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Hypersensitivity Pneumonitis-Like Reaction and Occupational Asthma Associated With 1,3-Bis(Isocyanatomethyl) Cyclohexane Pre-Polymer

Cathy Simpson, MD, MPH, David Garabrant, MD, MPH, Stephen Torrey, DO, MPH, Thomas Robins, MD, MPH, and Alfred Franzblau, MD

Twenty-three of 34 workers who had worked in the injection molding operation making polyurethane foam parts at an automobile parts manufacturing plant developed respiratory symptoms and/or systemic symptoms over a 2-month period following the full production use of a new diisocyanate paint that contained 1,3-bis(isocyanatomethyl)cyclohexane pre-polymer (BIC) (CAS #75138-76-0, 38661-72-2). At 3 months, all subjects underwent an interview, physical examination, pre- and post-shift pulmonary function tests, and either methacholine challenge test or bronchodilator challenge at an occupational health clinic. The most frequently cited symptoms were dyspnea (65%), cough (61%), chest tightness (57%), chills (57%), wheezing (30%), and myalgias, arthralgias, and nausea (26%). Thirteen subjects had either a positive methacholine challenge test or a positive response to bronchodilator challenge, making the overall prevalence of airway hyperresponsiveness 38%. The overall prevalence of hypersensitivity pneumonitis-like reactions among line operators in the injection molding process was 27%. This disease outbreak suggests that 1,3-bis(isocyanatomethyl)cyclohexane pre-polymer may cause asthma and hypersensitivity pneumonitis-like reactions. The use of BIC was discontinued 6 months after the first workers developed symptoms.

KEY WORDS: hypersensitivity pneumonitis, isocyanates, diioscyanates, asthma, occupational respiratory disease

INTRODUCTION

Exposure to diisocyanates is a leading cause of occupational asthma and has been demonstrated for toluene diisocyanate (TDI), diphenylmethane diisocyanate (MDI), and hexamethylene diisocyanate (HDI) [Butcher et al., 1993]. Hypersensitivity pneumonitis is also caused by diisocyanates, although this association has not been described as extensively as for asthma [Bernstein et al., 1993; Fink and Schlueter, 1978; Malo et al., 1983; Malo and Zeiss, 1982; Nielsen et al., 1985; Selden et al., 1989; Vandenplas et al., 1993; Yoshizawa et al., 1989]. The knowledge that adverse respiratory effects are associated with isomeric isocyanates having high vapor pressures has led to the use of high-molecular-weight oligomers (having lower vapor pressures), which are believed to carry a lower risk of sensitization. We report an investigation of an outbreak of asthma and a hypersensitivity pneumonitis-like reaction among workers in an automobile parts manufacturing operation in which a new diisocyanate oligomer (1,3-bis(isocyanatomethyl)cyclohexane pre-polymer) was introduced into production.

Department of Environmental and Industrial Health, Occupational Medicine Program, University of Michigan, School of Public Health, Ann Arbor, Michigan.
Address reprint requests to Cathy Simpson, M.D., Department of Environmental and Industrial Health, Occupational Medicine Program, University of Michigan, School of Public Health, 1420 Washington Heights, Ann Arbor, MI 48109-2029.

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METHODS

Manufacturing Operation

The workers made automotive parts in a reaction injection molding process. Molds were first cleaned and sprayed with a mold release agent, then were sprayed with a toner that contained 1,3-bis(isocyanatomethyl)cyclohexane pre-polymer. The spraying operation was performed by hand by line operators and took about 30 sec approximately 10 times per hour. Visible "bounce back" into the breathing zone occurred during spraying, requiring face shields and frequent cleaning of the face shields. Inhalation of spray and skin contamination were common. The mold was then closed and automatically injected with an MDI–polyol mixture, which polymerized in the mold. The molds were housed in individual ventilation hoods. After curing for about two minutes, finished parts were removed. Parts were later transported to a trimming area where flash was removed, inspected, and minor defects were repaired. The reaction injection molding area had seven molding stations in a large open space approximately 40 × 100 ft with a 20-ft ceiling.

