Published in final edited form as:
Am J Ind Med. 2014 November ; 57(11): 1207–1215. doi:10.1002/ajim.22385.

Inception Cohort Study of Workers Exposed to Toluene Diisocyanate at a Polyurethane Foam Factory: Initial One-Year Follow-up

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Abstract

Background—Isocyanates are one of the most commonly reported causes of occupational asthma; however, the risks of developing isocyanate asthma in modern production facilities remain poorly defined. We evaluated TDI exposure and respiratory health among an inception cohort of workers during their first year of employment at a new polyurethane foam production factory.

Methods—Forty-nine newly hired workers were evaluated pre-employment, 6-months, and 12-months post-employment through questionnaire, spirometry and TDI-specific serology. Airborne TDI levels were monitored by fixed-point air sampling and limited personal sampling. Qualitative surface SWYPE™ tests were performed to evaluate potential sources of skin exposure.

Results—Airborne TDI levels overall were low; over 90% of fixed-point air measurements were below the limit of detection (0.1 ppb). Over the first year of employment,12 of the 49 original workers (24.5%) were lost to follow-up, no additional workers were enrolled, and seven of the 49 original workers (14.2%) developed either new asthma symptoms (N=3), TDI-specific IgG (N=1), new airflow obstruction (N=1) and/or a decline in FEV_1 ≥15% (N=3), findings that could indicate TDI-related health effects.The prevalence of current asthma symptoms was significantly higher in the workers lost to follow-up compared to those who completed the 12 month follow-up (25% vs. 2.7%; p=0.04).

Conclusions—The findings suggest possible early TDI-related health effects in a modern polyurethane production plant. These findings also highlight the need for further longitudinal evaluation of these workers and the challenges of studying workers at risk for isocyanate asthma.

Keywords

Toluene diisocyanate; TDI; isocyanate; occupational asthma; inception cohort; TDI-IgG

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INTRODUCTION

Isocyanates (N=C=O), highly reactive chemical compounds essential to polyurethane production, are used to make a variety of foams, adhesives, coatings, and elastomers, and are well-known to cause occupational asthma [Fisseler-Eckhoff, et al. 2011, Raulf-Heimsoth and Baur 1998]. Although isocyanates remain one of the most commonly reported causes of occupational asthma [Tarlo and Liss 2002], the prevalence, incidence, and risk factors for development of isocyanate asthma under current work conditions are not well defined, as there have been few recent epidemiology studies of isocyanate-exposed workers, despite the increasing use of polyurethane products in numerous industries [Creely, et al. 2006]. More recent studies have largely been limited to cross-sectional studies of end-users such as spray painters, rather than factory workers producing polyurethane products [Pronk, et al. 2007, Redlich, et al. 2001]. Further, the majority of epidemiology studies of isocyanate-exposed workers, past or recent, have been cross-sectional in design, and prone to the healthy worker effect [Le Moual, et al. 2008]. The few longitudinal studies have been conducted largely at primary isocyanate production facilities [Ott, et al. 2000, Ott 2002], rather than secondary production plants.

The present investigation of workers from a newly built modern TDI-based polyurethane foam factory in Eastern Europe provides a rare opportunity to evaluate the risk of TDI asthma among workers employing state-of-the-art polyurethane foam production technology. A prospective inception cohort study was initiated with the initial group of workers (N=49) employed at the plant. Respiratory health and TDI-specific IgG and IgE were assessed pre-employment, and reassessed along with exposure potential at 6-month intervals post-employment. Data from the 12-month study period showed that almost 25% of the initial workers were not available for follow-up and 14.2% had findings that could indicate risk for the development of isocyanate asthma.

METHODS

Overall Study Design

The study was conducted at a newly built modern TDI polyurethane foam factory in Eastern Europe with an on-site health clinic. The entire initial production workforce (N=49) was recruited to participate in the study following a brief informational session, during which employees learned about the study and informed consent was obtained. Workers completed an interviewer-administered questionnaire, underwent spirometry testing, and provided peripheral blood for serology pre-employment and at 6 and 12 months after employment. The human subjects study protocol was approved by oversight committees at the authors' respective home institutions; the Human Investigations Committee at Yale University, New Haven, CT, USA, and the Institutional Review Board at Environmental Health Center, Cluj-Napoca, Romania.

