

occupational and environmental lung disease

Role of Inhalation Challenge Testing in the Diagnosis of Isocyanate-induced Asthma*

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Results of isocyanate challenge tests performed on 63 workers referred with a diagnosis of probable isocyanate asthma between 1974 and 1988 were reviewed. Thirty (48 percent) had an acute episode of asthma with a greater than 20 percent decline in FEV₁ following subirritant exposure to isocyanates. No difference in the frequency or type of respiratory complaints between isocyanate reactors and nonreactors was found. No differences in lung function results were present when comparing smoking and ex-smoking reactors and nonreactors. In never-smokers with complaints consistent with isocyanate-induced asthma, the presence of obstructive lung disease increased the likelihood that isocyanate-induced asthma was present. Bronchial responsiveness to methacholine occurred in nearly all isocyanate reactors but predicted isocyanate-induced asthma in only 68 percent of the workers. In nearly all

cases of challenge-confirmed toluene diisocyanate (TDI)-induced asthma, a 15-min exposure to 20 ppb of the commercial TDI mixture (80:20 2,4:2,6) provoked asthma. Conversely, in the absence of an asthmatic response following exposure to this dose for this duration, a second exposure at this concentration for a longer time would be reasonable to confirm the absence of isocyanate-induced asthma. Among workers employed in the production of polyurethane foam and confirmed to have TDI-induced asthma by inhalation challenge to the different TDI isomers, there appeared to be increased airway reactivity to the 2,6 isomer. This may have relevance to the frequency and intensity of respiratory symptoms that workers with TDI-induced asthma develop in differing industrial settings.

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Isocyanates are low molecular weight compounds used in the manufacture of polyurethane foams, varnishes, paints, and plastics. Toluene diisocyanate (TDI), methylene diphenyl diisocyanate (MDI), and hexamethylene diisocyanate (HDI) are the most commonly used. Worldwide, as many as a half million workers are exposed to these agents.¹ In 1975, 400 million lb of TDI and 300 million lb of MDI were produced.²

In 1986, the worldwide capacity for TDI production had increased to 645 million lb, while the worldwide capacity for MDI production had increased to 850

million lb.³

In 1951, Fuchs and Valade⁴ described seven workers with TDI-induced asthma following exposure to this agent, detailing the immediate and now well-recognized late asthmatic reaction common in this illness. Since then, many investigators have identified workers with isocyanate-induced asthma in the numerous industries where isocyanates are used.⁵ A 1977 report showed asthma to occur in approximately 5 percent of workers exposed during TDI production.⁶ In industrialized countries isocyanates are probably the most common cause of occupational asthma.

In this report the results of isocyanate challenge studies performed on 63 workers between 1974 and 1988 are reviewed, and the difficulties encountered diagnosing isocyanate-induced asthma based on clinical information are reported.

MATERIALS AND METHODS

Patient Population

Sixty-three workers were referred for isocyanate challenge testing. All had a diagnosis of probable isocyanate-induced asthma. Twenty (32 percent) were referred by Tulane University chest physicians during the five years of a longitudinal assessment of respiratory

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health of workers employed in the manufacture of TDI.⁷ Nine (14 percent) were tested in the course of an epidemiologic survey of workers employed in TDI polyurethane foam manufacturing, all having been evaluated jointly by the corporate physician and a Tulane University chest physician.⁸ Nine (14 percent) were referred by physicians of another large TDI manufacturer. Another nine (14 percent) were referred by corporate physicians of two refrigerator manufacturing facilities, where workers were exposed to TDI vapors released during polyurethane foaming for refrigerator insulation. Finally, 16 (25 percent) were referred by academic or workplace physicians who knew of our interest in isocyanate-induced asthma.

Of these 63, all but five were challenged exclusively to TDI. The five included two workers tested solely to MDI, one worker tested solely to HDI, another worker tested to MDI and HDI, and a final worker tested to MDI and TDI.

Respiratory medications were discontinued in all workers at least 48 hours before challenge testing. All workers signed consent forms that permitted challenge tests with subirritant isocyanate exposures.

Definitions and Clinical Features of the Workers Tested

Atopy: Childhood atopy was defined by a history of childhood asthma, atopic dermatitis, or positive skin tests to common inhalant allergens. Current atopy was defined by complaints of seasonal rhinitis or by positive skin prick tests to at least two common inhalant allergens.

Respiratory complaints: Current asthma was defined by episodic or persistent wheeze of variable severity, occurring outside the isocyanate workplace exposure. Shortness of breath, sputum production, cough, rhinitis, or skin rash was also recorded. Respiratory symptoms occurring during the workshift or improving away from the workplace (*ie*, on weekends or extended holidays) were also noted.

Smoking: Smoking categories included current, exsmokers, and never-smokers. Exsmokers were defined as those who had not smoked for at least one year. Never-smokers were those who claimed a lifelong history of nonsmoking.

Isocyanate exposure history: Each worker provided information regarding the time from first isocyanate exposure to the onset of chest symptoms, the time from initial respiratory complaints to challenge testing, and the time from last isocyanate exposure to challenge testing.

Workplace exposures were reported as chronic (occurring most days), episodic (occurring occasionally), or accidental (occurring with isocyanate spills).

Lung Function Testing

Spirometric tests were performed using the Pulmolab model 5000 system (Cardio-Pulmonary Instruments), which includes a dry rolling-seal spirometer capable of measuring forced expiratory flows and volumes. Calibration was performed immediately before each test.

