Trends in Pulmonary Function and Prevalence of Asthma in Hexamethylene Diisocyanate Workers During a 19-Year Period

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Objective: To identify if 1,6-hexamethylene diisocyanate (HDI) workers demonstrated an increased prevalence of occupational asthma or accelerated decline in pulmonary function. **Methods:** Employees from two plants manufacturing or producing 1,6-HDI monomer and/or HDI polyisocyanates were matched to a control population by age, gender, race, and smoking status. A random coefficient regression analysis compared the decline in pulmonary function test values over time. Retrospective medical review was used to identify potential cases of occupationally induced asthma. **Results:** No significantly accelerated annual decline in force expiratory volume after 1 second in the HDI exposure group compared to the matched control group was observed. No cases of adult onset asthma, beyond those present at time of hire, and no cases of occupational asthma were identified. **Conclusions:** This study provides support for the current American Conference of Governmental Industrial Hygienists threshold limit value time-weighted average of 5 ppb.

Isocyanates are a family of chemicals characterized by the presence of reactive NCO groups some of which include the aliphatic diisocyanate, 1,6-hexamethylene diisocyanate (HDI). Diisocyanates are known respiratory sensitizers[1,2] and have been reported to cause occupational asthma in the United Kingdom[3] and in industrialized countries.[4]

HDI is used in the manufacture of high performance paints and surface coatings. It is also used in the preparation of adhesives, sealants, elastomers, and other specialized products. Potential worker exposure to HDI can occur in the production of the basic monomer, or the isocyanurate and biuret forms of HDI homopolymers (HDI "polyisocyanates"). Potential, although limited, worker exposures to residual HDI monomer in polyisocyanate blends may also occur during polyurethane manufacturing, spray coating, or curing (heated) operations.

1,6-HDI monomer contains two reactive NCO groups. Studies conducted using well-validated animal models strongly support the heightened sensitization potential of monomeric HDI compared with HDI homopolymers.[5] Thus, all other factors being equal, monomeric HDI workers should be the population most vulnerable to HDI mediated sensitization. Other factors that may increase the potential for sensitization include electrophilic and lipophilic status, tertiary/quaternary and steric structure, and physical phase.[6–8] Potential health effects resulting from exposure to airborne 1,6-HDI, as for most other isocyanate moieties, can include asthma, and rarely, hypersensitivity pneumonitis, chemical bronchitis and accelerated decline in pulmonary function.[2,9–14]

Although previous studies of other diisocyanates have reported declines in pulmonary function, these were at higher measured airborne levels, which may have exceeded the 5 parts per billion (ppb) American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) as an 8-hour time-weighted-average (TWA).[1–3,15–18] Accelerated Pulmonary Function Test (PFT) decline has also been described in one study of HDI polyisocyanate workers.[17] Hathaway et al,[19] in a retrospective study of workers engaged in HDI polyisocyanate production, did not confirm accelerated decline in either the Force Expiratory Volume after 1 second (FEV-1) or the Forced Vital Capacity (FVC) when workers were exposed to occasional peak airborne HDI concentrations between 1 and 10 ppb or to an average 12-hour TWA of ≤0.1 ppb. However, the study population included in the analysis was relatively small ($n = 32$). The study reported here is a retrospective study that expands on that work and includes employees from an additional plant (called plant 1, Bayer MaterialScience) over a longer duration of follow-up yielding a larger cohort of workers ($n = 100$) potentially exposed to airborne HDI monomer. This comprises over five times the average person years of exposure when compared with the initial study. This includes the site from the Hathaway et al study (called plant 2, Perstorp Coatings Inc. [Perstorp purchased Plant 2 From Rhodia in 2008]) and an additional, plant 1. Plant 1 produces both HDI monomer and HDI polyisocyanates and plant 2 produces HDI polyisocyanates from purchased HDI monomer. Although HDI polyisocyanates are present in both plants, any employee inhalation exposure would be expected to be minimal given the low volatility of these compounds.