Questionnaire

A questionnaire-based pre-employment interview was administered to each worker to gather baseline data regarding demographics, general health, smoking history, respiratory

symptoms, occupational history, and expected job duties/department assignment. Follow-up interviewer-administered questionnaires contained additional questions regarding skin exposure, use of personal protective equipment (PPE) and temporal relationships of respiratory symptoms to work. Asthma-like symptoms included at least one of the following: cough, wheeze, chest tightness, and shortness of breath, and were classified as work-related if they worsened while at work and improved while away from work. Possible TDI skin exposure was determined from the questionnaire by assessing whether workers reported frequently touching or handling recently cured (within minutes of production) polyurethane foams.

Spirometry Testing

Spirometry at 6 and 12 months was performed with the PC Portable Microlyser (P&A Medical Limited, Blackrod, UK) according to ATS/ERS Guidelines [Miller, et al. 2005], including proper calibration and a minimum of 3 acceptable spirograms. Due to logistical issues pre-employment spirometry was performed on only 23 of the workers and at an alternate facility. The largest FVC and FEV_1 from all acceptable curves were chosen and compared to predicted values and lower limit of normal (LLN), and airflow obstruction was defined as FEV1/FVC < LLN, as recommended by the ATS/ERS [Pellegrino, et al. 2005]. Excessive longitudinal decline in FEV1 over the follow-up period was identified using a threshold of 15% decline from baseline, as recommended by ATS and ACOEM [Pellegrino, et al. 2005, Townsend, et al. 2011].

Blood Samples

Workers were invited to the factory's health clinic for venipuncture conducted by a licensed laboratory nurse. Approximately 20 ml of blood was collected from each worker via BD Vacutainer SST Plus Blood Collection Tubes (Becton, Dickenson and Company, Franklin Lakes, NJ). The blood was subsequently centrifuged at 400 x *g* and the serum fraction was aliquoted, and cryopreserved at -80°C.

TDI-Specific Antibodies

TDI-specific IgG and IgE levels in serum samples from each worker at baseline, 6-, and 12-months post-employment were measured using previously described enzyme-linked immunosorbent assays (ELISA) [Ye, et al. 2006]. Briefly, TDI-albumin conjugates (10 μg/ml) prepared by mixed phase (vapor/liquid) exposure methods were used to coat 96-well NUNC Maxisorp ELISA plates (Thermo Fisher Scientific Inc., Waltham, MA), followed by blocking with 3% dry milk in phosphate buffered saline (PBS). Workers' sera were diluted in 3% milk + PBS + 0.05% Tween 20 and TDI-specific IgG was detected with horseradish peroxidase linked anti-human IgG antibodies from Pharmingen (San Jose, CA), and expressed as an end-titer. For detecting TDI-specific IgE, plates were developed with biotinylated goat anti-human IgE (Bethyl; Montgomery, TX) followed by alkaline phosphatase conjugated streptavidin, and pNPP substrate from Thermo Fisher Scientific Inc.

Exposure Assessment

Airborne exposure information from the factory's foaming hall and cutting area was collected through continuous fixed-point air sampling with 18 minute sampling intervals using ChemLogic 1 direct reading instruments (DOD Technologies, Inc., Chrystal Lake, IL). Personal quantitative sampling was performed using flow pumps from Gilian (Sensidyne, LP, Clearwater, FL) and DuPont (E.I. du Pont de Nemours and Co., Wilmington, DE), which were calibrated before and after sampling to approximately 300 cc/min. Personal breathing zone samples were collected at 0.3 L/minute flow for 20-30 minutes on silica gel coated cartridges, and preserved at 4°C until analysis. TDI was extracted from cartridges by adding 2 mL methanol with shaking for two minutes. Following filtration, samples were analyzed by GC-MS (Shimadzu QP 2010 Plus; Kyoto, Japan), on an AT-502.2 capillary column, 60 m length, 0.32 mm diameter and 1.8 μm film thickness. Surface exposure was qualitatively assessed using colorimetric SWYPE™ wipes that develop color on contact with TDI, with depth of color roughly proportional to TDI concentration (Colormetric Laboratories, Inc., Des Plaines, IL) as previously described [Liu, et al. 2000]. Skin exposure was similarly evaluated using the colorimetric SWYPE™ on a single foam line worker.