Subjects

We were invited to the plant as consultants to evaluate workers in the reaction injection molding operation who had recently developed quite similar respiratory symptoms. Plant management was concerned that the development of similar respiratory symptoms among workers at the same operation might be associated with exposure to that operation. We were asked to assess whether there could be an association between these workers' symptoms and exposure to the reaction injection molding operation. In November 1992, we examined 23 symptomatic workers of the 34 workers who were currently employed in the reaction injection molding (RIM) area. All 23 subjects had worked in this operation for at least 2 months prior to when 1,3-bis-(isocyanatomethyl)cyclohexane pre-polymer was put in full production use in August 1992. Four of the 23 had had previous exposure to isocyanates before working in this plant. Each of the 23 workers was working as a line operator in the RIM area at the time of onset of symptoms. A few subjects had been evaluated initially at a local occupational health clinic (not affiliated with our institution) as there was no medical department in the plant. Prior to and during the outbreak of symptoms, none used respiratory protection. In mid-October 1992, all workers who worked on the line in the RIM area were required to wear air-supplied respirators and at the time of our evaluation, all subjects were asymptomatic. The pre-polymer was removed from the production process in January of 1993, although air-supplied respirators continued in use.

Selected Case Summaries

Case 1

A 33-year-old woman had worked at the plant as a RIM operator since July 1992. On September 15, 1992, she felt well upon arrival at work but developed a sore throat and chest tightness several hours into her shift. Her symptoms progressed to include cough, chills, myalgias, arthralgias, nausea, and vomiting. A chest X-ray performed on the same day of the onset of her symptoms was normal, and her white blood cell (WBC) count was 10,400/mm^3. She was prescribed an antibiotic, which she took for 1 week. She felt better and she returned to the RIM operation the following day. Her symptoms recurred every day and would abate within 4–5 hr after leaving work. When she tried a canister-type respirator, she had no change in her symptoms. Occasionally she was transferred to another department and her symptoms improved. In the middle of October 1992, she began using an air-supplied respirator, and she has had no recurrence of her symptoms.

Case 7

A 26-year-old man began working at the plant as a RIM operator in June 1992. One day during the first week of September 1992, he went to work feeling well and within 3 hr after starting work noted the sudden onset of chest tightness followed by dyspnea, fever, myalgias, arthralgias, nausea, chills, and diaphoresis. He was noted to have an oral temperature of 102°F. A chest X-ray taken the following day was within normal limits, and his WBC count was 26,900/mm^3. Pulmonary function tests done the day after the onset of his symptoms were normal. He was not treated with antibiotics. He stopped working almost immediately after the onset of his symptoms, but went back to work the next day. He did not return to the RIM operation and his symptoms completely disappeared after 48 hr. After 1 week, he returned to the RIM operation and wore a filter respirator. He had no problems for a week; however, during the second week, he experienced a second episode of symptoms almost identical to the first episode except he vomited once. His oral temperature was 100.8°F, rhonchi were noted bilaterally on chest auscultation, but no chest X-ray was done. Since the second episode, he has only returned to the RIM operation once and at that time wore an air supplied respirator. He has not had a recurrence of his symptoms.

Case 9

A 34-year-old woman began working in the RIM operation at the end of September 1992. One day, approximately 3 weeks after working in the RIM area, she experienced the sudden onset of chills, dizziness, dyspnea,

myalgias, and fatigue 1½ hr into her work shift. Her oral temperature was 101°F, and her WBC count was 20,000/mm^3. Pulmonary function testing performed several hours after symptom onset revealed an FVC 71% of predicted, and an FEV_1 70% of predicted. There were no infiltrates on her chest X-ray, and she was not treated with antibiotics. She did not return to the RIM area, and her symptoms resolved in 3 days without recurrence.