Few studies in the literature document the health status of workers exposed primarily to HDI monomer, and none were found that reported the associated prevalence of occupational asthma. Therefore, the purpose of this study was to identify if HDI workers potentially exposed to HDI monomer demonstrated an increased prevalence of occupational asthma or accelerated decline in pulmonary function compared to a matched control group.

METHODS

This matched retrospective cohort study includes employees from two chemical manufacturing facilities operated by separate companies, both located in the Southern United States. Inclusion criteria specified a minimum of three PFTs per person, which is equivalent to a minimum employment period of 2 years. The observation period for plant 1 was January 1, 1988, through June 30, 2007, and for plant 2 was January 1, 1987, through December 31, 2006. Plant 2 did not start-up until 1987, and the observation period for plant 1 began in 1988 because of the availability of medical chart records. The study group is defined as employees who worked in areas where HDI monomer was manufactured and/or where HDI monomer was used to produce HDI polyisocya-

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DOI: 10.1097/JOM.0b013e3181f2e086

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TABLE 1. Demographics of the Cohort by Plant

	Plant 1	Plant 2
Number of matched cases and controls*	57	43
Date of birth range	1943–1975	1930–1973
Date of hire range	1972–2001	1987–2003
Age at hire	19–46	19–57
Ever smoked (%)	37	71
Race (%)		
White	72	82
Non-White	28	18
Male (%)	95	89
Mean number of PFT's (range)		
Exposed	21 (5–38)	8 (3–15)
Controls	13 (6–28)	8 (5–14)
Mean yr of observation		
Exposed	13.5 ± 5.6	9.9 ± 4.2
Controls	12.9 ± 4.7	9.4 ± 2.3

*A total of 17 exposed plant 2 workers were matched to plant 1 controls.

nates. At plant 1, other aliphatic diisocyanates were also produced; however, study subjects only were selected from those employees who worked primarily with HDI monomer based on a rigorous evaluation of their potential workplace exposures.

The control population consisted of plant workers without a documented history of exposure to any of the diisocyanates (ie, HDI, 4,4′-methylenebis(phenyl isocyanate) [MDI], and toluene diisocyanate [TDI]). A single control was matched to each study subject by age, gender, race and smoking status (ever vs never), date of birth ±2 years, and date of hire ±6 years. Because a sufficient number of potential controls were not available at plant 2, some plant 1 controls were matched to plant 2 study subjects.

Table 1 displays the demographics of the two cohorts and control groups. There were 57 potentially exposed workers in plant 1 and 43 in plant 2. The age at hire was similar in both plants with plant 2 reporting a slightly larger range. Plant 2 had a higher percentage reporting to have ever smoked (71% vs 37%) with a slightly lower percentage of non-White employees (18% vs 28%) and a somewhat higher percentage of men (95% vs 89%). The average number of PFT's was higher in plant 1 in both the exposed and control group with the exposed group being higher than the controls. The average duration of observation was 13.5 ± 5.6 years for the exposed in plant 1 and 12.9 ± 4.7 years for the controls compared with 9.9 ± 4.2 years for the exposed in plant 2 and 9.4 ± 2.3 for the plant 2 controls. The plant 1 employees often had more than one PFT in a given calendar year. Duration of follow-up is variable because some participants were employed for the entire study duration, and other participants were hired at some point in time during the study period, whereas a small number left employment for retirement or other job opportunities. A small number of participants were terminated because of performance issues and some were laid off as fewer employees were needed. Because of the retrospective nature of the study, precise data on the reasons for leaving employment were not always available. Overall, this has been a fairly stable workforce and no one left employment because of associated respiratory problems.

Pulmonary Function Test

Annual PFT results including FEV-1 and FVC were reviewed. At plant 1, all PFTs were performed throughout the study period in the plant medical department. At plant 2, testing before 1992 was conducted by a mobile testing van and thereafter in a local clinic. Testing equipment was calibrated with a 3-L syringe at a minimum of daily and/or every 12 tests. Results were adjusted for temperature and pressure. Three satisfactory maneuvers were obtained and the best FEV-1 and FVC results were recorded. All technicians performing PFT tests had received National Institute for Occupational Health (NIOSH) approved training and were certified to perform PFTs. Each test result was to be within 5% of each other and when not was repeated. All providers were compliant with the stipulated procedure.

