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Work-Related Asthma from Exposure to Isocyanate Levels Below the Michigan OSHA Permissible Exposure Limit

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Abstract: This paper examines the characteristics of 261 work-related asthma (WRA) cases exposed to isocyanates reported to an occupational disease surveillance system in Michigan from 1988-1998, and reviews Michigan Occupational Safety and Health Act (OSHA) inspections at 42 of the facilities where they worked. After October of 1993 when the Michigan OSHA program implemented a newer sampling methodology for isocyanates, 42 inspections were conducted in relation to the WRA cases reported. Samples for isocyanates were not collected in one facility. Isocyanate air levels at 40 of the 41 companies where measurements were taken revealed exposures <0.005 parts per million (ppm), as a time-weighted average (TWA). Sampling for isocyanates at one company revealed a level of 0.005 ppm for TDI (TWA).

At 36 of the 42 inspections, similarly exposed co-workers as the index cases completed a breathing symptom questionnaire. Although non-significant, companies were more likely to have co-workers indicate breathing symptoms where the index case reported exposure to one or more isocyanate spills (11 of 13 companies with spills vs. 15 of 23 companies without spills; OR 2.93, 95% CL 0.43-34), and a higher average percent of symptomatic co-workers compared to the companies where the index case reported no spills (23% vs. 16%; OR 1.42, 95% CL 0.99-2.03). Again, although non-significant, there were more MDI-using companies in which at least one co-worker reported breathing problems than TDI or HDI-users (83% vs. 67% vs. 56%; chi-square 2.49, p=0.29). MDI-using companies had a higher average percentage of symptomatic co-

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workers than TDI-users and HDI-users (23% vs. 15% vs. 14%; chi-square 9.92, p=0.007).

Michigan workers are exposed to isocyanates below permissible exposure limits yet continue to develop WRA. Spills may account for some but not all of these cases. Despite the lower volatility of MDI, co-workers with exposure to MDI were more likely to have respiratory symptoms than co-workers exposed to TDI or HDI. The majority of these 42 isocyanate-using companies (72%) had no medical surveillance program to monitor for worker sensitization. Compliance with OSHA laws, or "being within permissible exposure limits " will not guarantee the prevention of WRA. Effective engineering controls, established spill clean-up procedures, a comprehensive hazard communication program, and a medical surveillance program to identify newly sensitized workers for prompt removal from exposure may help to prevent isocyanate-induced WRA. Further work is needed to determine the relative effectiveness of each of these components in preventing isocyanate-exposed workers from developing asthma.

Keywords: work-related asthma, isocyanates, occupational, inspections, medical surveillance

Introduction

Since the introduction of isocyanates in the 1930s, their application has increased worldwide. Workers are exposed to isocyanates in many industries, including: automotive and other plastic and foam-based parts manufacturing; construction; foundries; paint-using industries such as automotive repair shops; varnish-using industries such as furniture manufacturing; and in the manufacture of isocyanates themselves. The relationship between isocyanates and adverse health effects among workers exposed to them has been recognized in the scientific literature since the early 1950s. The spectrum of health effects from exposure to isocyanates ranges from dermatitis and allergic rhinitis to hypersensitivity pneumonitis, asthma, and, even death. Especially since the early 1980s, researchers have studied isocyanate-induced asthma from many perspectives including clinical, epidemiological, socioeconomic and industrial hygiene.

Several key points have been repeatedly documented: individuals may develop asthma from exposure to low levels of isocyanates; peak exposures such as spills or leaks can be responsible for acute onset of asthma either through sensitization or Reactive Airways Dysfunction Syndrome (RADS); monomers as well as prepolymers can cause work-related asthma; many sensitized workers remain working in isocyanates for financial reasons rather than take a cut in pay at a non-exposure job; and, perhaps most importantly from a clinical perspective, the sooner an individual is recognized as having isocyanate-induced asthma and removed permanently from such exposures the greater the likelihood that the asthma symptoms will improve or cease [*1-10*]. In an effort to address some of the documented health effects of the isocyanates, new forms have been

developed, such as naphthalene diisocyanate (NDI). However, the effect that these new forms of isocyanates will have on worker health has yet to be fully studied [*11*].