All participants performed at least three satisfactory forced expiratory maneuvers before isocyanate challenge testing. Spirometry was repeated until at least two curves of satisfactory shape, with forced vital capacity (FVC) within 5 percent of the largest, were recorded. The mean value of the spirometric parameters was computed for the two tests with the largest sum of the forced expiratory volume in one second (FEV₁) and FVC. The FVC, FEV₁, FEV₁/FVC, and forced expiratory flow rate between 25 and 75 percent of the FVC (FEF_{25-75%}), expressed as percent predicted, were used in the data analysis. Predicted values were those of Knudson et al.⁹ For blacks, the predicted values were multiplied by 0.90.

Measurement of Airway Responsiveness to Methacholine

Airway responsiveness to methacholine was measured before isocyanate challenge testing in 46 workers. Eighteen workers were

tested using a Mark 8 pressure respirator (Bird Corporation) driven by oxygen at 100 L/min, to nebulize a continuous flow of methacholine in dilutions of 5 or 25 mg/ml. The maximal cumulative dose provided was 150 breath units. Measurements of FEV₁ were recorded using the Pulmolab model 5000 system described above. After baseline measurement, five inhalations of the 5 mg/ml dilution were performed, and the maximal FEV₁ was recorded from three forced expiratory maneuvers. If the FEV₁ remained above 80 percent of baseline, the procedure was repeated with the 25 mg/ml dilution and the maximal FEV₁ again measured after 5 min.

Twenty-eight workers were tested using a modification of the French-Rosenthal dosimeter method.⁸ Nebulized methacholine dilutions varying from 0.06 to 32 mg/ml (providing doubling cumulative doses from 0.3 to 640 cumulative breath units) were administered. The FEV₁ was measured using a Pulmonaire bellows spirometer (Jones Medical Instruments Company). After baseline FEV₁ measurements maximal FEV₁ was determined from three expiratory maneuvers 5 min after each incremental dose of methacholine was given.

For both methods, bronchial responsiveness was estimated as the cumulative dose provoking a 20 percent decrement in FEV₁ (PD₂₀ FEV₁). The test was considered positive if the PD₂₀ was 150 cumulative breath units or less.

Isocyanate Inhalation Challenge Testing

From 1974 to 1981, 38 workers were challenged with the commercial isomer mixture of TDI (80:20 2,4:2,6) in a small room with an air-lock observation area. Our protocol for generating isocyanate atmospheres in this chamber has been reported.¹⁰

For 24 workers tested from 1982 to 1988, subirritant MDI and TDI atmospheres were produced in a dynamic flow chamber. Our method of generating isocyanate atmosphere in this chamber has also been reported.^{11,12} Four workers were challenged with MDI (including one challenged to MDI and TDI, and another exposed to MDI and HDI). Because MDI has a low vapor pressure, minimal doses of acetone are necessary to solubilize and disperse it as an aerosol. Eight received exposure to the commercial TDI mixture. Thirteen workers, all employed in industries where polyurethane foam was produced, were exposed to an isomer of TDI. If no asthma episode occurred following the initial isomer exposure, these workers were exposed to the other isomer or the commercial mixture of TDI.

In earliest studies, workers were exposed to isocyanates without being hospitalized or without measurement of bronchial responsiveness to methacholine. With experience, it became clear that hospitalization was important to document and treat (when necessary) late asthmatic reactions. The practical value of measuring methacholine responsiveness was also recognized. When levels of bronchial responsiveness to methacholine were low, short isocyanate exposure of small doses were omitted from the isocyanate challenge sequence. Conversely, when levels of bronchial responsiveness to methacholine were high, small isocyanate exposures of short duration were provided.

Since the dynamic challenge chamber was built in 1982, the following approach to challenge testing has been used whenever possible. On the first day of hospitalization, the worker undergoes complete lung function tests and a methacholine inhalation test. Day 2 is the "placebo" day. The worker is placed in the challenge chamber, unaware that no isocyanate exposure is provided. Days 3, 4, and 5 are specific challenge days, typically beginning with an isocyanate exposure of 20 ppb (the permissible exposure limit) for 15 minutes, although lower initial isocyanate exposures are sometimes used, dictated by the degree of methacholine responsiveness. In the absence of an unequivocally positive reaction, an exposure of 20 ppb is delivered on successive days for as long as 5 h. In two of the cases in this series, challenge concentrations approximating 30 ppb were used, since such subirritant levels occur in the workplace.

Table 1—Challenge Testing with Isocyanates*

Group	No.	Men	Women	Age, yr	TDI	MDI	HDI
Reactors	30	25	5	40 ± 10	27	3	1
Nonreactors	33	29	4	40 ± 11	32	1	1

*Among the reactors, one worker was tested to both MDI and TDI—reacting only to TDI. In the nonreactor group, one worker was tested to both HDI and MDI, not reacting to either.

For all TDI and MDI challenges, isocyanate concentration was monitored by a calibrated MDA Scientific model 7000 series isocyanate monitor. In those exposed to MDI, acetone levels were measured by a Miran model 1A infrared gas analyzer monitor.

Two workers were exposed to HDI. Both were tested in the spray paint booth of the University's maintenance department. Airborne levels of HDI were collected throughout the spray painting period and analyzed by high-performance liquid chromatography.¹³

A positive challenge test was defined by development of asthma symptoms and an accompanying decline in FEV₁ greater than 20 percent compared with both baseline and the matched values from the "placebo" day. When these features occurred within 1 h of initiation of challenge, the reaction was termed "immediate." More delayed timing defined a "late" reaction. Both types of reactions constituted a "dual" reaction.