Spirometry tests were reviewed by a physician for quality, including examination of volume-time and flow-volume curves to assess the adequacy of each maneuver effort and to determine if any results were invalid. For example, occasional tests indicating significant improvement in PFT values were discarded if they were not sustained. A limited number of tests were also excluded when the relevant employee indicated a respiratory problem at the time of testing, and when subsequent test results indicated that the poor performance at that time no longer was observed.

Medical Histories

Workers at each study plant routinely completed an annual medical surveillance history form which included questions about their respiratory health status and smoking habits (past and present) and included questions such as "have you ever had asthma" and "have you had asthma within the past year." The history forms also included questions on respiratory symptoms suggestive of asthma such as cough, chest tightness, wheezing, or dyspnea. If any cohort members left employment for medical reasons, this was investigated and documented within the plant medical record system. Smoking and respiratory information were abstracted from the medical records.

Occupational asthma cases were defined by a medical history of contemporaneous onset of respiratory symptoms consistent with potential exposure to airborne HDI. This included immediate and/or delayed onset asthma-like symptoms following exposure (typically the evening after exposure). Any suspect asthma cases identified through retrospective review were inspected further by a company physician for documentation of prior diagnostic confirmation of asthma (occupational, nonoccupational). Participants were also queried about potential dermal exposures to HDI monomer and/or polyisocyanates.

Statistical Analyses

Box plots were used to display the distribution of the PFT data over time. In the box plot, the median is shown by a thick black line. The boxes represent the interquartile range (25%le, 75%le) and the lines from the boxes approximately represent the range.

The changes in pulmonary function over time across subjects for exposed and controls were examined by a random coefficient regression model[20] with the factors of exposed/control group, time, and their interaction. Under this model, each subject has its own linear regression (intercept and slope), and the intercepts and slope overall is calculated as a weighted average where the weights reflect how well the line fits each subject. An interaction of exposed/control group (coded as a dummy variable) and time is used to detect if there is a difference in slopes.

Because the duration of follow-up was variable between subjects, the dropout pattern was examined to determine if there was a systematic pattern. Plots of the cumulative repeated observations were inspected to determine if there was any difference in groups based on those who had all of 3, 5, and 10 observations when compared with all observations. No difference was observed, therefore, the statistical analysis included all available PFT's.

Although the exposed group and controls were matched on smoking, separate analyses were also conducted to evaluate the

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effects of smoking on PFT's between groups because the smoking data are retrospective and the potential exists that they may be unreliable. In addition, "ever smoked" versus "never smoked" is a somewhat crude categorization that does not account for the amount or duration of smoking. Ultimately, four groups were considered: 1) exposed who ever smoked, 2) exposed that never smoked, 3) controls who ever smoked, and 4) controls who never smoked.

Height and weight at the earliest and latest recorded time were used to calculate body mass index (BMI). BMI changes among the exposed group and in the control group were compared using a paired Wilcoxon signed-rank test. A P-value ≤ 0.05 was considered statistically significant.

Industrial Hygiene Methods

Industrial hygiene personal sampling was performed during the study time period using several different sampling and analytical methods. Historical industrial hygiene sampling records (both hard copy and electronic) were reviewed to determine when and if personal protective equipment was worn. From this review, it was determined that workers at both plants used respiratory protection whenever exposures were known to be above permissible exposure limits or when such exposures were possible. When the record review indicated that respiratory protection was used during the shift, then this sampling record was removed from consideration. Thus, the summary exposure data presented is exclusive of respirator use and is more likely to reflect employee exposure. Further, for comparison to an 8-hour time-weighted average (TWA) occupational exposure limit (OEL), only sample durations that approximated a full shift (~6 to 9 hours) were included in the evaluation.

The following two methods were used by both plant sites.