As the use of isocyanates, both the monomers and prepolymers, has increased over the last few decades, an increasing number of workers are potentially exposed to some type of isocyanate. The highest estimated number of workers exposed to isocyanates in the United States comes from a NIOSH Hazard Alert, and indicates at least 280,000 workers potentially exposed to isocyanates [*12*]. An estimated 5-10% of isocyanate-using workers will develop asthma [*12*]. Researchers are documenting that isocyanate-induced asthma is one of the main causes of occupational asthma worldwide [*13-16*].

In Michigan, isocyanates account for approximately 20% of the total cases of work-related asthma (WRA) reported to the state's occupational disease registry. Michigan has required the reporting of all known or suspected occupational diseases since 1978. In 1988, the state of Michigan received federal funding to conduct active surveillance of occupational diseases, including work-related asthma. Since that time, surveillance of work-related asthma in the Michigan work force has found that isocyanates account for the greatest number of work-related asthma cases identified in Michigan.

In this paper we will review the epidemiology of isocyanate-induced asthma among the Michigan work force; summarize the results of related work place follow up inspections; and discuss the importance of medical surveillance in the early detection and removal of sensitized workers.

Methods

Subjects

Michigan law requires physicians, clinics, hospitals and employers to report work-related diseases to the state. All individuals reported with asthma or symptoms consistent with asthma were administered a standardized telephone questionnaire that documented each case's work and exposure history, breathing symptom history, cigarette smoking history, and medical care and breathing medication history. The questionnaire also asked workers if they had been exposed to spills and leaks of isocyanates in their work area. A definition for what constituted a spill or leak, such as the amount, was not given to the worker. The questionnaire was developed specifically for this project and has been used since 1988.

Based on review by a board certified occupational medicine physician (KR) of the medical records and the telephone-administered questionnaires for the 1765 cases reported to the state with asthma or symptoms consistent with asthma from 1988-1998, 1336 (76%) were confirmed as having WRA per criteria developed by the National Institute for Occupational Safety and Health (NIOSH) [*17*]. Medical records typically consisted of breathing tests and recent progress notes from outpatient care or a discharge

diagnosis from a hospitalization. This paper will examine the characteristics of 261 of those cases whose asthma was caused by isocyanates.

Work-Related Asthma Case Definition

The work-related asthma case definition was developed in conjunction with the National Institute for Occupational Safety and Health (NIOSH) and several states conducting work-related asthma surveillance [*17*]. The definition of work-related asthma was: (1) a diagnosis of asthma; and (2) an association between symptoms and work. The case definition allowed for four types of work-related asthma: work-aggravated asthma, reactive airways dysfunction syndrome (RADS), and occupational asthma with or without exposure to a known allergen. There are over 350 known WRA allergens that have been cited in the scientific literature [*18*].

Work Place Inspections

As part of Michigan's surveillance system for WRA, Michigan Occupational Safety and Health Act (OSHA) enforcement inspections were routinely conducted at facilities where individuals developed their asthma. Inspections were completed if: the facility was in Michigan and within Michigan OSHA jurisdiction; exposures were ongoing; if the index case's work-related asthma was not work-aggravated asthma (i.e., the case had to develop their asthma after beginning to work at the facility); and a similar inspection had not recently been conducted. The enforcement inspections typically conducted air monitoring for the suspected allergen, assessed compliance with state laws, and conducted a breathing symptom survey of the co-workers in similar exposures as the index case. After an inspection was completed, a copy of the Michigan OSHA inspector's findings was given to the facility that was inspected, to the union or worker representative for health and safety if no union existed, and to the physician who originally reported the index case.

Co-workers of the index cases from the WRA registry were interviewed during these inspections to assess the extent of breathing problems among similarly exposed individuals. At the 36 inspections where co-workers were interviewed, 730 co-workers completed a standardized questionnaire. All co-workers in the same area of exposure as the index case who were working at the time of the inspection were given the opportunity to complete the questionnaire.

The standardized questionnaire for co-workers was developed in 1988 and since then has been administered in 389 facilities to 7337 co-workers. The questionnaire asked questions regarding work history, medical care for respiratory problems, allergy history, cigarette smoking history and frequency of respiratory symptoms. The criteria for a worker to be classified as having breathing problems based on these co-worker interviews was the indication of being bothered at work by daily or weekly chest tightness, shortness of breath or wheezing, or if the worker indicated the development of asthma since

beginning to work at the facility. Interviews were not performed at six of the 42 companies inspected because the staff person that performed these interviews was not available to accompany the Michigan OSHA enforcement inspector.