Statistical Evaluation

Data are reported as the mean and standard deviation. The Student's *t* test was used to compare data expressed as continuous variables. For discrete variable data, the χ^2 test was used to determine differences. In both instances, a *p* value ≤ 0.05 was considered statistically significant.

RESULTS

Thirty (48 percent) workers have a positive reaction following isocyanate challenge: 27 to TDI, two to MDI, and one to HDI. Six (20 percent) reacted immediately, 12 (40 percent) were late reactors, and 12 (40 percent) had dual reactions. The mean age and gender distribution of those challenge positive and challenge negative was similar (Table 1).

There were no significant differences between reactors and nonreactors with respect to total months of isocyanate exposure, time from first exposure to initial respiratory complaints, time from first exposure to challenge testing, time from last exposure to challenge testing, or the nature of the occupational exposures

Table 2—Characteristics of Worker Exposure to Isocyanates

	Reactors (n = 30)	Nonreactors (n = 33)	<i>p</i> Value*
Total exposure†	85.4 ± 68	84.1 ± 80	.90
First exposure—symptoms†	45.3 ± 56	33.8 ± 39	.40
First symptoms—challenge†	41.2 ± 38	53.2 ± 67	.38
Last exposure—challenge†	3.8 ± 6.1	4.2 ± 5.6	.77
Chronic exposures, no. (%)	22 (73)	26 (79)	.83
Episodic exposures, no. (%)	8 (27)	7 (21)	.83
Accidental exposures, no. (%)	13 (43)	18 (55)	.52

*Student's *t* test used to detect differences in the first four parameters, and χ^2 test for the others.

†Duration expressed in months.

(chronic, episodic, or accidental) (Table 2). Among reactors, the time from the first episode of asthma to isocyanate challenge (*ie*, the duration of isocyanate-induced asthma) ranged from two to 151 months (median, 33 months). Six had ongoing asthma with continuing workplace exposures lasting between six and 12 years. Among those challenge-positive, the time from initial isocyanate exposure to the first episode of asthma ranged from one day to 21 years (median, 32 months). Seven workers were exposed to isocyanates for at least six years before developing symptoms.

Clinical findings are reported in Table 3. There was a tendency for never-smokers and those with current asthma to be more frequent among those challenge-positive, and for rhinitis to be more frequent in those challenge-negative (NS). No significant differences were found in the frequency of the clinical findings when analyzed by smoking category (never-smokers, exsmokers, and current smokers), comparing the challenge-positive and challenge-negative groups (data not shown). Neither were significant differences found in the frequency of the clinical findings when analyzed by the temporal occurrence of an acute episode of asthma (immediate, late, or dual) following challenge testing (data not shown).

No significant differences in baseline lung function measurements were found between challenge-positive and challenge-negative smokers and exsmokers. Among never-smokers, significantly lower values for FEF_{25-75%} and FEV₁/FVC were found in those with a positive challenge (Table 4).

Table 3—Clinical Findings and Smoking History in Isocyanate-challenged Subjects

	Reactor, No. (%) (n = 30)	Nonreactors No. (%) (n = 33)	<i>p</i> Value*
Work-related respiratory complaints	29 (97)	29 (88)	1.0
Improve away from work	27 (90)	32 (97)	.53
Cough	27 (90)	29 (88)	1.0
Wheeze > 1 h†	27 (90)	27 (82)	.57
Wheeze < 1 h†	19 (63)	19 (58)	.83
Current asthma	11 (37)	6 (18)	.17
Sputum	10 (33)	11 (33)	1.0
Current atopy	9 (30)	6 (18)	.42
Rhinitis	8 (27)	17 (52)	.08
Rash	3 (13)	3 (9)	1.0
Never-smoker	14 (47)	9 (27)	.18
Exsmoker	9 (30)	11 (33)	.99
Current smoker	7 (23)	13 (39)	.27
Positive skin tests‡	9/16 (56)	7/14 (50)	1.0
Childhood atopy	3/26 (11)	6/33 (18)	.73

**p* value calculated by χ^2 test.

†Onset of wheeze less than or more than 1 h after beginning isocyanate exposure.

‡More than two positive skin prick tests to ten common antigens (not all were tested).

Table 4 — Pulmonary Function Tests Results*

Values	Reactors	Nonreactors	P Value
Never-smokers	(n = 14)	(n = 9)	
FEV ₁	92.1 ± 17.7	105.2 ± 19.3	.11
FVC	105.5 ± 11.4	105.1 ± 15.9	.94
FEF _{25-75%}	56.1 ± 21.9	88.7 ± 23.8	<.01
FEV ₁ /FVC	84.2 ± 9.1	96.6 ± 7.3	<.01
Exsmokers	(n = 9)	(n = 11)	
FEV ₁	91.4 ± 13.6	98.4 ± 13.3	.28
FVC	99.7 ± 12.1	107.1 ± 15.3	.28
FEF _{25-75%}	60.0 ± 25.1	62.1 ± 20.2	.84
FEV ₁ /FVC	89.1 ± 11.4	88.6 ± 10.5	.92
Current smokers	(n = 7)	(n = 13)	
FEV ₁	97.8 ± 16.2	93.2 ± 15.3	.56
FVC	102.8 ± 10.0	99.2 ± 13.3	.56
FEF _{25-75%}	71.2 ± 29.2	64.2 ± 20.4	.55
FEV ₁ /FVC	91.8 ± 8.2	90.8 ± 7.2	.78

*Expressed as percent predicted.

