Occupational asthma caused by a prepolymer but not the monomer of toluene diisocyanate (TDI)

Olivier Vandenplas, MD,* André Cartier, MD,* Jacques Lesage, MSc, Guy Perrault, PhD,** Leslie C. Grammer, MD,*** and Jean-Luc Malo, MD*, ***** *Montreal, Quebec, Canada, and Chicago, Ill.*

Isocyanates are the most common cause of occupational asthma. Isocyanate monomers and prepolymers are widely used in the manufacture of polyurethane compounds. However, prepolymers are generating increasing interest because of their lower volatility. No distinction has yet been made between asthmatic reactions caused by the monomers and the prepolymers of isocyanates, and asthmatic reactions caused by one type of isocyanate but not the other type have not been reported. We describe two wood-roof maintenance workers who developed asthma after being exposed to a varnish containing a prepolymer of toluene diisocyanate (TDI) with only small amounts of the monomer. Specific inhalation-challenge tests with the TDI monomer did not elicit significant airway obstruction, whereas exposure to the varnish and to the purified TDI prepolymer induced late asthmatic reactions. Specific antibodies against TDI monomer human serum albumin and TDI prepolymer human serum albumin conjugates could not be demonstrated. These observations demonstrate that isocyanate prepolymers can cause occupational asthma and that asthmatic reactions caused by isocyanate prepolymers, but not to the corresponding monomer, can occur in some exposed workers. (J ALLERGY CLIN IMMUNOL 1992;89:1183-8.)

Key words: *Asthma, occupational asthma, bronchial provocation tests, isocyanates*

The highly volatile TDI monomer is widely used in the production of polyurethane compounds, primarily in flexible foams and surface coatings.[1, 2] In the last two decades, modified isocyanates, such as prepolymers, have become increasingly important in the polyurethane industry because of their advantageous physicochemical properties. The prepolymers are the result of the reaction between polyhydroxyl compounds and an excess of diisocyanate monomer molecules.[2] As illustrated in Fig. 1, the reaction elicits rise to a chemical intermediate that has still unreacted isocyanate groups. These functional groups can be subsequently combined with additional hydroxyl radicals or water molecules to generate the final polyurethane. Isocyanate prepolymers have a higher molecular weight and are thus less volatile than the initial monomers. Furthermore, the prepolymers of isocyanate are less reactive than monomers, which allows for a better control over the rate of the final reaction of polyurethane production, leading to optimization of the end-product characteristics.

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Abbreviations used

HDI:	Hexamethylene diisocyanate
HSA:	Human serum albumin
MDI:	Diphenylmethane diisocyanate
PC_{20}:	Concentration of methacholine (milligrams per milliliter) causing a 20% fall in FEV_1
TDI:	Toluene diisocyanate

From the *Department of Chest Medicine, Sacré-Coeur Hospital, and **Institut de Recherche en Santé et Sécurité du Travail, Montreal, Canada, and ***the Department of Medicine, Sections of Allergy-Immunology and Occupational Medicine, Northwestern University Medical School, Chicago, Ill.

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Reprint requests: J. L. Malo, MD, Department of Chest Medicine, Sacré-Coeur Hospital, 5400 Gouin West, Montreal, Canada H4J 1C5.

***Dr. J-L Malo is a senior researcher with the Montreal University School of Medicine and the Fonds de la recherche en santé du Québec.

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pational asthma in industrialized countries, accounting for about 25% of identified cases.[3, 4] Isocyanate monomers have been documented to cause asthma in 5% to 10% of exposed workers.[1, 5, 6] In contrast, it has never been specifically determined whether isocyanate prepolymers induce bronchial reactions. In this study, we describe two subjects in whom specific inhalation tests demonstrated occupational asthma caused by a TDI prepolymer, but not caused by the TDI monomer.

MATERIAL AND METHODS

Case reports

Subject No. 1. A 38-year-old man had worked for 14 years in wood-roof maintenance when he first experienced cough, wheezing, and shortness of breath in the evening after having applied varnishes to wood. He had used various lacquers containing TDI monomer, primarily a product made of 2.5% TDI, 31.5% TDI prepolymer, 57% xylene, and 3% propylene glycol ether acetate. This lacquer was applied onto wooden surfaces with a brush or a roller and were not sprayed. At that time, he was symptom free on weekends and during vacations. He took inhaled salbutamol, when it was necessary, and sustained-release theophylline. During the next 4 years, his respiratory symptoms progressively worsened. Symptoms occurred sooner (about 1 hour) after exposure to varnishes and no longer improved during days off work. Since his symptomatology required steadily increasing use of inhaled bronchodilators, he was put on sick leave. During the next 3 months, his respiratory symptoms gradually remitted. He was a lifelong nonsmoker. He had a history of seasonal but not work-related rhinitis. At the initial office visit, his physical examination was unremarkable. The white blood cell count was 4600/mm^3 with 57% neutrophils and 4% eosinophils. Skin tests performed by the prick method with a battery of 15 common inhalant allergens demonstrated a positive immediate reaction to tree and ragweed pollens, house dust, cat and dog danders, and molds.

