 12 months at the beginning of the study indicating most workers in the study had long-term potential exposure to TDI. It is also possible that workers who developed asthma before the study onset had left employment or moved away from TDI exposure. Also, the latency period may not have been exceeded in this study and we may have missed additional workers that may develop work-related asthma sometime after the study ended. Second, despite the use of one protocol and training of staff at each of the three plants, the data completeness and quality varied by plant as the data were collected through existing surveillance programs at three separate plants. For

example, the clinical evaluation protocol was not fully implemented for most of the 42 eligible workers.[18] Third, contract workers at these plants were not included in the study. It is possible that exposures to TDI could have been higher for contract workers than for plant employed workers. Fourth, we examined both peak and cumulative exposure as they relate to asthma risk. While these two exposure measures are most frequently used in occupational studies, some other combination of exposure intensity, frequency, and duration may be more relevant for assessing asthma risk. In addition, our study uses the 95th percentile of cumulative exposure as an indicator of the potential for peak exposures. We did not formally measure peak exposure which may have been higher or lower than the estimates we used. Fifth, we used study start date as the date of first exposure for the nearly three-fourths of participants who did not provide a date of first exposure to TDI. Thus, some participants likely had higher cumulative exposures to TDI than we used in our study. Sixth, although this study surveyed all TDI producing facilities in the United States, the study was relatively small and thus not able to precisely estimate the incidence of cases consistent with TDI-induced asthma for all potentially exposed workers. Seventh, the small number of cases consistent with TDI-induced asthma made it difficult to employ models to assess the role of TDI exposures. Eighth, the clinical evaluation in the study protocol was not applied to all possible cases. Therefore the sensitivity and specificity of the determination of asthma and TDI-induced asthma is unknown. Ninth, the incidence if TDI-induced asthma may be underestimated in this study because workers with lung impairment may be excluded from being hired, or once hired may leave work or be transferred if TDI-induced asthma occurs.[29] Finally, measuring asthma incidence is difficult. Although adult asthma rarely resolves, it is a condition that sometimes occurs, regresses and then reoccurs, thereby making it difficult to determine the precise date of asthma development.[3]

Our study of 197 workers followed over a 5-year period reported an incidence rate of 0.009 per person-years (0.9%) for cases consistent with TDI-induced asthma based on seven cases. If we also consider the asthma indeterminate regarding work-relatedness the rate increases to 0.012 per person-years (1.2%). Studies conducted prior to 1980 demonstrated annual incidence rates of 5% or higher, but more recent longitudinal studies (those conducted since 1980) show rates similar to this study.[14,27,28,30–33], As a point of reference, background rates of adult-onset asthma are estimated to be 0.4% per year.[34,35] Nevertheless, TDI-induced asthma remains a concern as cases still occur in workplaces with relatively low exposures.

We found weak evidence of an association of short-term FEV_1 decline of 350 mL or 10% or more in any 12-month period with cumulative exposure. We did not adjust for smoking, height, or weight, which are all possible confounding factors. However, a detailed analysis including other predictors of longitudinal pulmonary function decline over the course of the study, such as smoking, height, and weight, in these same workers in an accompanying paper found little evidence of a TDI exposure relationship.[24,36] The outcome measure in the present study is different than these previous studies. For example, the Wang et al[24] analysis is a longitudinal analysis of a continuous outcome and the analysis in the present study is a cross-sectional analysis of a discrete outcome, a substantial decline in lung function in a single year. Also, only two of the 19 workers with short-term FEV_1 declines had findings consistent with work-related asthma and none of the 19 reported symptoms of asthma on the questionnaire.

Reported symptoms of asthma did not show a relationship with exposure, but did show an association with noticing odor of TDI. It may be that these asthma-like symptoms without the development of asthma are not related to TDI or represent irritant conditions resulting from acute TDI exposure that may resolve quickly. However, it could also be that workers with asthma symptoms without findings consistent with TDI-induced asthma are at early stages in the latency period for full asthma, or were not evaluated sufficiently to be classified as having asthma.

We did find an inhalation exposure association with cases consistent with TDI-induced asthma for both cumulative and peak exposures. Two studies of workers in the flexible polyurethane foam industry conducted in the early 1990s found occupational asthma occurring to some workers with peak exposures of TDI above 20 ppb.[26,27] Our study lends support to the hypothesis that peak exposures above 20 ppb are a risk factor for cases consistent with TDI-induced asthma. A prior study in the TDI manufacturing and polyurethane foam industries found that respiratory sensitization occurs mostly among jobs where exposures exceeded 20 ppb.[14] Middendorf[23] estimated that over the 7 years of sampling for this study, over 1000 tasks performed resulted in short-term exposures of more than 20 ppb, not accounting for respirator use. Accounting for reported respirator use, there were none. While our study demonstrates a lower incidence of cases consistent with TDI-induced asthma than past studies,[14] we find more evidence that peak exposures are related to increased risk. Despite the relatively low exposures to TDI experienced by the workers in this study, we did identify seven cases classified as consistent with TDI-induced asthma, two cases of asthma indeterminate regarding work-relatedness and 36 additional cases meriting further evaluation. Notwithstanding low TDI exposures in today's production workplace, continued exposure vigilance is necessary. Because TDI-induced asthma may fully resolve with early recognition and removal from exposure, strategies to identify potential cases early are important to implement.[3]