1. NIOSH Physical and Chemical Analysis Method (P+CAM) 347 that drew the atmosphere through a 37-mm glass fiber filter coated with nitro-reagent at a flow rate of 1 L per minute.[21]
2. OSHA Method 42 or 47 where samples were collected by drawing atmosphere through glass fiber filters coated with 1-(2-pyridyl) piperazine (1-2PP) at a flow rate of 1 L per minute.[22]

An additional method was also used at plant 1.

3. Impinger sampling that drew the atmosphere through a mixture of 50/50 hydrochloric acid and dimethylsulfoxide at a flow rate of 2 L per minute.[23]

An additional method was also used at the plant 2.

4. Sampling was performed with a GMD Personal Continuous Monitor (Bacharach, Henderson, PA). This instrument uses a paper strip and reads color changes. The limit of detection (LOD) is 0.1 ppb for a 15-minute sampling period. It measures exposures in 4 minute intervals to give peak readings, 15 minute STEL readings, and TWA's for the period sampled. Only TWA measurements were included in this article.

Samples collected at both plants were analyzed at on-site laboratories; however, beginning in 2002, plant 1 samples were analyzed at the corporate industrial hygiene laboratory.

RESULTS

PFT Analysis

Table 2 shows the random regression results for the average change in pulmonary function as measured by the FEV-1 and FVC. The FEV-1 intercept was 3.94 L for exposed, whereas that for the controls was 3.97 L; therefore, the initial FEV-1's of the groups are similar. The average annual change in FEV-1 was −0.041 L for the controls and −0.023 L for the study group. The effects of exposed/control group, time, and the interaction of study/control group and time are all statistically significant (all P-values <0.0001). This suggests that the FEV-1 for the control group decreased faster than that for the study group over time. The FVC results displayed a similar pattern. The intercept was 4.88 L for exposed and 4.85 L for the control group indicating similar initial FVC measurements for both groups. The average annual change in FVC was −0.040 L for the controls and −0.024 L for the exposed.

TABLE 2. Mixed Model Results for FEV-1 and FVC

	ΔFEV-1	*P*	ΔFVC	*P*
Group				
Exposed*	−0.023	<0.001	−0.024	<0.001
Control	−0.041		−0.040	
Smoking comparison				
Exposed & ever smoked	−0.028	0.29	−0.026	0.34
Exposed & never smoked	−0.019		−0.020	
Control & ever smoked	−0.050	<0.001	−0.047	<0.001
Control & never smoked	−0.030		−0.031	

*A change of −0.023 is equivalent to an average decline in pulmonary function of 0.023 L per year or 23 mL per year.