†p value calculated by Student's *t* test.

Twenty-one of 23 (91 percent) challenge-positive subjects were reactive to methacholine, and ten of 23 (43 percent) challenge-negative subjects had a positive methacholine inhalation test (*p* < .001). Isocyanate challenge positivity occurred in 21/31 (68 percent) with bronchial hyperresponsiveness to methacholine.

Forty-six workers were tested to the commercial mixture of TDI, of whom 18 were challenge-positive. A summary of the concentrations and durations of TDI exposure which provoked an episode of asthma is reported in Table 5. The maximal TDI concentration and duration of exposure for the 28 challenge-negative workers is also reported.

Features of Workers Tested to the Toluene Diisocyanate Isomers

Thirteen polyurethane foam workers were tested to at least one of the isomers and occasionally to the commercial mixture (Table 6). Workers 1 and 2 were

Table 5 — Doses and Duration of 80:20 2,4:2,6 TDI Inhalation Exposures

Dose and Exposure Duration	Challenge-Positive (n = 18)	Challenge-Negative (n = 28)
9 ppb for 270 min	1	
4-10 ppb for 12-15 min	11	
10 ppb for 30 min	2	
16 ppb for 90 min	1	
20 ppb for 15 min	1	
20 ppb for 45 min	1	
20 ppb for 180 min	1	
15-22 ppb for 15 min		17
18-23 ppb for 60 min		6
19-23 ppb for 180-300 min		5

*Worker initially unreactive to an exposure of 10 ppb for 30 minutes, but reactive to 20 ppb for three hours on the next day.

challenge-negative to the 2,4 isomer for 15 minutes, but reacted to a subirritant exposure to the commercial mixture for a longer duration. Workers 3, 4 and 5 reacted to each isomer, but with differing degrees of airway reactivity. Because this variability in airway reactivity to the isomers has not been previously shown in detail, short case histories and graphs of challenge test results of these five workers (cases 1 to 5 in Table 6) are presented.

Three additional workers were exposed only to the 2,4 isomer and reacted, one with recurrent nocturnal asthma. Another reacted to the 2,6 isomer, again with

Table 6 — Results of TDI Isomer Challenges*

Case No.	Methacholine Reactivity†	Exposures				
		Day 2	Day 3	Day 4	Day 5	
1	20	- ‡ 2,4§ (5/15)	- 2,4 (19/15)	+ 2,4:2,6 (20/60)		
2	15	- 2,4 (5/15)	- 2,4 (19/15)	+ 2,4:2,6 (26/45)		
3	30	+ 2,6 (21/15)	- None	- None	+ 2,4 (21/15)	
4	1.6	- 2,4 (19/15)	+ 2,4 (16/60)	- None	+ 2,6 (16/42)	
5	2.5	+ 2,4 (17/15)	- None	- None	+ 2,6 (18/15)	
6	3.6	+ 2,4 (9/15)				
7	5	- 2,4 (5/15)	+ 2,4 (19/15)	+ 2,4 (21/30)		
8	5	+ 2,4 (10/15)	+ None	+ None		
9	30	+ None	+ (31/30)	+ None		
10	8	- 2,6 (21/15)	- 2,6 (22/240)	- None	- 2,4 (9/240)	
11	6	- 2,4 (5/15)	- 2,4 (21/30)	- 2,4 (19/60)	- 2,4:2,6 (20/240)	
12	1	- 2,6 (21/15)	- 2,6 (20/60)	- 2,4 (20/60)	- 2,4 (15/60)	
13	Not done	- 2,6 (21/15)	- 2,6 (20/60)	- 2,4 (20/60)	- 2,4 (16/60)	

