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Inception Cohort Study of Workers Exposed to Toluene Diisocyanate at a Polyurethane
Foam Factory

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Wei Gui
2014

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. The purpose of the present investigation was to evaluate 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 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 FEV1 $\geq 15\%$ (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 study (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.

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INTRODUCTION:

Isocyanates are highly reactive chemical compounds characterized by the presence of N=C=O groups widely used for the production of a variety of products including foams, adhesives, coating materials, and elastomers^{1,2}. There are many different forms of isocyanates used in the various industries, of which the most commonly used are the monoisocyanate (one functional N=C=O group per molecule) methyl isocyanate (MIC) and the diisocyanates (two functional N=C=O groups per molecule) toluene diisocyanate (TDI), diphenyl-methane diisocyanate (MDI), hexamethane diisocyanate (HDI), and isophorone diisocyanate (IPDI)^{2,3}. Previous studies have clearly shown that exposure to isocyanates may lead to occupational asthma¹.

Although isocyanates remain one of the most commonly reported causes of occupational asthma⁴, 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 industries⁵. 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^{6,7}. 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 effect⁸. The few longitudinal studies have been conducted largely at primary isocyanate production facilities^{9,10}, rather than secondary polyurethane 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. The factory is located in the city of Baia Mare in the Maramureş region of northwest Romania, approximately 600 kilometres away from the capital city of Bucharest, 70 kilometres away from the Hungarian border, and 50 kilometres away from the Ukrainian border. 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 initial 12-month study period showed that almost 25% of the initial workers were lost to follow-up and 14.2% had findings that could indicate risk for the development of isocyanate asthma.

The data contained in the present investigation were obtained from January 2010 to January 2011 as an international collaborative research effort between investigators at the Yale University School of Medicine in the New Haven, Connecticut, United States and the Environmental Health Center in Cluj-Napoca, Romania. After careful compilation of the data, analysis and interpretation were subsequently undertaken and the final findings are presented in this report. The author of this Yale University School of Medicine thesis,

W.G., takes full responsibility for the contents and all efforts have been made to ensure the accuracy of the data.

SPECIFIC AIMS:

- 1) To characterize TDI exposure, TDI sensitization, and TDI-health effects in a modern TDI polyurethane plant via air sampling monitoring, questionnaires, serum antibody immunoassays, and spirometry.
- 2) To better understand the incidence and natural history of TDI sensitization and TDI-induced occupational asthma (OA) through the longitudinal inception cohort study design.
- 3) To apply the results from the study to reduce TDI exposures and the risk of TDI-sensitization and related health effects.

HYPOTHESIS:

Despite the presence of state of the art control measures to limit the exposure to isocyanates at the newly built, modern polyurethane production factory, opportunities for isocyanate exposure, sensitization and subsequent health effects in the workers may occur.

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 of the Human Investigations Committee (HIC) at Yale University, New Haven, Connecticut, United States, and the Institutional Review Board at Environmental Health Center, Cluj-Napoca, Romania.

The HIC protocol was predominantly prepared and updated by Dr. Meredith Stowe at the Yale Occupational and Environmental Medicine Program. I provided input and recommendations where appropriate.

Questionnaire:

Pre-employment questionnaire:

A pre-employment questionnaire was created to gather baseline data regarding: a) demographics; b) respiratory health; c) smoking history; d) general health; e) employment history; f) personal protective equipment; g) ventilation at the workplace; h) cleaning at the workplace.

This baseline questionnaire was developed by our colleagues at the Environmental Health Center in Romania based on previous experience with regional workplace populations and was implemented prior to employment for the workers.

6-month follow-up questionnaire:

Questionnaires were administered in an interview-based format. Workers were invited to the health clinic, as a private environment, for completion of the questionnaires. The workers were informed that their employers did not have any access to their confidential responses and were asked to answer each question truthfully. If they did not have an answer to a question, they answered with the phrase “I Don’t Know”. 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: 1) cough, 2) wheeze, 3) chest tightness, and 4) 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 polyurethane foams.

I was responsible for creating the follow-up questionnaire and providing directions for implementation. The questionnaire was administered by our colleagues in Romanian with consultation from our team at the Yale Occupational and Environmental Medicine Program. Once the gathering of data was complete, I compiled the data and performed the analyses.