Case 23

A 46-year-old man was a supervisor of the RIM operation. He had two episodes (within the first 2 weeks of October 1992) of sudden onset chest discomfort, wheezing, shortness of breath, shaking chills, nonproductive cough, diaphoresis, and an oral temperature of 101°F. He was evaluated after the second episode, and pulmonary function tests performed while he was symptomatic revealed an FVC 58% of predicted and an FEV_1 48% of predicted. There was a right lower lobe infiltrate on his chest X-ray, and his WBC count was 17,500/mm^3. His physical examination was reported to be normal. He was given bronchodilators at this time and showed a 19% increase in FVC and a 48% increase in FEV_1. Both episodes began approximately 6 hr after he began work. His chest X-ray was clear 1 week later (no antibiotics were prescribed), and his pulmonary function tests improved. He had no history of wheezing or shortness of breath prior to working at this plant; however, he had prior history of working with isocyanates. Whereas his episodes of respiratory symptoms did not recur, repeat measurements of FVC and FEV_1 demonstrated a steady decline over the following 2 months, and it was noted that although nonexposure to isocyanates was recommended, he was unable to eliminate his exposure completely.

Interview and Pulmonary Function Tests

Subjects were interviewed to determine their occupational history, symptoms, the dates of onset of symptoms, where they were working at the onset of symptoms, smoking status, medical history, and demographic information. Spirometry was performed according to American Thoracic Society 1987 guidelines [American Thoracic Society, 1987] using a Collins Survey II 13.5-liter water seal spirometer. A minimum of three acceptable forced expiratory maneuvers was obtained, and the FVC, FEV_1, PEFR, MMEF, FEF_{25}, FEF_{50}, and FEF_{75} were recorded. The largest FVC and FEV_1 were taken, and the other measures were taken from the tracing having the largest sum of FVC and FEV_1. Spirograms were taken prior to entering the plant on the first day of the work week, after work on that same day, and again before and after work on the last day of the same work week. Methacholine challenge tests were performed in 19 of the 23 subjects and for the other four, whose baseline pulmonary function indicated significant airflow obstruction, spirometry was performed before and after the administration of a bronchodilator. The protocol used tidal breathing and a saline control similar to protocols reported in the literature, modified with respect to number of methacholine doses administered [Cockcroft and Bersheid, 1982; Chai et al., 1975; Nieminen, 1975]. The subject initially inhaled 2 ml of sterile buffered saline using oxygen as the carrier gas at 6 Ls/min for 2 min followed by spirometry immediately and again after 5 min. The normal saline solution was a control inhalation and was followed by methacholine at increasing concentrations of 0.05, 0.5, 5.0, and 20 mg/ml. At each concentration of methacholine, the subjects used slightly exaggerated breathing with a slight breathold and expired normally for 2 min. Spirometry was repeated followed by a 5-min wait before the next concentration of methacholine was delivered. Inhalation was discontinued if the FEV_1 fell by 20% or more from the baseline after the control inhalation or any dose of methacholine. From this, the concentration of methacholine required to cause a 20% fall in the FEV_1 (the PC20) was calculated by interpolation. A positive methacholine challenge test was taken as a PC20 of less than 8 mg/ml. A positive response to bronchodilator was defined as an increase in the FEV_1 of at least 15% from the pre-bronchodilator baseline.

Diagnostic Criteria

Asthma was defined as the presence of respiratory symptoms (cough, wheeze, chest tightness, or breathlessness) with either a positive response to bronchodilator or a positive methacholine challenge test. The following data were available (from the local occupational health clinic that initially evaluated the subjects) for evaluation of hypersensitivity pneumonitis-like reaction: WBC count (15 subjects), temperature (18 subjects), and chest x-ray (15). Hypersensitivity pneumonitis-like reaction was diagnosed as the presence of systemic symptoms (myalgias/arthralgias, chills, nausea, diaphoresis, headache) with either an elevated white blood count (>10,000/ml), documented fever (>100°F), or pulmonary infiltrate on chest X-ray of which all were done within 2 weeks of the last symptomatic period. Symptoms were required to be reported in a pattern related to work (symptoms had to begin 2–12 hr after starting work and resolve 2–3 days of onset) in order for us to consider the diagnoses of both asthma and hypersensitivity pneumonitis-like reactions. Subjects who reported symptoms that were not temporally associated with work were not classified as meeting the diagnostic criteria.