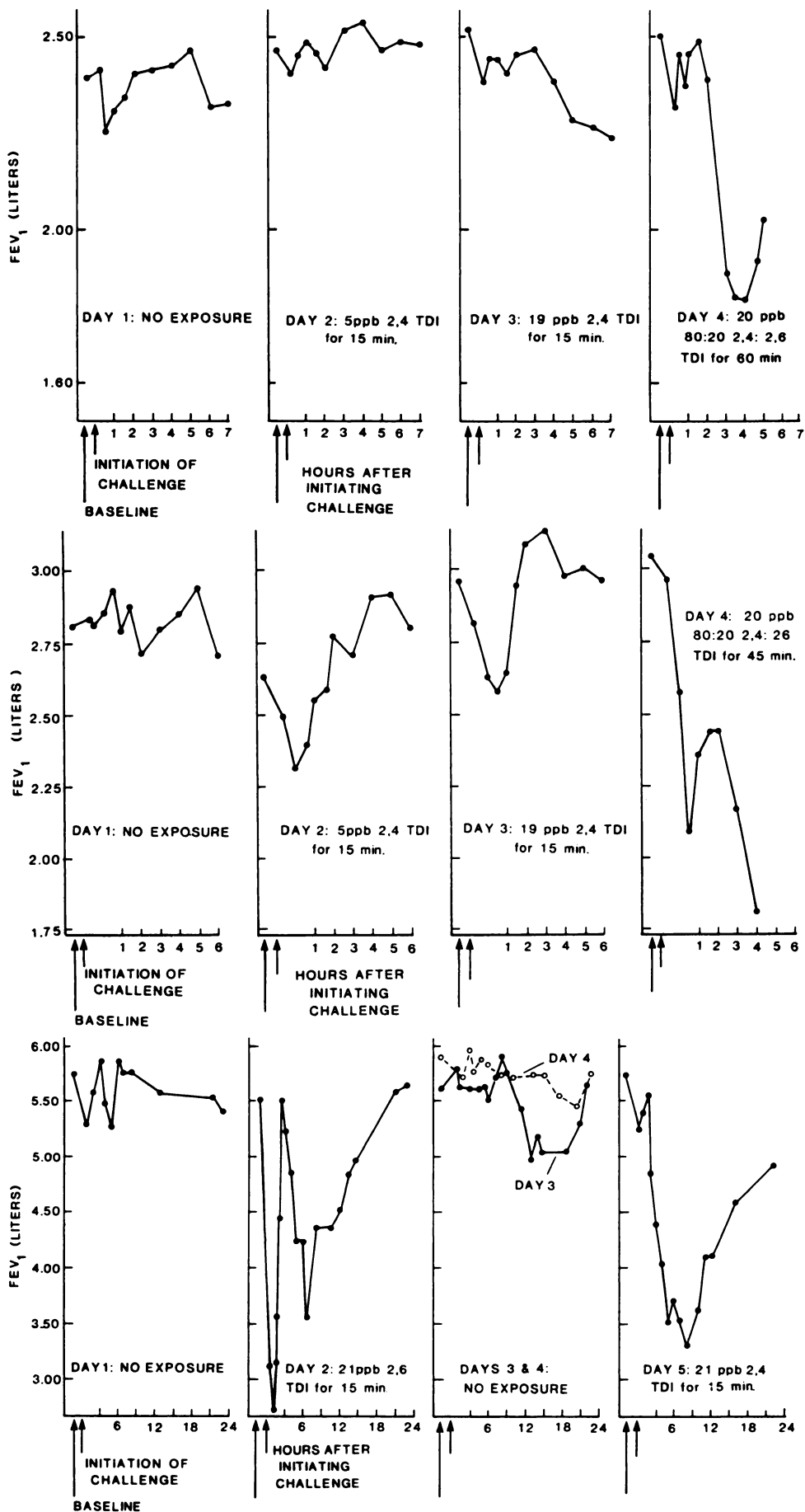
*In all cases no isocyanate exposure was provided on day 1.

†See Reference 8 for methacholine challenge inhalation technique.

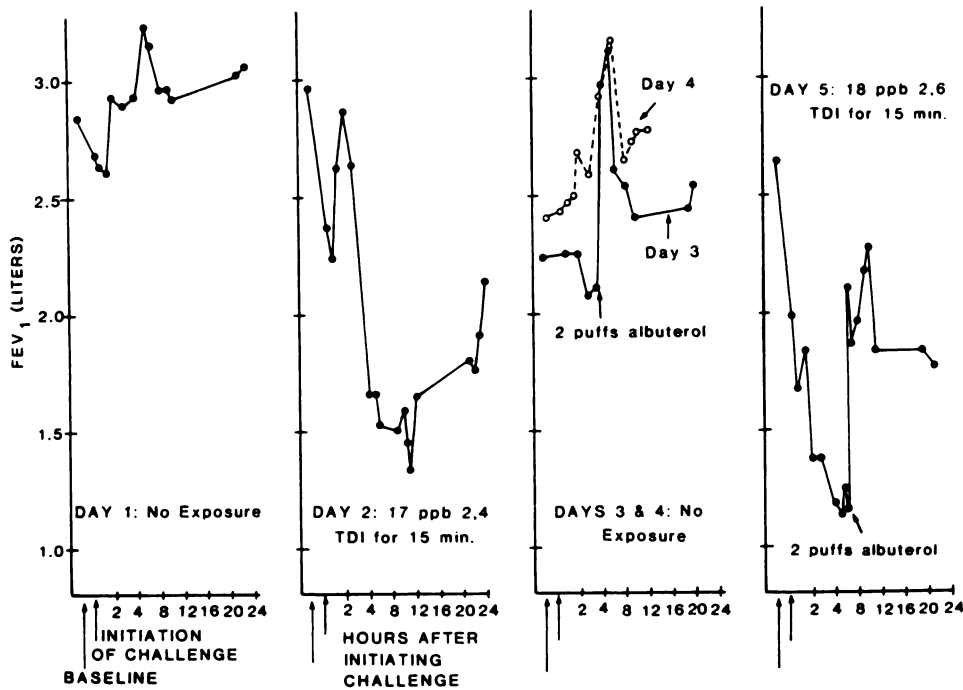
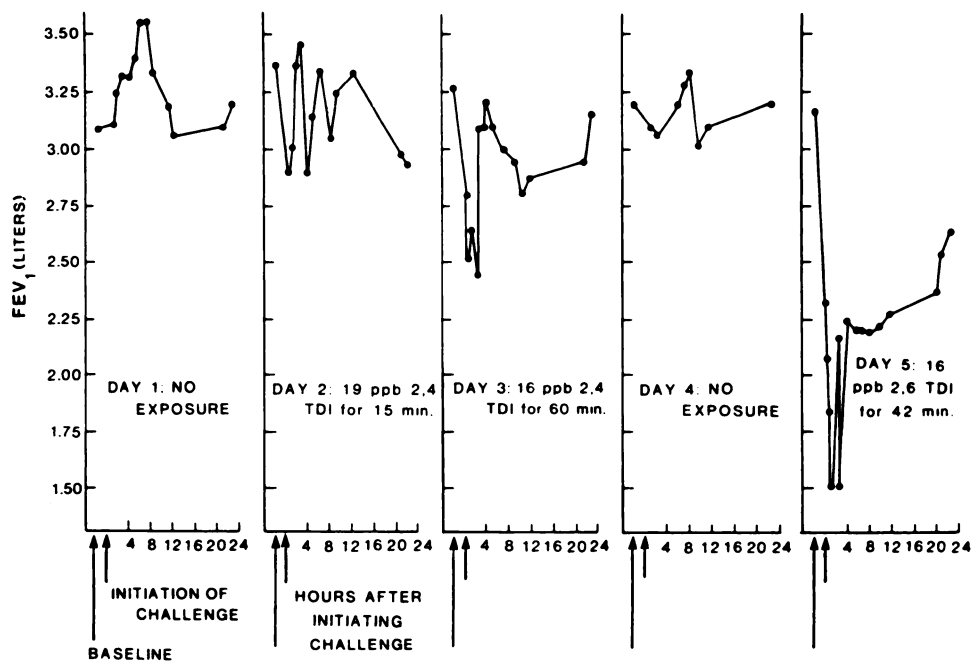
‡Challenge-positive [+] or challenge-negative [-].