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 Guidelines¹¹, including proper calibration and a minimum of 3 acceptable spirograms. Due to logistical issues pre-employment spirometry was performed on only 24 of the workers and at an alternate facility.

The largest FVC and FEV1 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/ERS¹². 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^{12,13}.

All of the spirometry testing was performed by our colleagues in Romania. Once the testing was complete, I compiled all of the spirometry data and performed the analyses of the data.

Serology Testing:

Venipuncture:

Workers were invited to the health clinic at the factory site for venipuncture conducted by a trained and licensed laboratory nurse. The clinic was located in a building approximately 500 m away from the raw materials and manufacturing complex and was separated into three rooms: a) office and administrative duties room; b) exam and medicines room; c) venipuncture room.

The venipuncture room had the approximate dimensions of 3 m x 4 m and contained a sink, a counter, and a few chairs. Each worker was asked to sit down on the chair and extend each arm for the nurse to examine. Once the arm with the vein deemed most suitable for venipuncture was chosen, the worker extended the chosen arm and rested the arm on top of the back of a chair. The nurse then applied an elastic band on the arm proximal to the site of venipuncture and asked the worker to make a fist with that arm. A BD Vacutainer SST Plus Blood Collection Tube (Becton, Dickenson and Company, Franklin Lakes, NJ) was attached to a standard phlebotomy needle and the worker's superficial cubital fossa was wiped with a cotton swab covered with isopropyl alcohol. The needle was then inserted into a suitable vein in the superficial cubital fossa and the

Vacutainer Tube began to fill with blood. Before the tube fully filled with blood, the rubber band was released from the worker's arm and the worker was asked to release the fist. When the tube was filled to approximately 10 mL of blood, the nurse released the tube from the needle. The needle was subsequently released and the cotton swab was applied to the place at which the needle was inserted. 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 enzyme linked immunosorbent assays (ELISA)¹⁴. 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. Plates were read using BioRad Model 550 Microplate Reader at dual wavelengths of 450 nm/550 nm for TDI-specific IgG assays and at 415 nm/550 nm for TDI-specific IgE assays.

The blood draws were completed by our colleagues in Romania and the antibody assays were performed by Jian Liu with direction from Dr. Wisnewski at the Yale Department of Internal Medicine. I was present in the laboratory for a significant portion of the assays. Once the results were available, I performed additional analyses.

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)¹⁵. Skin exposure was similarly evaluated using the colorimetric SWYPE™ on a single foam line worker.

Workers' Exposure Risk Groups:

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 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.

The exposure analyses were jointly performed by Judy Sparer and myself during our site visit to Romania and upon return to the Yale Occupational and Environmental Medicine Program. I was responsible for compiling the exposure data and for performing additional analyses.

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.

Statistical analyses were predominantly performed by Dr. Slade at the Yale Occupational and Environmental Medicine Program. However, I was present to answer questions and for consultation for the majority of the analyses performed.

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 (0.005 ppm; 36 ug NCO/m³), the occupational exposure limit used in the United Kingdom, and many European countries¹⁶. The brief peak exposures recorded were also well below the Permissible Exposure Limit (PEL) ceiling for TDI (0.020 ppm) set by the Occupational Safety and Health Administration (OSHA)¹⁶.

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.

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, before cutting the foam. 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 the 49 workers (20.4%) were no longer working at the plant at the time of follow-up, one of whom was reported as being "sick" at 6-month follow-up, 4 workers were "unavailable" during 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 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 working and enrolled in the study (1/37; 2.7%) ($p=0.04$). However, considering only those workers who were lost to follow-up and had left the company compared to those who were reportedly still employed, 16.7% (1/6) who left the company had reported current asthma symptoms compared to 7.0% (3/43) who were still employed. The only worker who reported new asthma symptoms that were work-related had resigned and left the workplace. Three workers reported new asthma-like symptoms over the 12 months (7.1%), including the worker noted above, who reported a relationship between his symptoms and work (at 6 months) and at 12 months was lost to follow-up (as noted above).

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 (titer 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 I. Spirometry was obtained on all workers not lost to follow-up at 6 and 12 months. However, due to logistical issues, spirometry was available 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 FEV1, FVC and FEV1/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). Of note, no workers had airflow obstruction ($FEV1/FVC < LLN$) 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, a decrease in FEV1 of $> 15\%$ was noted in 3 workers (9.1%) between baseline and 12 months, one of whom reported new asthma symptoms.