Workers' Exposure Risk Goups

Workers were grouped with regard to their potential risk of TDI exposure (high, medium, low), based on their primary work location and duties, with the input of an industrial hygienist (JS) who had evaluated the plant. Workers who spent most of their time in the foaming hall, where foam was produced from raw materials including TDI were classified into the high exposure risk group; those who spent most of their time in the cutting area where foam blocks are cut to size after a period of curing, in the laboratory, where production samples are tested, and in maintenance were included in the medium exposure risk group, and the remaining workers, such as administrative, quality and warehouse, were included in the low exposure risk group.

Statistical Analysis

Statistical analysis was performed using SAS (SAS Institute, Cary, NC). Summary descriptive statistics were calculated for baseline variable characteristics. Associations between categorical variables were tested using Fisher's exact test, while continuous variables were compared using generalized linear modeling. A p value < 0.05 was considered statistically significant.

RESULTS

Plant, Demographics and Workforce Exposure Risk Groups

The plant, a new large modern facility with extensive engineering controls, was built to produce TDI-based polyurethane foams for home furnishings and related uses. Demographic and workforce characteristics of the initial 49 workers who were hired and enrolled, the 37 workers remaining at one-year follow-up in the study, and the 12 workers lost to follow-up are summarized in Table I. No new employees were enrolled during this time period. At baseline, the workers were predominately male (69.4%), middle-aged (mean 39 years),

smokers (40.8% current smokers), and none reported a past diagnosis of asthma. The potential risk of TDI exposure was estimated to be high for 13 subjects (26.5%) who worked in the foaming hall, medium for 28 subjects (57.1%) who worked in cutting, maintenance and laboratory areas, and low for the remaining 8 subjects (16.3%), based on job category. There were no significant differences in demographics or exposure risk group, comparing baseline, follow-up and lost to follow-up groups of workers.

Exposure Assessment

Continuous fixed-point air sampling performed in the foaming hall and cutting areas over the 1-year study period showed that airborne TDI concentrations were low, below the limit of detection (LOD) of 0.1 ppb in over 87% of the air recordings obtained in the cutting areas and over 95% of the readings from the foaming hall. Over the entire 12-month study period, the maximum TDI vapor concentration recorded was 10.0 ppb in the foaming hall and 5.4 ppb in the cutting area, and no air sampling period exceeded the threshold limit value (TLV) for a 8-hr workday assigned by the American Conference of Governmental Industrial Hygienists (ACGIH) for TDI (5.0 ppb; 36 ug NCO/m^3), the occupational exposure limit used in the United Kingdom, and many European countries[Bello, et al. 2004]. The peak exposures recorded were also below the Permissible Exposure Limit (PEL) ceiling for TDI (20 ppb) set by the Occupational Safety and Health Administration (OSHA)[Bello, et al. 2004].

Representative TDI air sample data from the cutting area for a 6-week period between November and December 2010 is shown in Figure 1. While most levels are below the LOD (0.1 ppb), brief intermittent TDI exposures were noted, the majority of these below 5 ppb. A 6-day period within the 6-week period shows several peak exposures in the cutting area on production days between 10 am and 2 pm(peak production time periods) and non-detectable airborne TDI levels during non-production hours (e.g. weekends). Consistent with the fixed-point air sample monitoring, the limited personal quantitative air sampling performed on 7 different workers in the foaming hall and cutting area all showed TDI levels below the LOD (data not shown).

The potential for TDI skin exposure was evaluated using TDI qualitative SWYPE™ sampling of selected environmental surfaces in the plant and worker questionnaires. Eleven surfaces in the cutting room and foaming hall, including tables, handrails, machinery, and foam were sampled. Three of the 11 (27.2%) surface SWYPE™ samples were positive, including two SWYPE™ samples taken of the paper lining that had been peeled from the cured polyurethane foam at the end of the line, obtained within minutes of emerging from the curing oven, immediately before initial cuts are made. Additionally the hands of one worker who had just cleaned the foaming head sampled positive for TDI using the SWYPE™ wipes. Based on the questionnaire data, thirteen workers (28.2%) reported potential TDI skin contact (e.g. from handling freshly cured product or recently used machine part).

Workers Lost to Follow-up

Twelve of the initial 49 workers (24.5%) in this inception cohort were no longer available for follow-up by the end of their first 12-months of employment, as shown in Tables I and II. Six of these 49 workers (12.2 %) had resigned and were no longer working at the plant at the time of follow-up, 4 workers were still employed by the company but not available for follow-up, and two workers refused subsequent participation. There were no differences in demographics or exposure risk group, comparing the lost to follow-up group to the other workers.