§TDI isomer(s).

||ppb/min.



FIGURES 1-5. Results of lung function tests following exposure to subirritant levels of isocyanates for workers 1-5 in Table 6. Figures 1 and 2 represent the results of lung function tests following exposure of the first two workers to the 2,4 isomer and then the commercial mixture. FIGURES 3, 4, and 5 show the results of lung function tests of workers 3, 4, and 5 following exposures to the separate isomers.



FIGURES 4 and 5. See legend on preceding page.

recurrent nocturnal asthma. Finally, four failed to react to either the individual isomers or the commercial TDI mixture.

Figure 1 represents the results of challenge testing of a 52-year-old man who had childhood asthma, but no respiratory complaints as an adult until four years before challenge testing, when he began having immediate asthma following exposure to freshly produced foam. These respiratory complaints resolved spontaneously if he left the workplace. If he remained, late asthma developed. Episodes of asthma occurred

only at work. He spent part of his workday as a maintenance worker and the rest in foam production. He was able to continue working on therapy with daily theophylline and inhaled albuterol.

Immediately before challenge testing, chest examination showed no wheezing. Lung function tests showed a mild obstructive ventilatory impairment.

There was no adverse airway response or respiratory symptom on the first three days of testing. Following a 60-min exposure to the commercial mixture of TDI, there was a 23 percent fall from baseline, with wheeze

and chest tightness in the 3- to 5-h postchallenge period.

Figure 2 reflects the results of challenge testing in a 30-year-old worker who developed asthma symptoms following a chest cold after nearly five years of employment and nearly nine months before testing. Asthma episodes occurred immediately on entering the workplace. He was able to continue working using oral theophylline and inhaled albuterol therapy, but was transferred from the foam production area to the shipping area (an area of lesser exposure).

Chest examination before challenge testing showed mild wheeziness. Spirometric test results showed severe obstructive impairment.

Minimal chest symptoms and lung function decline occurred during the half hour or so following challenge on days 2 and 3. Exposure on day 4 resulted in an immediate FEV₁ decline of 31 percent from baseline, a partial spontaneous recovery over the next 2 h, and then a late reaction.

The results of isocyanate challenge testing of a 29-year-old man, employed for six years before challenge testing in the shipping area of a polyurethane foam manufacturing plant, are reported in Figure 3. He developed asthma two weeks after beginning employment. He had normal results of chest examination and spirometric study immediately before the challenge testing.

Exposure to the 2,6 isomer (day 2) provoked marked immediate and late declines in FEV₁ with asthmatic symptoms. On days 3 and 4, when no isocyanate exposures were provided, no chest symptoms or clinically important declines in FEV₁ occurred. Testing to the 2,4 isomer (day 5) resulted in a striking late reaction only.

Results of testing of a 39-year-old worker employed for 14 years in a polyurethane foam production facility are reported in Figure 4. He developed immediate and late asthma during his first year of employment. For the first six years he worked as a general laborer. Because of worsening symptoms, he was transferred to the laboratory to minimize isocyanate exposures. In the workplace, he commented that only certain polyurethane foams provoked episodes of asthma. He had no asthma away from the workplace. Chest examination was unremarkable, and lung function test results showed moderate obstructive ventilatory impairment.

On day 2, he had a 15 percent FEV₁ decline, but no respiratory symptoms several hours after initiating exposure to the 2,4 isomer. Day 3 exposure to the same isomer caused a 25 percent FEV₁ decline and chest tightness beginning 90 mins after initiating exposure. No respiratory complaints or lung function decline occurred on day 4, a day without isocyanate exposure. The 2,6 isomer exposure on day 5 was abbreviated because the worker developed severe

respiratory symptoms and marked immediate and persistent late FEV₁ declines.