Air Sampling for Isocyanates

The Michigan OSHA permissible exposure limits for isocyanates vary by type of isocyanate. For the more frequently encountered isocyanates used in Michigan industry, methylene bisphenyl diisocyanate (MDI) has a ceiling limit of 0.02 parts per million (ppm); toluene diisocyanate (TDI) has an 8-hour time-weighted average (TWA) limit of 0.005 ppm and a short-term exposure limit (STEL) of 0.02 ppm; and hexamethylene diisocyanate (HDI) does not have a limit, although NIOSH and the American Conference of Governmental Industrial Hygienists (ACGIH) have a recommended TWA limit of 0.005 ppm. There are other isocyanate types that are regulated by Michigan OSHA. However, the only isocyanates types used at the 42 companies inspected were TDI, MDI and HDI.

In October of 1993, the Michigan OSHA program changed their sampling methodology for isocyanates by switching their sampling from a closed face with a 37mm glass fiber filter with a nitro reagent followed by HPLC/UV, based upon NIOSH method 347 to a three-piece open-faced cassette based upon OSHA methods 42 and 47. Prior to October of 1993, Michigan OSHA inspectors were not consistently using open-faced sampling, which may have resulted in the isocyanates contacting the cassette before they reached the filter and derivatizing agent (nitro reagent); this would have resulted in sampling results that were lower than the actual exposures.

Since that time 42 Michigan OSHA enforcement inspections were conducted from October 1993 through 1999, based on the 261 isocyanate-induced asthma cases identified through the WRA registry. A total of 160 breathing zone and ten area air samples for isocyanates were collected at 41 of the companies, compliance with Michigan OSHA laws was assessed at all 42 companies and confidential co-worker interviews were administered at 36 of the companies. The location and number of air samples that were collected was determined by the Michigan OSHA inspector who was assigned to that inspection. The intent of the Michigan OSHA inspector was to determine compliance with the OSHA permissible exposure limit (PEL) among co-workers in the area in which the index case worked.

Statistics

Mantel-Haenszel odds ratios were calculated to compare the risk of having symptomatic co-workers in companies with spills versus companies without spills. The Chi Square statistic was calculated to determine if there were any differences in the percentage of companies with symptomatic co-workers by isocyanate type.

Results

Case History

A 30-year-old female began working in the late 1980s at a company that made doors for houses and garages. She was exposed to MDI in her job, which was to sandwich the two sides of a door together and fill it with urethane insulation before taking them to a press. She was classified as a "urethane assembler." She wore rubber gloves and a paper filter mask, as well as safety glasses and safety shoes at work. She noted that the paper mask "didn't seem to work." She developed wheezing, chest tightness and shortness of breath approximately 2¾ years after beginning to work at the facility. Her symptoms were worse at work. She had no past history of asthma. An occupational medicine physician diagnosed her with occupational asthma. She went on medical leave 10 months after her symptoms first began. Approximately one year after she was last exposed to MDI her breathing symptoms were still present, although the symptoms were less severe. In addition, she was still taking asthma medications, but less frequently. She had smoked cigarettes for less than a year when she was 17 years old.

A Michigan OSHA enforcement inspection was conducted at her workplace. The plant had been in operation for 20 years. The company did not conduct any medical monitoring, including a questionnaire for respiratory symptoms, breathing tests or blood tests, of employees for sensitization to MDI. Five breathing zone air samples and two area samples for MDI were collected during the inspection; none of the samples had any MDI detected. The limit of detection for these samples ranged from 0.001 ppm to 0.005 ppm. During the inspection, 25 co-workers similarly exposed as the index case completed a breathing symptom questionnaire. Six of those individuals had daily or weekly chest tightness, shortness of breath or wheezing in relation to work. A medical monitoring program for workers exposed to MDI was recommended, and the six symptomatic co-workers were sent letters to their homes advising them to see their physician about their breathing symptoms. The company was cited for several violations of Michigan OSHA regulations including: the lack of a hazardous waste operations and emergency response plan; an incomplete blood borne pathogens exposure control plan; an incomplete hazard communication plan; and the lack of suitable eye wash and first aid facilities.