Asthma Symptoms

The asthma symptom data at baseline, 6 and 12-month follow-up is summarized in Table II, including the available data on the 12 workers lost to follow-up during this 1 year follow-up period. The overall prevalence of symptoms was low, and similar comparing baseline and the 2 follow-up times. However, a significantly higher proportion of workers lost to follow-up (3/12; 25%) reported current asthma-like symptoms, compared to those who remained enrolled in the study (1/37; 2.7%) (p=0.04). Considering only those workers no longer employed at the company, 1/6 (16.7%) reported current asthma symptoms compared to 3/43 (7.0%) of those still employed by the company, whether or not available for follow-up. Three workers (7.1%) reported new asthma-like symptoms during the study, including one worker who reported a temporal relationship of his symptoms with work at 6 months, and by 12 months had resigned and left the workplace.

Isocyanate Serology

Serum TDI-specific IgG and IgE results are shown in Table II, with no significant differences noted between the groups of workers. Of note, one worker, a maintenance worker with prior occupational TDI exposure, exhibited an elevated TDI-specific IgG (titer 1:160) pre-employment, which was then negative at 6 and 12 months after employment at this new plant. Another worker developed a positive TDI-IgG (titre 1:40) between employment and the 6-month follow-up, which then resolved by 12 months, during which time the worker had been transferred to a low exposure job. All TDI-specific IgE tests were negative at 6 months, and not tested at the other time points due to sample limitations.

Spirometry

The results of spirometry testing at baseline, 6 months and 12 months follow-up are shown in Table II. Spirometry was obtained on all available workers at 6 and 12 months. However, due to logistical issues, spirometry was obtained on only 24 of the 49 (49 %) workers at baseline, and the baseline testing was performed at a different site than the follow-up testing. There were no significant differences in FEV_1, FVC and FEV_1/FVC comparing baseline, follow-up and the workers lost to follow-up, or when comparing only those workers with spirometry data at all 3 time points (N=16), although there was a trend towards lower FEV_1 and FVC values at baseline vs. follow-up in this sub-group (data not shown). Of note, no workers had airflow obstruction (FEV_1/FVC < LLN) at baseline, 1 worker (2.4%) had airflow obstruction at 6 months (initial test for that worker) and 2 workers (5.4%) had airflow obstruction at 12 months, one of whom had new onset airflow obstruction (1/37;

2.7%). Additionally, at 6 months follow-up no workers had a decrease in FEV_1 of > 15% and 6 /19 (31.6%) showed an increase in FEV_1> 15%, consistent with lower spirometry values noted at baseline. At 12 months follow-up, a decrease in FEV_1 of > 15% was measured in 3 workers (9.1%) between 6 and 12 months follow-up, one of whom reported new asthma symptoms. Three workers exhibited an increase in FEV > 15% between 6 and 12 months.

Relationships with Exposure Risk

The relationships between exposure risk groups, health outcomes, reported skin exposure and loss to follow-up were explored (Table III). No significant associations were observed between the assigned exposure risk group, based on job category, and new asthma-like symptoms, new eye irritation, baseline lung function, change in lung function over the year of follow-up, or workers lost to follow-up (Table III and data not shown). Self-reported glove use differed significantly between workers in the different exposure risk groups. All 13/13 workers (100%) of the high exposure risk group reported glove use, while only 8/25 workers (32.0%) in the medium risk group used gloves. The potential for skin exposure, reported by 28.3% of the workers, was similar in all exposure groups and was not significantly associated with glove use, symptoms, or lung function (data not shown). Together, the data suggest workers in the medium and low exposure risk groups, may benefit from additional protective equipment to prevent future exposures.

Workers with Possible Early TDI-Related Health Effects

Although the company reported no known cases of isocyanate-related allergy or asthma, over the first year of follow-up 7 of the 49 original workers (14.2%) developed either new asthma symptoms (N=3), a positive TDI-IgG (N=1), new airflow obstruction (N=1) or a decline in FEV_1 ≥15% (N=3), findings that could indicate TDI-related health effects. For example, one worker, a laboratory chemist, developed a 1:40 titer of TDI-IgG and new-onset eye irritation during the first 6 months of employment, after which she changed to a low exposure risk job, and at the 12 month follow-up evaluation both had both resolved. A second worker, from the cutting area, reported new asthma-like symptoms that were work related at 6 months and had left the company at the 1-year follow-up. A third worker, from the warehouse ,developed new asthma-like symptoms by 6 months, and exhibited a greater than >20% decrease in FEV_1 between 6 and 12 months post-employment. Together the findings in these workers suggest possible increased risk for isocyanate sensitization and asthma, despite very low measured airborne TDI exposures. More thorough medical evaluation of selected workers, such as bronchodilator testing or peak flow monitoring, was not possible.