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. 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.

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 FEV1 > 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 resolved. A second worker, from the cutting area, reported new asthma-like symptoms that were work related at 6 months and was then lost to follow-up at the 1-year follow-up. A third worker, from the warehouse (low exposure risk), developed new asthma-like symptoms by 6 months, and exhibited a greater than >20% decrease in FEV1 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 new 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, 12 of the initial 49 workers (24.5%) were lost to follow-up and 7 workers (14.2%) developed findings that could indicate TDI-related health effects. These findings highlight the potential risks of isocyanate exposure, even at very low levels, 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, almost 25% of the initial inception cohort of workers was lost to follow-up over the first year. 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 lost 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-up¹⁷⁻²⁰, or where follow-up was not clearly detailed^{21,22}.

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 during peak foam production hours (10 AM - 2 PM). 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.

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 FEV1 > 15%). These findings should be considered in the context of (the lack of) available diagnostic tests for isocyanate sensitization and asthma, as well as uncertainty regarding the natural history of disease. 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^{4,10,18,23}. With continuing improvements in industrial hygiene and reduction of airborne TDI levels, the latency period, if it occurs, may be further increased. More 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 may 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 in the foaming room during production, but more limited use of PPE in the cutting room (occasional gloves), consistent with the questionnaire data. Also noted was unprotected hand contact with uncured or just cured polyurethane during cleaning of the “foaming head”, where the positive skin and surface SWYPE™ samples were detected, and contact with just cured foam emerging from the production oven.

Based on the findings of the study, several recommendations have been made to further protect the workers from exposure to isocyanates. Although careful, conscious design of

the facilities has been implemented to limit airborne exposures, measures to protect workers against skin exposure are suggested. Further testing should be performed with greater sensitivity to ensure that the polyurethane foam is safe to handle when it is cut. Additionally, gloves that are impervious to both isocyanates and other potential co-exposures should be provided and enforced for workers cleaning the foaming head due to potentially significant exposure to isocyanates.

Several limitations of the study should be recognized, mainly related to limited size of the cohort, the limited 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 resigned, refused, or were not present was not generally available. Efforts are on-going to follow-up these workers. Further medical evaluation of the 7 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 exposure assessment.

In summary, the present investigation describes a unique inception cohort from a new modern polyurethane foam factory with very low measured airborne TDI levels. Twelve of the initial 49 workers (24.5%) were lost to follow-up in the first year. These workers were significantly more likely to report current asthma symptoms, and also included the only worker with new asthma symptoms that were work-related, suggesting a possible healthy worker effect. Among the 37 workers that completed the study, 7 workers either developed respiratory symptoms, TDI-specific IgG and/or changes in spirometry that may represent early TDI-related health effects. 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.

REFERENCES:

1. Fisseler-Eckhoff A, Bartsch H, Zinsky R, Schirren J. 2011. Environmental isocyanate-induced asthma: morphologic and pathogenetic aspects of an increasing occupational disease. *Int J Environ Res Public Health* 8: 3672-3687.
2. Raulf-Heimsoth M, Baur X. 1998. Pathomechanisms and pathophysiology of isocyanate-induced diseases--summary of present knowledge. *Am J Ind Med* 34: 137-143.
3. Redlich CA, Karol MH. Diisocyanate asthma: clinical aspects and immunopathogenesis. *International Immunopharmacology*. 2: 213–224. 2002.
4. Tarlo SM, Liss GM. 2002. Diisocyanate-induced asthma: diagnosis, prognosis, and effects of medical surveillance measures. *Appl Occup Environ Hyg* 17: 902-908.
- Townsend MC, Occupational, Environmental Lung Disorders C. 2011. Spirometry in the occupational health setting--2011 update. *J Occup Environ Med* 53: 569-584.
5. Creely KS, Hughson GW, Cocker J, Jones K. 2006. Assessing isocyanate exposures in polyurethane industry sectors using biological and air monitoring methods. *Ann Occup Hyg* 50: 609-621.
6. Pronk A, Preller L, Raulf-Heimsoth M, Jonkers IC, Lammers JW, Wouters IM, Doekes G, Wisnewski AV, Heederik D. 2007. Respiratory symptoms, sensitization, and exposure

response relationships in spray painters exposed to isocyanates. *Am J Respir Crit Care Med* 176: 1090-1097.