Interviews with 261 Isocyanate-Induced Asthma Cases

From 1988-1998, physicians, hospitals, workers' compensation or co-workers reported a total of 1765 individuals with known or suspected work-related asthma to the State of Michigan. Of the 1765 individuals identified, 1336 were confirmed as having work-related asthma. Approximately 20% (261/1336) of those individuals with WRA developed their asthma from exposure to isocyanates at work. Of the 261 isocyanate-induced asthma cases, 248 (95%) were classified as occupational asthma; 7 (3%) were

classified as aggravated asthma; and 6 (2%) were classified as RADS. Over half (56%) of the 261 isocyanate-induced asthma cases were men and 79% were white. Sixteen percent of the 261 cases were African American; the remaining 5% were Asian, American Indian, or listed as "Other".

Approximately one third of the isocyanate WRA cases were from exposure to toluene diisocyanate (TDI). Table 1 shows the type of isocyanate exposure of the 261 cases.

Table 1. *Type of Isocyanate Exposure Among 261 Individuals Reported to Michigan, from 1988-1998*

Type of Isocyanate*	Number of Cases	(Percent)
TDI	84	(32)
MDI	69	(26)
HDI	14	(5)
TDI and MDI	10	(4)
NDI	8	(3)
Unknown Type	76	(29)
Total	261	

*TDI=toluene diisocyanate; MDI=methylene bisphenyl diisocyanate; HDI=hexamethylene diisocyanate; NDI=naphthalene diisocyanate.

Michigan has a large manufacturing sector, with 961000 workers, of which 272000 people were working in automotive manufacturing in 1999 [*19*]. The total working population in Michigan in 1999 was 4894000 individuals. The majority of the 261 cases were exposed to isocyanates at facilities involved in manufacturing, especially in automotive parts manufacturing. Over half (133/243) of the cases who worked at manufacturing facilities were reported by the medical departments at those facilities. Table 2 shows the types of industries where the isocyanate-induced asthma cases worked.

We examined the type of industry where exposure occurred by type of isocyanate used. The automotive manufacturing industry accounted for the highest percentage of cases exposed to TDI (73%, n=61/84), followed by the rubber and plastics manufacturing industry (12%, n=10/84). Automotive manufacturing also accounted for the greatest percentage of MDI-exposed individuals, with 52% (n=36/69), followed by foundries, with 17% (n=12/69). The automotive repair industry accounted for 14% (n=2/14) of the HDI-exposed workers; the automotive manufacturing industry accounted for 71% (n=10/14) of those HDI-exposed cases.

One hundred twenty-one (50%) of the 241 individuals with isocyanate-induced asthma where the use of health care services was known had presented at a hospital emergency room (ER) since their asthma symptoms began, with an average number of 4.9 ER visits. For 20 of the 261 individuals, the use of health care services was unknown. Sixty (25%) of the 241 individuals with known health care service use had

been hospitalized at least once for their asthma symptoms, with an average of 2.8 hospital stays. We also examined the frequency of ER visits and hospital stays by the type of isocyanate to which the workers were exposed. Five of the eight (63%) NDI-exposed workers had at least one ER visit, and 39 of the 69 (57%) MDI-exposed workers, 40 of the 84 (48%) TDI-exposed workers, and 5 of the 14 (36%) HDI-exposed workers had at least one ER visit. Further, three of the eight (38%) NDI-exposed workers had at least one hospital stay, and 20 of the 84 (24%) TDI-exposed workers, 16 of the 69 (23%) MDI-exposed workers, and 2 of the 14 (14%) HDI-exposed workers had at least one hospital stay. These figures underscore the serious nature of this disease, especially MDI, which is typically viewed as a "safer" isocyanate since it is less volatile than TDI.

Table 2. *Industry of Isocyanate-Induced Asthma Cases Reported to Michigan, From 1988-1998*

Industry	Number of Cases	(Percent)
Automotive Mfg.	165	(63)
Miscellaneous Mfg.	24	(9)
Rubber and Plastics Mfg.	23	(9)
Chemical Mfg.	16	(6)
Foundry	15	(6)
Trade	7	(3)
Automotive Repair and Sales	6	(2)
Construction	2	(1)
Research Lab	2	(1)
Trucking	1	(<1)
Total	261	

Fifty-five of the 261 workers (21%) who developed isocyanate-induced asthma were still exposed to isocyanates in their job at the time of their telephone-administered medical questionnaire. One hundred ninety-two (74%) workers were no longer exposed to isocyanates. For fourteen (5%) individuals exposure status was unknown. Of the 192 workers no longer exposed to isocyanates: 41% (n=67) of the individuals had been reassigned to a new job; 18% (n=29) were on medical leave or workers' compensation; 14% (n=23) had quit their job for health reasons, either on their own or upon the advice of their physician; 4% (n=6) were fired; 2% (n=2) had a substitute chemical or engineering change to reduce their exposures; and the remaining 35 workers were no longer exposed to isocyanates for other reasons.