The results of isocyanate inhalation challenge testing on a 33-year-old never-smoker, employed for the past 15 years at a polyurethane foam manufacturing plant, are reported in Figure 5. For the first nine years he worked as a general laborer within the plant. He was then transferred to a retail store adjacent to the workplace because he developed respiratory symptoms following workplace exposure. He developed asthma episodes only after polyurethane foam exposure. His lung examination was unremarkable. Lung function tests showed moderate obstructive ventilatory impairment.

On day 2, he had an immediate and late FEV₁ decline with symptoms of asthma. This persisted into day 3, and his lung function returned to baseline following inhalation of albuterol.

Day 4 spirometric test results were variable but without a decline in FEV₁ or the development of respiratory symptoms. Day 5 exposure to the 2,6 isomer provoked an FEV₁ decline that appeared more extensive than that which occurred on day 2 exposure.

DISCUSSION

In this series of workers referred with suspected isocyanate-induced asthma, work-related respiratory complaints, improvement in these complaints away from work, asthma unrelated to workplace exposure (current asthma), cough, wheeze, past or current atopy, or the worker's smoking history, were not different between those who reacted to isocyanate inhalation challenge testing and those who failed to react. Although respiratory complaints caused these workers to seek the attention of the physician, in less than half of this referred population could we prove asthma induced by isocyanates.

Is isocyanate inhalation challenge testing the "gold standard" for proving isocyanate-induced asthma? In those who develop an episode of asthma with a greater than 20 percent FEV₁ decline following a subirritant isocyanate exposure, the diagnosis of isocyanate-induced asthma appears straightforward. The difficulties exist in assessing the degree of confidence with which occupational asthma can be excluded after a negative isocyanate inhalation challenge test. First, because other chemicals which may induce asthma can be present along with isocyanates in workplaces, a negative isocyanate inhalation test does not rule out occupational asthma caused by these other agents. Second, in retrospective evaluation, workers with isocyanate-induced asthma may leave the workplace and recover from sensitivity to isocyanates. In this series, the average time from last isocyanate exposure to challenge testing in the reactor and nonreactor groups was not different. This implies that recovery from asthma

following an extended time away from isocyanate exposure was not the explanation for the high percentage of nonreactors. However, this does not rule out the possibility that one or several workers found to be challenge-negative to isocyanates had recovered from isocyanate-induced asthma.

It can be concluded that a negative isocyanate inhalation challenge test performed while a worker is still employed or soon after he ceases employment at a workplace where isocyanate exposures exist provides strong evidence against isocyanate-induced asthma. In such a clinical situation, other explanations for respiratory symptoms need to be investigated.

As in all studies of referred patients, one must consider the possibility that this sample may not be representative of all workers evaluated for isocyanate asthma. Although we cannot exclude this possibility, this seems unlikely for several reasons. First, challenge subjects were referred from different workplaces by different physicians. Second, the high prevalence of the same respiratory complaints suggests that the clinical data collected by the referring physicians were similar. Importantly, our percentage of positive isocyanate challenge tests (48 percent of those tested) approximates that reported by others. Mapp et al,¹⁴ evaluating 165 workers clinically suspected to have TDI asthma, showed only 56 percent had a positive challenge test. Moller et al¹⁵ reported challenge testing results on 12 workers with a clinical and occupational history consistent with isocyanate-induced asthma. Eight were challenge-positive. These studies also point out the difficulty of diagnosing occupational asthma based solely on historical information.

Significantly lower mean values for FEF_{25-75%} and FEV₁/FVC existed in the challenge-positive workers who had never smoked. No significant differences in the spirometric values for the current or exsmoking groups were found. In this series, obstructive ventilatory impairment in a never-smoker with respiratory complaints consistent with occupational asthma was somewhat predictive of the challenge status of the worker. We do not suggest, however, that obstructive ventilatory impairment and respiratory complaints consistent with occupational asthma in a never-smoker establishes a diagnosis of isocyanate-induced asthma and mitigates the need for challenge testing. For example, an isocyanate exposure, at irritant levels, could provoke an episode of asthma in a worker with asthma unrelated to workplace exposure. Such a worker could have physiologic evidence of airway obstruction without isocyanate sensitivity and be negative to a challenge with subirritant levels of isocyanates.

While bronchial hyperresponsiveness to methacholine was not found in all those who had a positive challenge test to isocyanates, 91 percent of the isocya-

nate reactors were positive, while only 43 percent of the nonreactors were methacholine positive. This test should be performed before isocyanate challenge testing. It measures the degree of bronchial responsiveness and can guide the initial dose and duration of the challenge exposure. For example, workers with extreme hyperresponsiveness to methacholine were initially exposed to a minimal isocyanate dose for a short duration (*ie*, 10 ppb for 15 min), while others with lesser reactivity could begin exposure to higher doses for longer periods. In the absence of bronchial responsiveness to methacholine, we began isocyanate exposures at a concentration of 20 ppb for several hours.

Although bronchial hyperresponsiveness to methacholine was present in 31 of 46 workers in this series, only 21 (68 percent) were challenge-positive to isocyanates. The fact that 32 percent of these workers had bronchial hyperresponsiveness to methacholine, and yet were challenge-negative on isocyanate testing, made this test an unacceptable predictor of isocyanate challenge test status in this population.

The temporal pattern of asthma resulting from isocyanate challenge testing in our laboratory did not always correlate with that reported by the worker to occur following workplace exposure. In only 13 (43 percent) was the same type of reported temporal workplace reaction (immediate, late, or dual) reproduced by challenge testing. It may be that the pattern of asthma associated with the workplace exposure depends on the length of exposure. The short duration of exposure during laboratory challenge testing, particularly after time away from the workplace, may be adequate to provoke asthma in those sensitized but insufficient to reproduce the worker's full asthma complaints.