RESULTS

The average age of the 23 subjects was 31.3 years and the population was predominantly white males (65% male,

TABLE I. Summary Demographics and Clinical History of Subjects Exposed to 1,3-Bis(Isocyanatomethyl)Cyclohexane in an Automobile Parts Manufacturing Plant: 1992

Case no.	Age	Race/sex	Current smoker	Date of hire	Symp began	Prior asthma	Systemic Sx	Resp Sx	Rash/ rhinitis	Temp (°F)	WBC (/mm^3)	CXR	MCT/BD	DX
1	33	WF	yes	7/27/92	9/15/92		ch,ar,my,na	ct,co,ti	rash	NL	10,400	NL	+	HPLR, A
2	24	WM	no	6/15/92	9/15/92		na	co,ti,ct,wh		NL	14,500	NL	+	HPLR, A
3	28	WM	yes	1/7/92	8/1/92		my,ar	ct,sob		NL	7,000	NL	+	A
4	44	HF	yes	7/28/92	9/15/92	+	ch,dia	sob,wh	rash	NL	11,800	NL	NL	HPLR
5	30	WM	no	6/28/92	10/2/92	+	—	ct,co,wh,ti	rhin/rash	ND	ND	ND	+BD	A
6	43	WM	yes	8/17/92	9/15/92		dia,ch,ar	co,ti,sob		ND	ND	ND	NL	Neither DX
7	26	WM	yes	6/15/92	9/7/92		my,ar,ch,na,dia	ct,sob		102	26,900	NL	NL	HPLR
8	34	WM	yes	8/1/92	9/15/92		ch,my	sob,co	rhinitis	NL	ND	NL	NL	Neither DX
9	34	WF	yes	8/25/92	9/15/92		ch,my	sob		NL	20,000	ND	NL	HPLR
10	32	WM	yes	8/1/92	10/7/92		ar,ch,dia	ct,co		NL	7,100	ND	+	A
11	41	WF	yes	7/25/92	9/1/92		ch,ha	—		NL	12,800	NL	+	HPLR
12	21	WF	yes	7/16/92	8/15/92		—	co,wh,sob	rash	NL	8,000	ND	+	A
13	28	WF	yes	6/2/92	9/15/92		my,ha	sob,ct,		100.2	8,800	NL	+	HPLR, A
14	19	WM	no	8/1/92	9/25/92		na,ha	ct,sob	rash	ND	6,300	NL	+	A
15	36	AM	yes	8/4/92	8/9/92		ch,na	co,ct,wh		ND	7,000	NL	NL	Neither DX
16	38	WM	yes	6/15/92	9/15/92		ar,na,ha	sob	rhinitis	ND	16,000	ND	NL	HPLR
17	24	WM	yes	8/30/92	10/15/92		ch	co,ti(+strep)		101.2	ND	ND	+	A
18	27	BM	yes	6/15/92	10/8/92		dia,ch	co,sob,wh		NL	8,900	NL	+	A
19	44	WF	yes	8/10/92	8/20/92		—	co,ct		NL	ND	ND	+BD	A
20	23	BM	no	6/15/92	9/15/92		na	ct,sob,co		NL	ND	NL	NL	Neither DX
21	22	WF	yes	7/20/92	8/25/92		ch	ti,ct,co,sob	rhinitis	NL	ND	NL	+	A
22	23	WM	yes	7/1/92	8/1/92		—	ct,co,sob		NL	ND	NL	+BD	A
23	46	WM	no	1/6/92	10/7/92		ch,dia	cou,wh,sob	rash	NL	17,500	RLL infiltrate	+BD	HPLR, A
	Avg age: 31.3	83% white; 65% male	78% current smokers				Sx+=87%	Sx+=96%	Sx+=39%					HPLR=9 A=14

ch, chills; my, myalgias; ar, arthralgia; dia, diaphoresis; na, nausea; ha, headache; co, cough; wh, wheezing; sob, shortness of breath; ct, chest tightness; ti, throat irritation; temp, temperature taken at the time seen in either occupational medicine clinic or at an emergency room; NL, normal; ND, not done; HPLR, hypersensitivity pneumonitis-like reaction; A, asthma; MCT, methacholine challenge test; BD, bronchodilator response.