7. Redlich CA, Stowe MH, Wisnewski AV, Eisen EA, Karol MH, Lemus R, Holm CT, Chung JS, Sparer J, Liu Y, Woskie SR, Appiah-Pippim J, Gore R, Cullen MR. 2001. Subclinical immunologic and physiologic responses in hexamethylene diisocyanate-exposed auto body shop workers. *Am J Ind Med* 39: 587-597.

8. Le Moual N, Kauffmann F, Eisen EA, Kennedy SM. 2008. The healthy worker effect in asthma: work may cause asthma, but asthma may also influence work. *Am J Respir Crit Care Med* 177: 4-10.

9. Ott MG. 2002. Occupational asthma, lung function decrement, and toluene diisocyanate (TDI) exposure: a critical review of exposure-response relationships. *Appl Occup Environ Hyg* 17: 891-901.

10. Ott MG, Klees JE, Poche SL. 2000. Respiratory health surveillance in a toluene diisocyanate production unit, 1967-97: clinical observations and lung function analyses. *Occup Environ Med* 57: 43-52.

11. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N,

McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, Force AET. 2005. Standardisation of spirometry. *Eur Respir J* 26: 319-338.

12. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. 2005. Interpretative strategies for lung function tests. *Eur Respir J* 26: 948-968.

13. Townsend MC, Occupational, Environmental Lung Disorders C. 2011. Spirometry in the occupational health setting--2011 update. *J Occup Environ Med* 53: 569-584.

14. Ye YM, Kim CW, Kim HR, Kim HM, Suh CH, Nahm DH, Park HS, Redlich CA, Wisnewski AV. 2006. Biophysical determinants of toluene diisocyanate antigenicity associated with exposure and asthma. *J Allergy Clin Immunol* 118: 885-891.

15. Liu Y, Sparer J, Woskie SR, Cullen MR, Chung JS, Holm CT, Redlich CA. 2000. Qualitative assessment of isocyanate skin exposure in auto body shops: a pilot study. *Am J Ind Med* 37: 265- 274.

16. Bello D, Woskie SR, Streicher RP, Liu Y, Stowe MH, Eisen EA, Ellenbecker MJ, Sparer J, Youngs F, Cullen MR, Redlich CA. 2004. Polyisocyanates in occupational environments: a critical review of exposure limits and metrics. *Am J Ind Med* 46: 480-491.

17. Grammer LC, Eggum P, Silverstein M, Shaughnessy MA, Liotta JL, Patterson R. 1988. Prospective immunologic and clinical study of a population exposed to hexamethylene diisocyanate. *J Allergy Clin Immunol* 82: 627-633.
18. Petsonk EL, Wang ML, Lewis DM, Siegel PD, Husberg BJ. 2000. Asthma-like symptoms in wood product plant workers exposed to methylene diphenyl diisocyanate. *Chest* 118: 1183-1193.
19. Redlich CA, Stowe MH, Coren BA, Wisnewski AV, Holm CT, Cullen MR. 2002. Diisocyanate exposed auto body shop workers: a one-year follow-up. *Am J Ind Med* 42: 511-518.
20. Wegman DH, Musk AW, Main DM, Pagnotto LD. 1982. Accelerated loss of FEV- in polyurethane production workers: a four-year prospective study. *Am J Ind Med* 3: 209-215.
21. Cassidy LD, Molenaar DM, Hathaway JA, Feeley TM, Cummings BJ, Simpson P, Li SH. 2010. Trends in pulmonary function and prevalence of asthma in hexamethylene diisocyanate workers during a 19-year period. *J Occup Environ Med* 52: 988-994.

22. Clark RL, Bugler J, McDermott M, Hill ID, Allport DC, Chamberlain JD. 1998. An epidemiology study of lung function changes of toluene diisocyanate foam workers in the United Kingdom. *Int Arch Occup Environ Health* 71: 169-179.

23. Malo JL, Ghezzo H, D'Aquino C, L'Archeveque J, Cartier A, Chan-Yeung M. 1992. Natural history of occupational asthma: relevance of type of agent and other factors in the rate of development of symptoms in affected subjects. *J Allergy Clin Immunol* 90: 937-944.