Subject No. 2. The second subject was a 47-year-old man who had worked for 25 years sandblasting and varnishing wood roofs when he began experiencing cough, wheezing, and chest tightness. He had been exposed to the same types of compounds as subject No. 1, including the varnish containing a prepolymer of TDI. The compounds were applied in the same way as did subject No. 1. His respiratory symptoms were more pronounced on the days he used varnishes, and symptoms improved on weekends, and even more improvement during vacations. He was treated with an inhaled β_2-agent, when it was necessary, which he took less than once per day. The symptoms progressively worsened during the next 5 years despite his attempts to avoid direct exposure to the above-mentioned compounds. The frequency of his nocturnal awakenings caused by respiratory symptoms also increased. He was a current smoker with a 15 pack-year history of cigarette smoking. He was affected by perennial rhinitis that was not exacerbated by being at work. At the time of the initial visit, the subject was still working. Chest auscultation revealed end-expiratory wheezes. The white blood cell count was 12,600/mm^3 with 64% neutrophils and 2% eosinophils. Skin prick tests were positive for grass and ragweed pollens, house dust, and *Alternaria tenuis*.

Functional investigations

Spirometry was assessed according to recommended standards[7] on a Vitalograph apparatus (Vitalograph Ltd., Buckingham, England) for the specific inhalation tests and on a Collins spirometer (W. E. Collins Ltd., Braintree, Mass.) for methacholine challenges. Reference values were taken according to the method of Knudson et al.[8]

Nonspecific bronchial responsiveness to methacholine was determined at the end of each control day with a Wright nebulizer (output, 0.14 L/min) at tidal breathing for 2 minutes according to the procedure outlined by Cockcroft et al.[9] The PC_{20} was interpolated on the individual dose-response curves drawn on a semilogarithmic noncumulative scale. PC_{20} values <16 mg/ml were considered to represent significant bronchial hyperresponsiveness.[10] Changes in PC_{20} ≥ 3.2-fold from one assessment to the next were considered to be significant based on the reproducibility of the procedure in our laboratory.[11]

Specific inhalation challenges

Subject No. 1 underwent specific inhalation tests 8 months after complete removal from exposure at work, and subject No. 2, after 4 months. The tests were performed in an 8 m^3 challenge room according to a standardized protocol.[12, 13] The following sequence of tests were performed:

Series No. 1. On the control day, subjects were exposed for 30 minutes to a nebulized varnish diluent made of various organic hydrocarbons and polyols. The diluent was nebulized in the air of the challenge room in which circulation was enhanced by a small fan. The subjects were asked to breath normally, approximately 1 m distance from the nebulizer. On subsequent days, subjects were exposed to TDI vapors generated by evaporation at ambient temperature of 100 ml of pure TDI (8% 2,4-TDI and 20% 2,6-TDI isomers) placed in an open flask. Duration of exposure to TDI was progressively increased from a total of 1 minute for the first day to 5, 30, 60, and 120 minutes on subsequent test days. Three days separated the end of the first series of test from the second.

Series No. 2. Subjects were then challenged with the varnish made of a TDI prepolymer (31.5% of total volume) and a small amount of TDI monomer (2.5%). Subjects were asked to breathe for 2 hours near an open flask containing the varnish. At the time these challenges were administered, we had no reason to suspect that the varnish would induce an asthmatic reaction, since results of the previous sequences of tests with the TDI had remained negative. Therefore, we readily decided to expose the subjects for 120 minutes, although this total exposure period was separated into increasing intervals (from 1 minute, 2 minutes, 5 minutes, etc.). The two subjects did not have a history that suggested marked immediate asthmatic reactions at work, and their baseline airway caliber and responsiveness at the time of challenges were not severely impaired. We believed that

TABLE I. Main anthropometric, clinical, and functional data

Subject No.	Sex	Age (yr)	Atopy*	Smoking habit	Duration of exposure (yr)	Duration of symptoms (yr)	FEV_1 (L)	FEV_1 (% pred)†	FEV_1/FVC (%)	Methacholine PC_{20} (mg/ml)
1	M	39	+	Nonsmoker	18	4	3.15	83	81	0.3
2	M	47	+	Current smoker	25	5	2.58	65	70	0.3

*Atopy is defined as the presence of one or more positive skin test to common inhalant allergens.
†See text for source of predicted values.

exposing these subjects for 120 minutes would not be risky.