Although our challenge testing protocol varied during these years, there were several common aspects. First, an exposure of 20 ppb or less of the commercial mixture for up to 15 min resulted in asthma in nearly all of the challenge-positive workers. One worker was exposed to 10 ppb for 30 min without developing respiratory symptoms or lung function decline. He reacted to an exposure of 20 ppb for a longer time on the next day. Second, all 11 workers initially negative to a 20 ppb TDI exposure of 15 min duration, were also negative following exposures to this concentration for up to 5 h on successive days. This negative challenge information reinforces our conclusion that the commercial mixture exposure protocol of 20 ppb concentration for 15 min will provoke asthma in nearly all who would be shown to be positive with longer exposures. This also points out that in workplaces where TDI exposures approach the permissible exposure limit of 20 ppb, asthma is not likely to be prevented in those sensitized.

Although accurately quantifying the level of isocya-

nate exposure has been a part of this challenge testing protocol from the start, techniques of generating and characterizing isocyanate challenge test atmospheres have evolved during these years. For example, the recognition that MDI exists as both an aerosol and vapor presented both problems and opportunities in generating and characterizing challenge atmospheres. It was necessary not only to quantify the concentration of MDI in the challenge atmosphere, but also to define the amounts in aerosol and vapor phases. Other parameters, particularly the size distribution, needed to be examined to accurately characterize the aerosol fraction.

Similarly, advances in liquid chromatographic techniques have allowed definition of isomeric composition of TDI in the workplace atmosphere. This has led to interest in the potential differences in the toxicities of the isomers. To make this comparison accurately, it was necessary to be able to deliver doses of either isomer within a narrow range of tolerance. To accomplish this, a dynamic exposure chamber was developed to generate isocyanate atmospheres within 10 percent of the target value.

Isomer challenge studies performed on the polyurethane foam workers showed apparent differences in the degree of airway reactivity to the different isomers. Interpretation of the differences in airway reactivity is difficult, because the duration of exposures to the isomers and the commercial mixtures were not identical (Fig 1 and 2). Although we provided at least one day without TDI exposure between inhalation tests to the two isomers (Fig 3 to 5), we cannot rule out the possible influence of an early-in-the-week isocyanate exposure affecting the severity or temporal manifestation of airway responses occurring later in the week. However, in these five polyurethane foam workers, the consistent pattern of apparently more intense bronchoconstriction following exposure to the 2,6 isomer or the commercial TDI mixture (containing the 2,6 isomer) compared with the 2,4 isomer alone may be the result of relatively higher workplace exposures of the 2,6 isomer and primary sensitization to that isomer.

That differing degrees of airway responsiveness to the separate isomers appear to exist is likely related to workplace exposure patterns. Although the most widely used commercial mixture of TDI contains 80 percent of the 2,4 isomer and 20 percent of the 2,6 isomer, the extent of exposure to the different isomers depends on whether TDI is being produced or utilized. In polyurethane foam production, where TDI is utilized, exposure is primarily to the 2,6 isomer. Despite the fact that the isomer ratio of the chemical feed stock is four parts 2,4 isomer to one part 2,6 isomer (the commercial mixture of 80 percent 2,4 and 20 percent 2,6 isomer), the isomer ratio is dramatically

different in the polyurethane foam plant atmosphere. In 90 percent of the air samples from these plants, the initial 4:1 2,4 to 2,6 ratio was reversed, with 2,6:2,4 ratios as high as 16:1.¹⁶ This increase in the amount of 2,6 isomer in the foaming atmosphere may be due to a lesser degree of chemical reactivity (compared with the 2,4 isomer) during the foam production process. This results in an increased amount of the 2,6 isomer remaining in the newly produced foam, with emission of this isomer during the exothermic curing process.

In TDI manufacturing, where the commercial mixture (80 percent 2,4: 20 percent 2,6 TDI) is being produced, exposure to the 2,4 isomer (*eg*, in chemical spills) predominates. Thus, there exists a dichotomy of exposure patterns for TDI in industry: primary exposure to 2,6 TDI in polyurethane foam manufacturing, and to 2,4 TDI in TDI production.

Our current challenge testing protocol depends largely on the degree of bronchial responsiveness to methacholine. Workers who react to very small doses of methacholine are initially exposed to a low isocyanate dose (*ie*, 10 ppb) for one-quarter of an hour. If a lesser degree of bronchial responsiveness to methacholine exists, we begin with an exposure of 20 ppb for 15 min. If the first exposure fails to provoke an episode of asthma, we provide a second exposure of similar dose for longer duration (up to 5 h) on the successive day. Although challenge testing to a single isomer may be informative, more data should be collected before deciding whether isomer-specific challenge testing would be an improvement over testing with the commercial TDI mixture.

The information provided by clinical evaluation is usually inadequate to establish the diagnosis of isocyanate-induced asthma. In some instances, proving the diagnosis of isocyanate-induced asthma may be as straightforward as showing the development of respiratory symptoms with an across-shift FEV₁ decline during a typical workday, or demonstrating increases in airway responsiveness to methacholine during the work week. In other cases, a laboratory-based isocyanate challenge is necessary. When such challenge protocols are used, assessing bronchial hyperresponsiveness to methacholine can help determine the initial isocyanate challenge dose and duration.

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