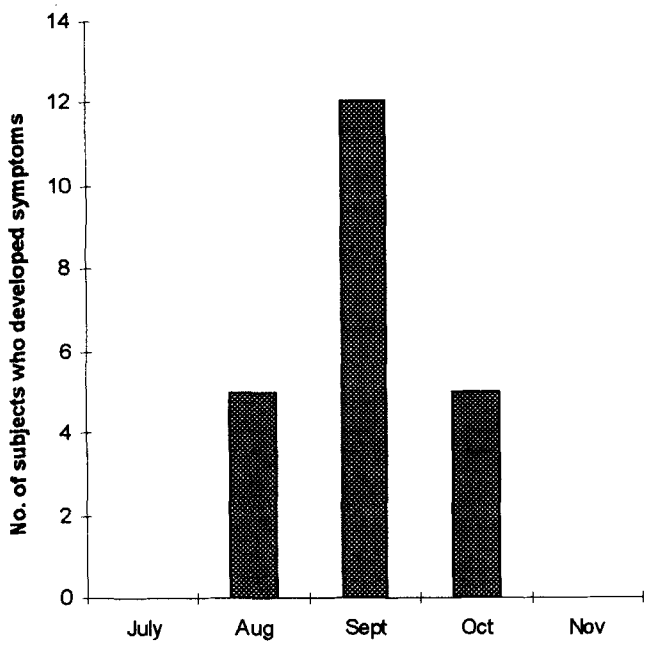

FIGURE 1. Distribution of automobile parts maufacturing workers exposed to 1,3-bis(isocyanatomethyl)cyclohexane pre-polymer by month of onset of their symptoms: 1992. Symptoms occured over a 3-month period with no new cases after October, corresponding to the introduction of air-supplied respirators.

83% white) (Table I). Seventy-eight percent were current smokers. Only two subjects had a history of asthma prior to working in the plant. Because the plant was new, all the subjects had been hired in 1992, with 21 having been hired since June. Symptoms began in 22 subjects during a 10-week period between August and October (Fig. 1) that followed the increased use of 1,3-bis(isocyanatomethyl) cyclohexane pre-polymer in production. The peak incidence of symptoms occurred in September, during which 12 subjects became ill, eight of whom had a hypersensitivity pneumonitis-like reaction and five of whom had new-onset asthma. The entire outbreak ended by the third week in October, when all workers on the injection molding line were required to wear air-supplied respirators and by which time 14 of the 23 (61%) subjects had new-onset asthma and 9 of 23 subjects (39%) had developed a hypersensitivity pneumonitis-like reaction. Four subjects had both diagnoses and 4 subjects (17%) had neither diagnosis.

Table II summarizes the distribution of symptoms. The most frequently reported respiratory symptom was dyspnea (65%), followed by cough (61%) and chest tightness (57%). The most frequently reported systemic symptom was chills (57%), followed by nausea (26%), myalgias (26%), and arthralgias (26%). A total of 22 subjects (96%) reported respiratory symptoms and a total of 20 subjects (87%) reported systemic symptoms at some point during the two month period. All 23 subjects reported either respiratory symptoms and/or systemic symptoms. Nine (39%) of the

TABLE II. Distribution of Symptoms Reported by Subjects Exposed to 1,3-Bis(isocyanatomethyl)Cyclohexane in an Automobile Parts Manufacturing Plant: 1992

Respiratory symptoms	No. of subjects reporting symptom (%)	Systemic symptoms	No. of subjects reporting symptom (%)
Dyspnea	15/23 (65)	Chills	13/23 (57)
Cough	14/23 (61)	Nausea	6/23 (26)
Chest tightness	13/23 (57)	Myalgias	6/23 (26)
Wheezing	7/23 (30)	Arthralgias	6/23 (26)
Throat irritation	6/23 (26)	Diaphoresis	6/23 (26)
Rhinitis	4/23 (17)	Headache	4/23 (17)

subjects reported either rhinitis or skin rash associated with work.

Thirty-five percent of the subjects had elevated WBC counts above 10,000/mm^3 at some point during the 10-week period following the introduction of 1,3-bis(isocyanatomethyl)cyclohexane into production. Chest x-rays were also performed on 15 of the 23 subjects, but only 1 subject had patchy infiltrates. At our evaluation in November 1992, 11 of the 19 subjects (58%) who underwent methacholine challenge tests had a positive response, and another 2 subjects had a positive response to bronchodilator challenge.