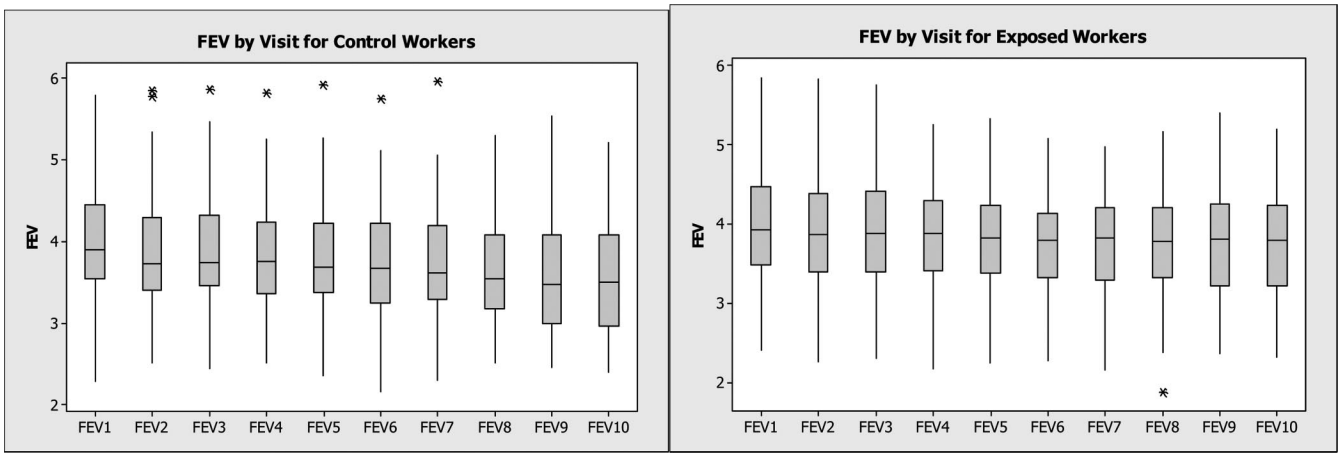

FIGURE 1. Box plots of FEV-1 and time by exposed and control groups.

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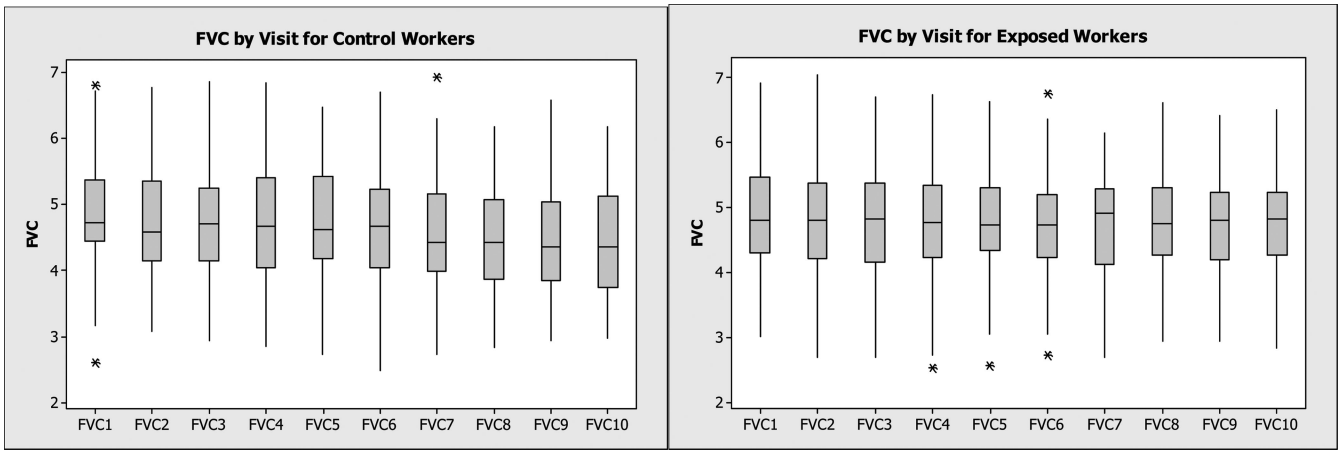

FIGURE 2. Box plots of FVC and time by exposed and control groups.

TABLE 3. Analysis of Median BMI Change in Exposed and Controls

BMI	Median	Innerquartile Range	*P*
Exposed initial	28.7	25.2–32.0	<0.001
Exposed final	29.8	26.9–33.7	
Control initial	29.0	25.8–33.0	<0.001
Control final	30.1	26.6–34.5	

Figures 1 and 2 display the box plots of the medians and interquartile ranges of the FEV-1's and FVC's, respectively, over time for the study group and controls displayed for up to 10 PFTs. These plots present a visual depiction demonstrating that the baseline pulmonary function of both groups is similar and the decline in pulmonary function were significantly greater in the control group.

The FEV-1 intercepts for the exposed group were 3.93 L and 3.96 L, respectively, for ever smoked and never smoked, and 4.01 L and 3.93 L, respectively for the control group. Consequently, the initial FEV-1's of the groups are similar. For the exposed group, the average annual declines in FEV-1 were 0.028 L and 0.019 L for the ever smoked and never smoked, respectively, and 0.030 L for control group never smoked but significantly higher for control group ever smoked 0.050 L ($P < 0.001$). The FVC results displayed a similar pattern. The intercepts for exposed group were 4.93 L and 4.80 L for ever and never smoked, respectively, and 4.92 L and 4.77 L, respectively, for the control group indicating similar initial FVC measurements for both groups. The average annual declines in FVC for the exposed group ever and never smoked were 0.026 L and 0.020 L, respectively. The average annual decline was 0.047 L and 0.031 for the controls ever smoked and controls never smoked, respectively ($P < 0.001$).