DISCUSSION

To our knowledge this is the first longitudinal inception cohort study of polyurethane foam production workers in a modern facility designed to minimize airborne TDI exposures, despite the expanding use of polyurethane in numerous industries and types of manufacturing. Data were obtained during the initial year of the modern factory's operation, with longitudinal evaluation of workers pre-employment, and at 6-month intervals post-

employment. Measured airborne TDI levels were very low, well below PELs for TDI established by advisory and/or regulatory agencies. Over the first year of follow-up, 7 workers (14.2%) developed findings that could indicate TDI-related health effects, and workers not available for follow-up were more likely to have reported current asthma symptoms. These findings highlight the potential risks of isocyanate exposure, even at levels traditionally considered very low, and the need for further epidemiology studies, ideally longitudinal inception cohort studies.

Several findings from this 1-year longitudinal follow-up of an inception cohort of polyurethane foam production workers are notable. First, follow-up evaluation could not be performed on almost 25% (12/49) of the initial workers over the first year; 6 of whom had resigned; the others had refused participation or were not available. These findings highlight the practical challenges of investigating isocyanate exposure risks, and the limitations of cross-sectional studies when studying workers at risk for occupational asthma [Kreiss and Heederik 2010, Le Moual, et al. 2008]. A priori, we expected excellent follow-up of the initial workers, given local economic considerations, the modern facilities, government-mandated medical surveillance of workers, and the established relationship between members of the investigative team and the plant. The large proportion of workers not available to follow-up, while unexpected, is consistent with other longitudinal studies of isocyanate exposed cohorts, where up to 50% (or more) of the workers were lost to follow-up [Grammer, et al. 1988, Petsonk, et al. 2000, Redlich, et al. 2002, Wegman, et al. 1982], or where follow-up was not clearly detailed [Cassidy, et al. 2010, Clark, et al. 1998].

A second notable finding from this study was the potential for exposure to TDI, despite the modern facilities and intensive industrial hygiene efforts, including ventilation, automated, enclosed production machinery, and continuous real-time monitoring of airborne concentrations. Although most area air sample measurements were below the limit of detection, and never exceeded OSHA's ceiling PEL, or the more conservative TLV recommended by the ACGIH and similar European advisory councils (see above), TDI vapor levels from 0.5 to 5 ppb were commonly measured at the 2 stationary monitors during peak foam production hours (10AM-2PM), and could have been higher at the source. Furthermore, intermittent low level spikes in TDI air levels occurred in both the foaming hall, where workers expect potential exposure and wear protective equipment, and the cutting area, where exposure is not expected and workers rarely wear protective equipment. Further exposure assessment, especially during peak foam production, could help target additional industrial hygiene controls.

The overall prevalence of asthma symptoms and/or immunologic sensitization to TDI was low among workers that completed their first year of employment at this modern TDI polyurethane production facility. However, 14.2% of the original workers developed findings suggestive of possible TDI-related health effects (new asthma symptoms, TDI-specific IgG, new airflow obstruction, and/or a decline in FEV_1 ≥15%). These findings should be considered in the context of available diagnostic tests for isocyanate sensitization and asthma, as well as uncertainty regarding the natural history of disease. There is no widely available diagnostic test to confirm isocyanate asthma and the time to onset can be highly variable. While isocyanate asthma has been reported to occur within weeks to months

of exposure, the latency period between onset of exposure, immune sensitization, and asthma symptoms may vary and has been difficult to define [Malo, et al. 1992, Ott, et al. 2000, Petsonk, et al. 2000, Tarlo and Liss 2002]. With continuing improvements in industrial hygiene and reduction of airborne TDI levels, the latency period, may be further increased. Long-term follow-up of the current cohort, while challenging, is needed, as well as further evaluation of those with findings suggestive of possible isocyanate asthma, to better understand the risks of isocyanate exposures, and to assess whether current work controls are effective at preventing isocyanate sensitization and asthma.