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TABLE 1

Incidence Rates for TDI-Induced Asthma, TDI-Induced Asthma or Asthma Indeterminate Regarding Work-Relatedness, FEV_1 Decline, and Respiratory Symptoms

Health Outcomes for 197 Workers	Cases	Incidence Rate (95% CI) (Cases/Person-years)
TDI-induced asthma	7	0.009 (0.002–0.016)[a]
TDI-induced asthma or asthma indeterminate regarding work-relatedness	9	0.012 (0.004–0.020)[b]
FEV_1 decline of 350 mL or 10% or more	19	0.026 (0.014–0.037)[c]
Respiratory symptoms qualifying for clinical examination for possible work-related asthma	23	0.030 (0.018–0.042)[d]

[a] 765.2 person-years.

[b] 762.7 person-years.

[c] 743.4 person-years.

[d] 755.4 person-years.

CI, confidence interval; FEV_1, forced expiratory volume in one second; TDI, toluene diisocyanate.

TABLE 2

Logistic Regression Results for an Association Between Log Cumulative Exposure to TDI for TDI-Induced Asthma, TDI-Induced Asthma or Asthma Indeterminate Regarding Work-Relatedness, FEV_1 Decline, and Respiratory Symptoms

Variable	Estimate[a]	SE	P*	OR (95% CI)
TDI-induced asthma (seven cases)				
Model 1				
Cumulative exposure[b]	0.7301	0.34	0.03	2.08 (1.07–4.05)
Model 2				
Peak exposure[c]	0.1667	0.06	0.003	1.18 (1.06–1.32)
TDI-induced asthma or indeterminate asthma (nine cases)				
Model 1				
Cumulative exposure	0.4411	0.27	0.10	1.55 (0.92–2.64)
Model 2				
Peak exposure	0.1235	0.04	0.004	1.13 (1.04–1.23)
FEV_1 decline[d] (19 Cases)				
Model 1				
Cumulative exposure	0.3331	0.18	0.06	1.40 (0.99–1.97)
Model 2				
Peak exposure	0.0598	0.03	0.07	1.06 (1.00–1.13)
Symptoms of asthma[e] (23 cases)				
Model 1				
Cumulative exposure	0.1840	0.16	0.26	1.20 (0.87–1.66)
Model 2				
Peak exposure	0.0433	0.03	0.15	1.04 (0.99–1.11)

[a] All models adjusted for age (continuous) in years.

[b] Log ppb-years.

[c] ppb.

[d] None of the workers with TDI-induced asthma or indeterminate asthma had a 10% FEV_1 decline in a year.

[e] All workers with TDI-induced asthma or indeterminate asthma reported symptoms of asthma.

* *P* for chi-square test using exact methods.

CI, confidence interval; FEV_1, forced expiratory volume in one second; OR, odds ratio; ppb, parts per billion; SE, standard error; TDI, toluene diisocyanate.

TABLE 3

Predicted Probability for Being a Case for Median Age of 42 and Some Selected Levels of Cumulative Exposure

Model 1	5 ppb-years	10 ppb-years	15 ppb-years	20 ppb-years
TDI-induced asthma (seven cases)				
Cumulative exposure	0.053	0.085	0.111	0.134
TDI-induced asthma or indeterminate asthma (nine cases)				
Cumulative exposure	0.061	0.081	0.096	0.107
FEV_1 decline (19 cases)				
Cumulative exposure	0.147	0.177	0.198	0.213
Symptoms of asthma (23 cases)				
Cumulative exposure	0.143	0.160	0.170	0.178

FEV_1, forced expiratory volume in one second; ppb, parts per billion.

TABLE 4

Predicted Probability for Being a Case for Median Age of 42 and Some Selected Levels of the Estimated 95th Percentile for the Workers' Highest TWA Potential Exposure

Model 2	5 ppb	10 ppb	15 ppb	20 ppb
TDI-induced asthma (seven cases)				
Peak exposure	0.013	0.029	0.065	0.138
TDI-induced asthma or indeterminate asthma (nine cases)				
Peak exposure	0.025	0.045	0.081	0.140
FEV_1 decline (19 cases)				
Peak exposure	0.090	0.118	0.153	0.196
Symptoms of asthma (23 cases)				
Peak exposure	0.109	0.132	0.159	0.190

FEV_1, forced expiratory volume in one second; ppb, parts per billion; TWA