Both the smoking and nonsmoking controls demonstrated a greater decline in FEV-1 values, which was an unexpected result. Therefore, other potential confounders such as BMI were evaluated. Table 3 shows the median weight, interquartile range, and *P*-value based on a paired Wilcoxon-signed rank test. There was a significant increase in BMI in both the study and control group. The BMI of the control group was slightly higher overall.

Prevalence of Asthma and/or Occupational Asthma Among Exposed Employees and Controls

During the time period of the study, there were two workers and two controls from plant 2 who indicated that they had been diagnosed with childhood asthma. One plant 2 control reported adult onset asthma. One study participant at plant 1 was identified with a history of childhood asthma as were two controls. All reported asthma cases were reviewed by company physicians who were familiar with the cohort. These physicians reported no additional cases of adult onset asthma and no cases of occupational asthma. Most of the study group reported some instances of dermal exposure to HDI monomer and/or polyisocyanates. During the entire study period, there were also no employees who had to be medically removed because of HDI exposures.

TABLE 4. Exposure to HDI From Personal Monitoring (in ppb) When Not Wearing Respiratory Protection, Plant 1

Results of Plant 1 IH Sampling	
Range of Sample Results in ppb	**Number of Samples**
Nondetectable*	88
0.03–0.09	21
0.10–0.19	27
0.20–0.49	51
0.50–0.99	23
1.00–2.99	20
3.00–9.99	3
>10.0	4

*The range of limits of detection were from <0.025 to <0.4 ppb.

Industrial Hygiene Monitoring

A total of 237 personal airborne HDI samples from plant 1 were included in the evaluation of employee exposure from 1983 through 2006 at (Table 4). One extreme outlier (341 ppb) was removed from the data based on a review that raised concerns about the validity of the result, particularly because the work activities that day were routine in nature and would not have been expected to have resulted in such a significant exposure to airborne HDI.

The remaining air monitoring data ranged from nondetectable to 31 ppb with a mean value of 0.78 ppb; therefore, the majority of the collected samples resulted in measured airborne concentrations well below the ACGIH TLV-TWA of 5 ppb. However, it should be noted that there were occasional documented airborne HDI concentrations (continuing even into the 1990s and 2000s), which were a significant fraction of the TLV, with a limited number of samples exceeding the TLV.

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TABLE 5. Exposure to HDI From Personal Monitoring (in ppb) When Not Wearing Respiratory Protection, Plant 2

Results of Plant 2 IH Sampling	
Range of Sample Results in ppb as 8-hr TWA	**Number of Samples**
Nondetectable*	6
0.03–0.09	—
0.10–0.19	7
0.20–0.49	9
0.50–0.99	6
1.00–2.99	1
3.00–9.99	—
>10.0	—

*The range of limits of detection were from <0.025 to <0.5 ppb.

Table 5 shows a summary of the air sampling data for plant 2 from 1992 to 1996. A total of 29 samples were included in the evaluation of employee exposure to airborne HDI. Airborne concentrations ranged from nondetectable to 2 ppb with a mean level of 0.3 ppb. Thus, all the measured airborne HDI concentrations were below the ACGIH TLV-TWA of 5 ppb.