Pulmonary function testing performed at work during the period November and December 1992, showed little change during the work day or across the work week. For the FVC, the mean percent change was −1.77% across the first day of the work week, −0.51% across the last day of the work week, and −3.76% across the work shift and the work week (Table III). For the FEV_1, the mean percent change was −0.79% across the first day of the work week, 1.36% across the last day of the work week, and −2.55% across the work shift and the work week. None of these changes was statistically significant.

DISCUSSION

We have described an outbreak of hypersensitivity pneumonitis-like reactions and asthma that occurred in a 10 week period that followed the introduction into production of a paint containing 1,3-bis(isocyanatomethyl)cyclohexane. Cases had regular, repeated symptoms incompatible with infection. Anecdotally, there were no reports of asthma, hypersensitivity pneumonitis-like illness or other respiratory illness among the remaining 70 or so workers in the plant. The attack rate for both of these respiratory disorders was high enough that it is difficult to suggest a plausible alternative explanation. Reactive airways dysfunction syndrome (RADS) is not a likely explanation, in part be-

TABLE III. Summary of Spirometry in Subjects Exposed to 1,3-Bis(isocyanatomethyl)Cyclohexane in an Automobile Parts Manufacturing Plant: 1992

	Mean (SD)	Mean % predicted prior to work on first day	Mean % cross-shift change on first day	Mean % cross-shift change last first day	Mean % cross-week change
FVC (liters)	4.49 (1.05)	96	−1.77	−0.51	−3.76
FEV_1 (liters)	3.61 (0.89)	97	−0.79	1.36	−2.55
MMEF (l/sec)	3.70 (1.36)	89	0.11	7.55	−0.33
FEF_{25} (l/sec)	7.05 (1.57)	95	−0.32	6.35	−1.47
FEF_{50} (l/sec)	4.36 (1.58)	78	8.57	12.20	10.07
FEF_{75} (l/sec)	1.71 (0.81)	55	−3.01	7.27	−2.44
PEFR (l/sec)	8.70 (1.55)	108	−0.50	3.37	−2.97

cause there was no history of an incident of high level exposure to BIC followed immediately by symptoms in all subjects [Brooks and Bernstein, 1993]. Our subjects developed their individual symptomatology over a 2-month period, and no subject reported a precipitating event. Furthermore, none of the subjects reported persistent symptoms when they were no longer exposed. Whereas other reactive materials such as perfluoro compounds released from heated fluoropolymers can cause similar systemic reactions, such compounds were not in use in the RIM operation.

Hypersensitivity pneumonitis-like reactions are rare consequences of exposure to diisocyanates [Vandenplas et al., 1993], and most of our knowledge of these reactions is based on case reports [Vandenplas et al., 1993; Charles et al., 1976; Fink and Schlueter, 1978; Zeiss et al., 1980; Malo and Zeiss, 1982; Malo et al., 1983; Baur et al., 1984; Nielsen et al., 1985; Bascom et al., 1985; Walker et al., 1989; Selden et al., 1989; Yoshizawa et al., 1989; Patterson et al., 1990]. Thus, the value of our observations derives in part from the identification of the entire exposed cohort and the observation that a high proportion of the exposed subjects was affected. We did not study the attack rate of these disorders among the nonexposed workers in this plant; therefore, we are unable to specify the relative risk associated with the exposure. Isocyanate inhalation challenges for BIC were not done in this investigation, and immunologic studies against TDI/MDI bound to human serum albumin were negative. Whereas IgG antibodies directed against isocyanates have been noted in subjects with isocyanate-associated hypersensitivity pneumonitis, their presence is not found in all subjects with the diagnosis [Vandenplas et al., 1993]. We were unable to perform specific inhalation challenge tests on the subjects, although these can aid in the diagnosis of sensitization to specific isocyanates [Bauer et al., 1984; Fink et al., 1978; Malo and Zeiss, 1982; Malo et al., 1983; Vandenplas et al., 1993]. For this reason, we cannot conclude sensitization of the subjects to BIC or a definitive diagnosis of hypersensitivity pneumonitis from this investigation. However, the exposure histories, and symptomatology were consistent between subjects and, therefore (we believe), adequately support a diagnosis of a hypersensitivity pneumonitis-like reaction.