This study data also demonstrated potential TDI skin exposure of the workers (based on limited SWYPE™ qualitative testing and questionnaire data), which may represent another exposure route (besides respiratory) capable of inducing systemic immune sensitization. Notably, TDI was detected on surfaces that workers touch when not wearing gloves (such as handrails, table) and 28.2% of all workers reported potential TDI skin contact by questionnaire. Site visits during the study documented extensive use of respiratory and skin PPE (masks, gloves, goggles, and coveralls) in the foaming room during production, but more limited use of PPE in the cutting room (coveralls and occasional gloves), consistent with the questionnaire data. Also noted was unprotected hand contact with uncured or just cured polyurethane (within minutes of production) during cleaning of the “foaming head”, where the positive skin and surface SWYPE™ samples were detected, and contact with just-cured foam,within minutes of emerging from the production oven. We are not aware of other studies that have evaluated skin exposure in polyurethane production facilities.

Several limitations of the study should be recognized, mainly related to the size of the cohort, the follow-up time period, and the suboptimal spirometry. The size of the inception cohort was constrained by the company’s production plans and an automated manufacturing process. As noted above, the 1-year follow-up duration limits insight into the prevalence of TDI sensitization and asthma, which can take longer than 1 year to develop, and almost 25% of the initial inception cohort was lost to follow-up. The reason(s) workers had resigned from the company or refused to participate was not available. Efforts are on-going to follow-up these workers. Further medical evaluation of workers with findings suggestive of possible isocyanate asthma could help clarify risk, but was not feasible. Unfortunately baseline spirometry was obtained on less than half of the workers and at a different facility, and the full spirometry data was not available, limiting quality assessment and analysis. These considerations were taken into account in interpreting the findings.

Another limitation of the study was the limited TDI air and skin exposure assessment and the job-based assignment to exposure risk groups, which may have misclassified some workers. Airborne TDI levels were based almost exclusively upon fixed area samples, which may not accurately reflect individual exposures, especially during selected tasks such as cleaning and maintenance, and localized TDI air levels may have been higher near the source. Methods for quantifying isocyanate skin exposure remain experimental; thus, the present investigation relied upon questionnaire data and qualitative approaches of assessment. The relatively small sample size and low prevalence of symptoms, TDI-IgG and other outcomes limited statistical power to compare workers in the different exposure risk

groups. Limited funding also prohibited more extensive quantitative isocyanate exposure assessment, or sampling for other sensitizers or irritants that might also be present.

In summary, the present investigation describes a unique inception cohort from a new modern polyurethane foam factory with very low measured airborne TDI levels, but also recurrent higher intermittent exposures during peak periods of foam production. Over the first year of follow-up 7 workers (14.2%) developed respiratory symptoms, TDI-specific IgG and/or changes in spirometry, findings that could represent early TDI-related health effects, and workers who were lost to follow-up were more likely to report current asthma symptoms than those still working. Further longitudinal follow-up of the current workforce, including those lost to follow-up, as well as better exposure assessment, are needed to better characterize the risks of TDI exposure in modern polyurethane production facilities.

Acknowledgments

The authors would like to thank the Environmental Health Center of Cluj-Napoca, Romania, for support in conducting the present study.

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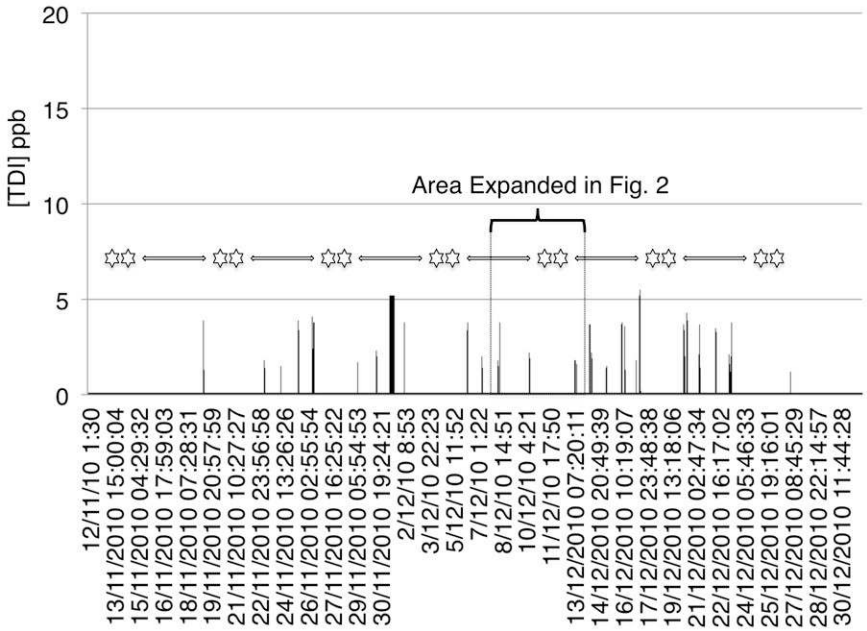

Figure 1.