Despite removal from exposure, 78% of workers continued to experience breathing symptoms, although 51% experienced symptoms less often since they were removed from exposure. Table 3 shows the exposure status of the 261 isocyanate-induced asthma cases and the persistence of their symptoms.

Of the 192 workers who were no longer exposed to isocyanates at the time of interview, 68% were still using asthma medications to control their symptoms. Table 4

shows the exposure status and asthma medication use of the 261 isocyanate-induced asthma cases. Twenty-eight percent of the workers no longer exposed were using fewer asthma medications than when they were working with isocyanates.

Table 3. *Persistence of Symptoms of Isocyanate-Induced Asthma Cases Reported to Michigan, from 1988-1998*

	Total	Persistence of Asthma Symptoms	
		Yes	Less
Exposure Status*	#	# (%)	# (%)
Still Exposed	55	55 (100)	18 (33)
No Longer Exposed	192	149 (78)	97 (51)

*Information unknown for 14 cases.

Table 4. *Use of Asthma Medications of Isocyanate-Induced Asthma Cases Reported to Michigan, from 1988-1998*

	Total	Use of Asthma Medications	
		Yes	Less
Exposure Status*	#	# (%)	# (%)
Still Exposed	55	40 (73)	9 (16)
No Longer Exposed	192	130 (68)	53 (28)

*Information unknown for 14 cases.

Tables 3 and 4 illustrate the chronic nature of this condition and highlight the importance of secondary prevention. We also looked at the length of time it took from when an individual's breathing problems began at the company, to the time that they were no longer exposed to isocyanates. Overall, workers left the exposure an average of 40.31 months after their symptoms first began. By type of isocyanate to which a worker was exposed, the amount of time from the development of breathing problems to last exposure to isocyanates varied. HDI-users left an average of 26.4 months after their symptoms began; NDI-users left an average of 29.14 months after their symptoms began; MDI-users left an average of 44.93 months after their symptoms began; and TDI-users left an average of 48.91 months after their symptoms began.

Inspections at 42 Facilities

Since October of 1993, when the Michigan OSHA program instituted a new sampling methodology for the isocyanates, 42 work place inspections were conducted in relation to the 261 index cases reported to the occupational disease registry. At 41 of these 42 inspections air monitoring was conducted for isocyanates. An isocyanate level of TDI at one of these facilities was 0.005 ppm (TWA). Isocyanates levels at the other 40 companies were below 0.005 ppm (TWA). Despite these low levels of isocyanates noted during monitoring, individuals continue to develop asthma.

Another measure to help document the extent of the problem during these inspections was the administration of breathing symptom questionnaires to similarly isocyanate-exposed co-workers of the index cases. At 36 of the 42 facilities inspected, co-workers were interviewed about the presence of breathing symptoms at work or physician-diagnosed asthma since beginning to work with isocyanates. A total of 730 interviews were conducted during these inspections, and 172 (24%) indicated being bothered at work by daily or weekly shortness of breath, chest tightness or wheezing, or as having been diagnosed with asthma since beginning to work at the facility. Ten of the 36 companies where co-workers were interviewed had no co-workers with daily or weekly breathing symptoms or asthma. Of the remaining 26 companies with at least one symptomatic co-worker, the average percent of symptomatic co-workers per company was 26% (SD 13%).

Since all but one of the companies had measured isocyanate levels below Michigan OSHA permissible exposure limits, we examined the relationship of spills or leaks at companies with symptomatic co-workers. In the interviews with the 261 index cases, the interviewer asked whether the worker had been exposed to any spills or leaks of isocyanates. Table 5 compares the number of companies with symptomatic co-workers for which the index case indicated at least one isocyanate spill to companies with symptomatic co-workers where the index case had not been exposed to a spill or leak. A greater percentage of companies had symptomatic co-workers where the index case had reported at least one isocyanate spill (85%) than companies at which the index case indicated there had been no spills (65%), although this was not statistically significant. Again, although not statistically significant, a company was almost three times more likely to have symptomatic co-workers if the index case indicated a spill had occurred. At those companies where the index case reported at least one spill, the average percent of symptomatic co-workers identified at a company was 23% compared to 16% at companies where the index case indicated there had not been any spills; this was also not statistically significant.