The lack of consistent findings on cross-shift and cross-week PFTs in the face of documented asthma, is most likely due to the mandatory use of supplied-air respirators at the point in time that these data were collected. The respirators were attached to air hoses at the workstations, so they were donned in the work area. The workstation was not operating until the worker turned the machine on although adjacent workstations may have been operating at the time a worker would begin working. It is likely that exposure was to a large droplet aerosol, which would account for the effectiveness of respirator use.

Levels of MDI measured at the periphery of the hoods were minimally detectable; however, no monitoring of 1,3-bis(isocyanatomethyl)cyclohexane was done. Our study was limited by our lack of opportunity to measure the exposures to 1,3-bis(isocyanatomethyl)cyclohexane. Thus, we are unable to comment on the exposure levels that are associated with either hypersensitivity pneumonitis-like reaction or asthma. We believe the respiratory reactions were not due to exposure to MDI because the MDI was used in a closed process in which there was little if any opportunity for exposure to unreacted material. Moreover, similar attack rates for hypersensitivity pneumonitis-like reaction have never been reported in multiple studies investigating MDI-related respiratory effects. In contrast, the 1,3-bis(isocyanatomethyl)cyclohexane was used in a manner that resulted in obvious contamination of the breathing zones of workers without adequate respiratory protection. The workers were observed to have spray residue on their faces, hands, and clothes. To our knowledge, this particular diisocyanate does not appear to have been used before in any industrial setting in the United States. In addition, although physical data on 1,3-bis(isocyanatomethyl)cyclohexane are not available, one would expect BIC pre-polymer to have a

substantially higher vapor pressure at room temperature than MDI based on its chemical structure.

Although we cannot comment on the mechanisms by which 1,3-bis(isocyanatomethyl)cyclohexane might cause hypersensitivity pneumonitis-like reactions, studies of subjects who have similar responses to TDI, MDI, and HDI suggest that diisocyanates cause parenchymal lung involvement by mechanisms that are similar to those that are involved in hypersensitivity pneumonitis caused by other organic agents [Vandenplas et al., 1993; Charles et al., 1976; Fink and Schlueter, 1978; Zeiss et al., 1980; Malo and Zeiss, 1982; Malo et al., 1983; Baur et al., 1984; Nielsen et al., 1985; Bascom et al., 1985; Walker et al., 1989; Selden et al., 1989; Yoshizawa et al., 1989; Patterson et al., 1990; Salvaggio, 1987]. Our findings of systemic symptoms accompanied by elevated WBC counts, fever, or pulmonary infiltrates is strongly suggestive of hypersensitivity pneumonitis. Although it is possible that our subjects overreported their symptoms, we relied on written medical records (the initial evaluation from the local occupational health clinic) for documentation of fevers, leukocytosis, and chest x-ray abnormalities; we relied on inhalation challenge tests for the determination of asthma. Thus, our findings are not explainable by reporting bias.

Although smoking has been reported to be associated with airway hyperreactivity [Welty et al., 1984; Tashkin et al., 1993; Burney et al., 1987; Sparrow et al., 1987, 1993] in our study there was no apparent association. Eleven of the 15 subjects who had hyperreactive airways smoked, in comparison to seven of the eight subjects who did not have airway hyperreactivity (odds ratio 0.39; 95% confidence interval 0.04–4.28). This observation does not support the interpretation that smoking contributed to the high prevalence of airway hyperreactivity.

To our knowledge, this is the first report linking 1,3-bis(isocyanatomethyl)cyclohexane with human disease. If there was a relative safety advantage in using BIC because of a presumed lower vapor pressure and higher molecular weight (pre-polymer), the process of aerosolization to large droplets of pre-polymer in the breathing zone may have negated this advantage. It should be noted that BIC monomer has only one more carbon than does TDI, which might minimize any apparent advantage. The risk of aerolization or heating should be kept in mind when designing industrial processes involving isocyanate monomers or pre-polymers.

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