Airborne TDI levels for representative 6-week period. Y-axis depicts TDI concentration in parts per billion, over time (X-axis). Each spike represents one 18 minute long period of measurement. Representative data from the cutting room are shown for a 6-week period (Nov-Dec 2010). Long dashes are weekdays and stars represent weekends. Boxed area is enlarged in Figure 2.

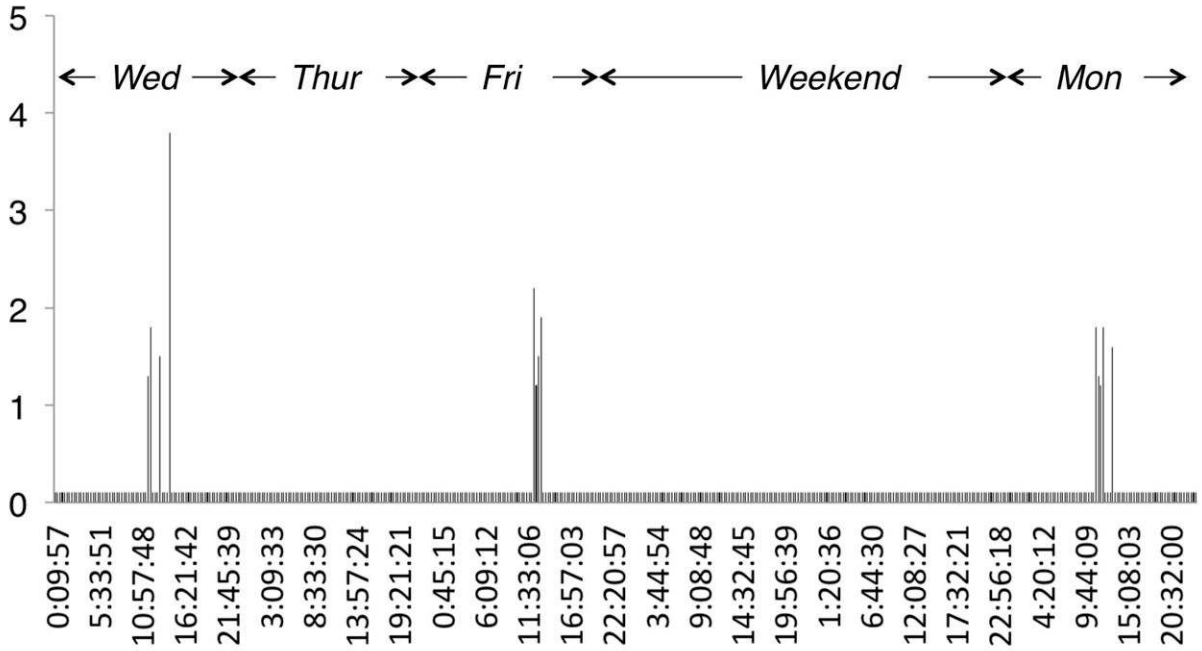

Figure 2.

Airborne TDI levels for representative 6-day period. Y-axis depicts TDI concentration in parts per billion, over time (X-axis). Area measurements for the 6-day period (indicated in Fig. 1) highlight typical patterns of daily fluctuation.

Table I

Demographic Characteristics and Workforce Exposure Risk Groups

Characteristic	Baseline N (% total)	12 month N (% total)	Workers lost to follow-up N (% total)*
Total workers	49 (100)	37 (100)	12 (100)
Gender			
Male	34 (69.4)	26 (70.3)	8 (66.6)
Female	15 (30.6)	11 (29.7)	4 (33.3)
Age (years)			
Mean±SD	39.1 ± 11.6	40.6 ± 11.8	37.8 ± 11.5
Range	20-59	21-59	24-59
Smoker			
Current	20 (40.8)	15 (40.5)	5 (41.7)
Former	8 (16.3)	6 (16.2)	2 (16.7)
Never	21 (42.9)	16 (43.2)	5 (41.7)
Diagnosed asthma			
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Job risk group			
Low[a]	8 (16.3)	8 (21.6)	2 (16.7)
Medium[b]	28 (57.1)	18 (48.6)	8 (66.7)
High[c]	13 (26.5)	11 (29.7)	2 (16.7)

N=number of workers/total number of workers for which data were available (%)

*Six workers had resigned and were no longer working at the plant, 4 were not present, and 2 refused to participate.