We also examined the spill status of the companies inspected by the type of isocyanate used. Workers from TDI-using companies reported a higher percentage of spills (45% of 11 companies) than workers from MDI- or HDI-using companies (with 37% of 19 companies and 33% of 9 companies, respectively). Spill status was unknown for 3 companies.

Since isocyanate properties such as volatility differ by type of isocyanate, we examined the relationship of symptomatic co-workers by the type of isocyanate used at the facilities inspected. Table 6 shows the numbers of symptomatic co-workers by type

of isocyanate used. A greater percentage of companies using MDI had symptomatic co-workers than companies using TDI or HDI. Further, the average percent of symptomatic co-workers at companies using MDI was higher than that of companies using TDI or HDI. The average duration of years exposed to isocyanates, by type of isocyanate used was 7.5 years for the interviewed co-workers in MDI-using companies, 7.1 years for the interviewed co-workers in the TDI-using companies, and 11.0 years for the interviewed co-workers in the HDI-using companies. Further, the percentage of interviewed co-workers who never smoked cigarettes was 40.8% in the MDI-using companies, compared to 33.9% in the TDI-using companies and 54.1% in the HDI-using companies.

Table 5. *Inspections at 36 of 42 Companies with Co-Worker Breathing Symptom Interviews, by Isocyanate Spill Status*

	One or More Spills/Leaks	No Spills
Companies with Symptomatic Co-Workers	11/13 (85%)	15/23 (65%)
	Odds Ratio: 2.93 (95% CL* 0.43 – 34)	
Average % Symptomatic Co-Workers	23%, SD 13% range 0 - 46%	16%, SD 17% range 0 - 60%
	Odds Ratio: 1.42 (95% CL 0.99 – 2.03)	

*CL Confidence Limit

For three companies the status of a medical surveillance program was unknown. The Michigan OSHA inspectors were able to document that 28 of the 39 facilities inspected did not have a medical surveillance program to monitor workers for sensitization to isocyanates. The other 11 companies did have such a medical surveillance program.

Of the 36 companies inspected where medical surveillance status was known and co-workers were interviewed, 19 of 25 (76%) of the companies had no medical surveillance program and had symptomatic co-workers. Seven of 11 (64%) of the companies had a medical surveillance program and symptomatic co-workers. Although not statistically significant, a company was less likely to have co-workers with breathing symptoms if they had a medical surveillance program (odds ratio: 0.55, 95% CL .092 – 3.29).

Table 6. *Inspections at 36 of 42 Companies with Co-Worker Breathing Symptom Interviews, by Type of Isocyanate*

Isocyanate Type	Companies with Symptomatic Co-Workers	Average Percent Symptomatic Co-Workers
MDI	15/18 (83%)	23%, SD 16%, range 0 – 60%
TDI	6/9 (67%)	15%, SD 13%, range 0 – 38%
HDI	5/9 (56%)	14%, SD 16%, range 0 – 30%
	(Chi-Square = 2.49, p=0.29)	(Chi-Square = 9.92, p=0.007)

Discussion

The Michigan surveillance system for WRA identified 261 cases of isocyanate-induced asthma. Michigan data shows that workers who develop isocyanate-induced asthma generally have severe and persistent asthma. While the majority of workers cease their exposure, some workers continue to work with isocyanates. Real life practical issues such as paying bills may override equally important medical issues such as removal from exposure to prevent further progression of disease. Since a newer sampling methodology was adopted in October of 1993, 42 inspections at facilities where these individuals worked and were exposed to isocyanates were conducted. Seven hundred and thirty co-workers of those index cases completed breathing symptom questionnaires as part of the enforcement inspections.

The Michigan experience of isocyanate-using facilities is probably not different from other states or from other countries. Being in compliance with the Michigan OSHA PEL does not preclude the development of work-related asthma. The reliance on air sampling data alone might give companies a false sense of security. The current Michigan and Federal work place standards for isocyanates do not include a requirement for medical surveillance, wage-retention for sensitized individuals, training, or procedures for the clean up of spills.