Table I. Demographic Characteristics and Workforce Exposure Risk Groups			
Characteristic	Baseline N (% total)	12 month N (% total)	Workers lost to follow-up N (% total)*
<i>Total workers</i>	49 (100)	37 (100)	12 (100)
<i>Gender</i>			
Male	34 (69.4)	26 (70.3)	8 (66.6)
Female	15 (30.6)	11 (29.7)	4 (33.3)
<i>Age (years)</i>			
Mean \pm SD	39.1 \pm 11.6	40.6 \pm 11.8	37.8 \pm 11.5
Range	20-59	21-59	24-59
<i>Smoker</i>			
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)
<i>Diagnosed asthma</i>			
Yes	0 (0.0)	0 (0.0)	0 (0.0)
<i>Job risk group</i>			
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 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			

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); % pred (mean ± SD)	3.27 ± 0.75 88.0 ± 12.0	3.77 ± 0.76 98.0 ± 13.0	3.88 ± 0.99 99.0 ± 15.0	3.72 ± 0.85 99.0 ± 14.0
FVC L (mean ± SD); % pred (mean ± SD)	4.02 ± 0.90 86.0 ± 11.0	4.48 ± 0.85 94.0 ± 13.0	4.55 ± 1.08 94.0 ± 14.0	4.46 ± 1.04 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
FEV ₁ /FVC < LLN (n, %)	0/23 (0.0)	1/42 (2.4)	2/37 (5.4)	0/9 (0.0)
Decline in 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)
<p>*Number of workers/total number of workers for which data were available (%)</p> <p>**Of the 12 subjects lost to follow-up, 10 were no longer at work at the plant, 4 were not present and 2 refused to participate.</p> <p>^aOne worker reported work-related asthma symptoms at 6 month follow-up.</p> <p>^bOne worker with TDI-IgG at baseline tested negative in the follow-up period.</p> <p>^cAnother worker with negative IgG at baseline developed positive IgG at 6-month follow-up.</p> <p>^dNT=Not tested</p> <p>^eA higher percentage of subjects lost to follow-up (25%) reported current asthma conditions than those that were not lost to follow-up (2.7%) ($p=0.04$). Fisher's exact test was utilized to test for association (categorical outcomes). Analysis of variance was used to test for differences in means for continuous outcomes.</p>				

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 airflow obstruction: (FEV1/FVC < LLN)	1/40 (2.5)	1/6 (16.7)	0/22 (0.0)	1/12 (0.0)
Decline in FEV1 >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.				

FIGURE LEGENDS:

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.

Figure 1

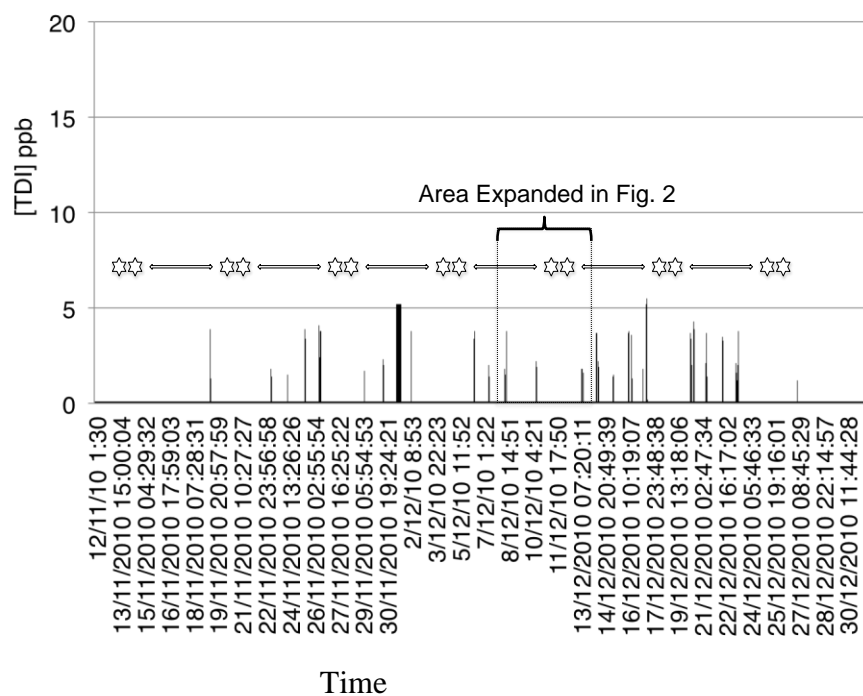


Figure 2