Potentially Confounding Exposures in the Study Population

In an effort to evaluate any possible impact from confounder agents on the plant 1 study population, historical exposure data for the other aliphatic isocyanates to which workers may have been exposed to a limited degree were also analyzed. Both methylene bis (4-cyclohexylisocyanate) (HMDI) and isophorone diisocyanate (IPDI) air sampling results were analyzed from 1989 through 2006 (earlier air sampling data was not available). In summary, the data indicated that 47 of 53 samples collected for HMDI were below the analytical LOD. Airborne concentrations for the remaining six samples ranged from 0.03 to 0.70 ppb. The ACGIH TLV-TWA for HMDI is 5 ppb. Further, 10 of the 21 airborne IPDI samples were less than the LOD. Results for the remaining 11 samples ranged from 0.02 to 0.67 ppb. The ACGIH TLV-TWA for IPDI is also 5 ppb. Overall, measured airborne HMDI and IPDI concentrations at plant 1 appear to be low, mostly below the LOD, and certainly below the TLVs.

There was very little potential for exposure to other diisocyanates at plant 2. A limited amount of IPDI was repackaged at the plant. This occurred infrequently over a short period of time and involved few workers. No exposure monitoring was performed, however, given the low vapor pressure, airborne IPDI concentrations were expected to have been well below the TLV.

Potentially Confounding Exposures in the Control Population

A review of the historic exposure data for chemical agents, in the areas where members of the plant 1 control group worked, showed that the majority of sample results were less than the LOD of the applicable analytical method. For some agents, however, there were a handful of measured airborne concentrations above the applicable OELs (eg, dinitrotoluene, hydrazine, methylene chloride, maleic anhydride, toluene diamine, and ethylene oxide).

Because it is considered an occupational respiratory sensitizer, and thus a potential confounding agent, exposure results for maleic anhydride were reviewed in some detail. Only 3 of the more than 50 sample results for maleic anhydride were over the OEL (0.1 parts per million [ppm]). Only two members of the control group worked in the maleic unit at plant 1. For these reasons, any confounding influence from maleic anhydride on the control group would be considered minimal.

Some controls from plant 2 worked in a Rare Earths production unit. There were four areas within the Rare Earths unit; Finishing, Batteries, Nitric Attack, and Effluents. The majority worked in the Finishing area, which had two operations (processing and packaging), and the majority of those worked in processing where the only significant exposures were to cerium and neodymium oxides. Dust exposures in processing since 1987 averaged 0.9 mg/m^3. Dust exposures in packaging before 1993 averaged 6.2 mg/m^3. After 1993, the results were similar to those found in processing. In the batteries area, there were potential exposures to nitric acid, ammonia, kerosene, and tributyl phosphate. Industrial hygiene monitoring for these exposures had been performed since 1992. Measured airborne concentrations before that time are thought to be similar to those since. Average 8-hour TWA's based on numerous personal samples were nitric acid, 0.012 ppm; ammonia, 1.8 ppm; kerosene, 1.6 ppm; and tributyl phosphate, 0.003 ppm. There were no measured chemical exposures in the nitric attack area regardless of what the name of the area might imply. The only potential airborne chemical exposure in the effluent area was ammonia, and it was lower than in the batteries area.

DISCUSSION

The results of this study do not demonstrate a statistically significant accelerated annual decline in FEV-1 among employees potentially exposed to airborne HDI compared with the matched control group. In addition, there were no identified new cases of adult onset asthma among the cohort and no cases of occupational asthma from any cause including HDI. Ott reported that during the 1960s and 1970s where employees worked with another diisocyanate (toluene diisocyanate) approximately 5 to 6% of employees developed occupational asthma annually. With lower measured workplace exposures in the 1980s and later, the annual incidence of diisocyanate related asthma was reported to decline to less than 1%.[24] In that article, the decline in new cases of occupational asthma was attributed to significantly lower measured workplace exposures during the 1980s and later. Measured airborne exposures during that time period were reported to be generally below the permissible exposure limit of 5 ppb with most results below 1 ppb although occasional short-term exposures exceeded 20 ppb. Ott et al also reported that no accelerated decline in FEV-1 was seen after about 1980.