[a]Administrative/quality and engineer/fire guard workers

[b]Cutting/laboratory/maintenance workers

[c]Foaming hall workers

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Table II

Questionnaire, Spirometry, and Serology Data at Baseline and Follow-up

	Baseline* N=49	6 month* N=42	12 month* N=37	Lost to Follow-up** N=12
Overall symptoms n (%)				
Current asthma symptoms	3/49 (6.1)	3/42[a] (7.1)	1/37 (2.7)	3/12 (25.0)[e]
New asthma symptoms	N/A	3/42 (7.1)	0/37 (0.0)	1/9 (11.1)
New eye irritation	N/A	1/42 (2.4)	1/37 (2.7)	0/9 (0.0)
Spirometry				
FEV_1 L (mean± SD);	3.27 ± 0.75	3.77 ± 0.76	3.88 ± 0.99	3.72 ± 0.85
% pred (mean ± SD)	88.0 ± 12.0	98.0 ± 13.0	99.0 ± 15.0	99.0 ± 14.0
FVC L (mean ± SD)	4.02 ± 0.90	4.48 ± 0.85	4.55 ± 1.08	4.46 ± 1.04
% pred (mean ± SD)	86.0 ± 11.0	94.0 ± 13.0	94.0 ± 14.0	95.0 ± 15.0
FEV_1/ FVC (mean± SD)	0.82 ± 0.08	0.84 ± 0.07	0.85 ± 0.09	0.84 ± 0.04
FEV1/FVC < LLN (n, %)	0/23 (0.0)	1/42 (2.4)	2/37 (5.4)	0/9 (0.0)
Declinein FEV_1 > 15% (n, %)	N/A	0/19 (0.0)	3/33 (9.1)	0/3 (0.0)
ELISA				
TDI IgG positive	1/48[b] (2.1)	1/39[c] (2.6)	0/37 (0.0)	0/11 (0.0)
TDI IgE positive	NT[d]	0/39 (0.0)	NT	0/12 (0.0)

*Number of workers/total number of workers for which data were available (%)

**Of the 12 subjects lost to follow-up, 6 were no longer working at the plant, 4 were not available and two refused to participate.

[a]One worker reported work-related asthma symptoms at 6 month follow-up

[b]One worker with TDI-IgG at baseline tested negative in the follow-up period.

[c]Another worker with negative IgG at baseline developed positive IgG at 6-month follow-up.

[d] NT=Not tested

[e] Current asthma symptoms were reported (at baseline or 6 months) in a higher percentage of workers subsequently lost to follow-up vs. those who completed the study (25 vs. 2.7%; p = 0.04).

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Table III

Comparison Across Workforce Exposure Risk Groups Over 1 Year Follow-Up Period

	All* N=49	Low risk* N=8	Medium risk* N=28	High risk* N=13
New asthma symptoms	3/46 (6.5)	1/8 (12.5)	2/25 (8.0)	0/13 (0.0)
New eye irritation	2/42 (4.8)	0/8 (0.0)	2/22 (9.1)	0/12 (0.0)
New air flow obstruction: (FEV_1/FVC < LLN)	1/40 (2.5)	1/6 (16.7)	0/22 (0.0)	1/12 (0.0)
Decline in FEV_1 > 15%	3/40 (7.5)	1/6 (16.7)	2/22 (9.1)	0/12 (0.0)
Gloves worn**	25/46 (54.3)	4/8 (50.0)	8/25 (32.0)	13/13 (100.0)
Self-reported skin exposure	13/46 (28.3)	2/8 (25.0)	8/25 (32.0)	3/13 (23.1)
Workers lost to follow-up	12/49 (24.5)	2/8 (25.0)	8/28 (28.6)	2/13 (15.4)

* Number of workers / total number in each category (% total)

** $p < 0.05$ comparing the exposure risk groups. Fisher's exact test was performed to generate p values.