The longer an individual continues to be exposed to isocyanates after a diagnosis of work-related asthma, the greater the likelihood that their symptoms will persist [*20*]. A medical surveillance program to monitor symptoms among isocyanate-exposed workers should, therefore, be an integral part of any isocyanate-using facility's health and safety plan. In Michigan, however, 72% of the 42 companies inspected where isocyanate-induced asthma cases worked had no medical surveillance program. Several groups have recommended removal from exposure of sensitized individuals in consensus statements [*21-25*]. Medical surveillance should not take the place of engineering controls and safe handling practices, but should be in addition to those features.

There are limitations to this study. First, it is not possible to determine if a spill or low-level exposure was responsible for the development of each individual's asthma. No definition for spill or leak was provided to the index cases during the administration of the questionnaire. This might lead to misclassification of workplaces if the index cases used different definitions of "spill" or "leak". Assuming the misclassification was not in any specific direction, the effect of the misclassification would be to decrease the likelihood of finding an association. Further, sampling for isocyanates during inspections may not reflect typical exposure levels experienced by the workers on a day-to-day basis, and therefore might over or under estimate the workers' true exposures. One can conclude, however, that the presence of allowable air levels during a typical Michigan OSHA inspection does not preclude the presence of symptomatic workers. In addition, it was not possible to determine whether other possible asthma sensitizers were present in the workplace, which could also contribute to index case and co-worker breathing symptoms and obscure the potential effects of isocyanates.

The diagnosis of work-related asthma among individuals reported to the Michigan surveillance system followed the standard of medical care in the United States. This means the diagnosis in 95% of the reported cases was dependent on the history of a temporal relationship between symptoms and work. Only 5% of the reports had objective pulmonary function tests performed in relationship to work. Medical literature indicates that clinical history is sensitive but not specific [*26-27*].

High percentages of co-workers of the index cases with work-related asthma had daily or weekly symptoms of shortness of breath, chest tightness or wheezing identified through interviews conducted with these co-workers during Michigan OSHA enforcement inspections. The number of co-workers with work-related breathing problems is likely to be an underestimate of the true number of symptomatic individuals, since the extremely symptomatic individuals would presumably leave the job in addition to the fact that we did not classify individuals with monthly or less frequent breathing problems at work as positive. The extent to which workers leave the environment because of breathing problems was not known; this would under estimate both the magnitude and severity of breathing symptoms. On the other hand, because the questionnaire is a screening tool, not all symptomatic co-workers will have asthma let alone isocyanate-related asthma.

Recent studies of isocyanate-exposed workers have shown mixed results concerning the occurrence of respiratory symptoms at low-level exposures. Studies of MDI-exposed workers from wood product manufacturing facilities in the United States showed increased respiratory symptoms among workers in higher potential exposure areas [*28*] and in jobs below the OSHA permissible exposure limit of 0.02 ppm [*29*]. The first study measured actual air levels of isocyanates. Another study where isocyanate levels were measured and found to be well below 0.005 ppm found reductions in pulmonary function of the workers exposed, although there was no increase in the proportion of workers who developed respiratory symptoms or asthma compared to workers not exposed to isocyanates at the plant [*30*]. Different levels of exposure, isocyanate types and definitions of positive responses on questionnaires will all contribute to the variations found in the results of these studies.

Isocyanates play a large role in the manufacture of polyurethane products and there are few, if any options for substitution of other chemicals in their place. As new

prepolymers are developed, the challenge to companies that manufacture and use these chemicals will be to determine the best way to ensure the safety of individuals who handle them. One way to work toward this challenge would be through the manufacturers of these chemicals to develop and promote medical surveillance programs for their own employees as well as for the employees at the companies to which they sell their product. It cannot be assumed that the new polymers will be safer than the original isocyanates. Further, despite its decreased volatility, our data does not suggest that MDI is "safer" than TDI. Although our results were not statistically significant, we found that a greater percentage of the MDI-exposed cases with isocyanate-induced WRA (57%) had at least one ER visit compared to the TDI-exposed cases (48%), and a similar percentage of hospital stays (MDI 23%, TDI 24%). In addition, the higher percentages of symptomatic co-workers of these index cases who were identified during inspections at the MDI-using companies were not explained by the duration of years worked in isocyanates or by cigarette smoking. The challenge to scientists and regulators will be to develop methods to sample for the new forms of isocyanates and institute new and more comprehensive workplace exposure standards to reduce the burden of isocyanate-induced asthma.

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