In this study, there only were three individuals with a history of nonoccupational asthma among the study group and five among the controls. All were noted at time of hire representing a prevalence of 4.0%. In the general population, lifetime prevalence of asthma in the United States has been reported as 9.2%.[25] Therefore, assuming that none of the study group or controls develop asthma later in life, the observed-to-expected rate of employees who reported diagnoses of asthma in our population (both study participants and controls) is 0.43 (95% confidence interval = 0.19 to 0.86) and is statistically significantly less than the reported prevalence of asthma in the general population.

At plant 1, individuals with active asthma were excluded from working in any operating areas with potential exposure to diisocyanates or other chemicals. Although persons with adult-onset asthma were not excluded from employment in operating areas at plant 2, there may have been some self-deselection of working in a chemical plant among individuals with preexisting asthma.

The average annual decline in FEV-1 for the exposed workers of 0.023 L is somewhat below the expected rate of 0.30 L in healthy adults. The rate of decline in our study is also below

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previous reports for healthy nonsmokers[26] and is also below the rate of decline in FEV-1 of 0.044 L previously reported by Hathaway et al.[19]

This study demonstrated a statistically significantly higher rate of FEV-1 decline among the control group compared with those within the exposure group even though the controls were matched according to potential confounders such as smoking. We considered several possible explanations for this difference. First, the study group might be in better physical condition with less weight gain over time. Excessive weight gain can lower both FVC and FEV-1 due to chest compression. The BMI data for both the study and control group were skewed toward obesity, and both groups had a significant gain in BMI over time with the control group having slightly higher BMI's. However, this difference is not sufficient to explain the difference in PFT values between the exposed and controls. Second, we also considered whether the inclusion of some newer employees in the exposed cohort could have resulted in a learning effect on FEV-1 in employees with a limited number of PFTs. Because studies have indicated that longitudinal measurements of FEV-1 are most reliable after at least five PFT tests,[27] we excluded all cohort members with less than five PFTs and repeated the analysis. There was no significant difference in the results (data not shown).

Finally, one possible explanation that we could not evaluate thoroughly was a possible difference in smoking exposures. While we matched on whether a subject ever smoked or never smoked, we did not have more detailed smoking information such as cumulative pack-years. It is possible that there may have been a difference in the amount of smoking between the cohort and controls. The statistically significant difference in decline in pulmonary function between the smoking controls and smoking exposed group strongly suggests that the controls may have been heavier smokers.

The possibility of an effect of other chemical exposures on FEV-1 decline within the control group was considered (for a discussion of those potential exposures see the results section). After review of the potential chemical exposures, it was considered that this was an unlikely explanation for the difference. Despite the fact that the rate of decline among the control group was higher at 0.041 L than in the exposed group at 0.023 L, they are both within the range of annual FEV-1 declines reported in other studies.[28–30]

The study reported here has several unique strengths because it includes two plants over a lengthy observation period with annual PFTs and data from medical evaluations. There is also a large amount of contemporaneous workplace exposure information. A limitation with this retrospective study is the inability to control for other potential confounders such as height or BMI. Another limitation is that the identification of a history of asthma in study population and controls is self-reported. However, the population participated in thorough annual medical examinations with further evaluation of symptoms associated with asthma when reported.

The current ACGIH TLV-TWA is 5 ppb. This study provides support for this limit. Although most airborne HDI concentrations were well below 5 ppb, there were some airborne levels between 1 and 5 ppb and occasional levels above 5 ppb, all based on an 8-hour TWA. Employees also reported occasional unprotected dermal contact with HDI monomer and HDI polyisocyanates. There were no cases of respiratory sensitization identified among this cohort. The average duration of observation was 13.5 years for the 57 plant 1 exposed group and 9.9 years for the 43 plant 2 exposed group. There were no cases of occupational asthma or accelerated decline in FEV-1 in 1195 person years of exposure in workplaces observing an ACGIH TLV-TWA of 5 ppb for airborne 1,6-HDI.

ACKNOWLEDGMENT

The study was supported in part by the Aliphatic Diisocyanates Panel of the American Chemistry Council (ACC) whose members include Bayer MaterialScience, Perstorp, Inc., and Evonik/Degussa.

This study was approved by the Institutional Review Board of the University of Pittsburgh.

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