Series No. 3. Finally, subjects were exposed to purified TDI prepolymer. Pure TDI prepolymer could not be obtained from the varnish manufacturer, but a purified extract of the prepolymer was prepared by evaporating the commercial product under vacuum. Analysis by high-performance liquid chromatography demonstrated that no monomer was present in the purified extract. Because of its high viscosity, the prepolymer extract was diluted in 40% (vol/vol) xylene and nebulized for 2 hours in the challenge room in the same way as for the diluent (see first series of tests above). Since several months had elapsed since the first set of tests (8 months for subject No. 1 and 4 months for subject No. 2) because of the delay in preparing the purified extract, a second control day was included before exposure to the prepolymer extract. The control substance was a mixture of xylene and propylene glycol ether acetate that was a component of the commercial varnish.

Methacholine PC_{20} was assessed between each series of tests to verify that it was back to baseline.[11] Spirometry was assessed before each exposure, every 10 minutes for the first hour, every 30 minutes for the second hour, and hourly for a total of at least 8 hours. The fall in FEV_1 had to be >20% of the preexposure value to be considered significant, provided that fluctuations in FEV_1 were <10% of baseline on control days. The pattern of asthmatic reactions was defined according to previously detailed criteria.[13, 14]

During the tests, the TDI concentration in the challenge room was assessed continuously with an MDA 7100 tape monitor (MDP Scientific, Inc., Glenview, Ill.). This apparatus can be calibrated for different diisocyanate monomers but is not appropriate for determining TDI prepolymer concentrations.[1]

Immunologic studies

The level of specific antibodies (IgE and IgG) against TDI monomer HSA and TDI prepolymer HSA conjugates was determined in the serum of the two subjects with an ELISA method that has been described previously in detail.[15, 16] The level of specific antibodies was considered significantly increased when the optical density was at least two times the mean value in negative controls. The titer was the last serum dilution at which the subject serum was at least twice the mean of the negative control sera.

RESULTS

The clinical and functional features of the two subjects are outlined in Table I. Subject No. 1 had normal baseline spirometry; subject No. 2 demonstrated mild airway obstruction. Marked bronchial hyperresponsiveness was present before the first series of inhalation challenges (first control day) in both subjects (0.3 mg/ml).

Inhalation of TDI monomer with a mean (SD) concentration of 16 (±3 SD) ppb for 2 hours did not elicit any significant change in FEV_1 in subject No. 1. PC_{20} was 0.3 mg/ml on the last day of exposure (120 minutes) (unchanged). In contrast, subsequent exposure to the varnish made of a TDI prepolymer induced a late asthmatic reaction with a maximum decline in FEV_1 of 34% from baseline 6 hours after exposure (Fig. 2, *A*). PC_{20} was unchanged 4 days later (0.3 mg/ml). However, PC_{20} improved to 3.6 mg/ml 8 months after these tests. At that time, when subject No. 1 was challenged with the purified TDI prepolymer, a maximum fall in FEV_1 of 23% 6 hours after the end of exposure (Fig. 2, *B*) was demonstrated.

The results of inhalation challenges in subject No. 2 were similar to results for subject No. 1, that is, no asthmatic reaction when subject No. 1 was exposed to the TDI monomer (mean SD) concentration, 18 (5 SD) ppb, whereas he developed a maximum fall in FEV_1 of 42% 3 hours after exposure to the varnish (Fig. 3, *A*). Methacholine PC_{20} was 0.8 mg/ml (unchanged) after exposure for 120 minutes to TDI monomer (first series of tests) and 0.9 mg/ml (unchanged) on the day after the asthmatic reaction to the varnish. As for subject No. 1, PC_{20} improved to 1.5 mg/ml as assessed 4 months after the second series of tests. At that time, inhalation challenge with the purified TDI prepolymer induced a fall in FEV_1 reaching 32% of the baseline value 3 hours after exposure ended (Fig. 3, *B*). The concentrations of TDI monomer were very low during challenge exposures to the commercial varnish, the highest observed concentration being 2 ppb. As expected, TDI monomer was not detected during exposures to the purified TDI prepolymer.

Neither of the subjects demonstrated an increased level of specific antibodies to TDI monomer HSA or TDI prepolymer HSA conjugates. The titers were <1:5 for specific IgE and <1:10 for specific IgG.

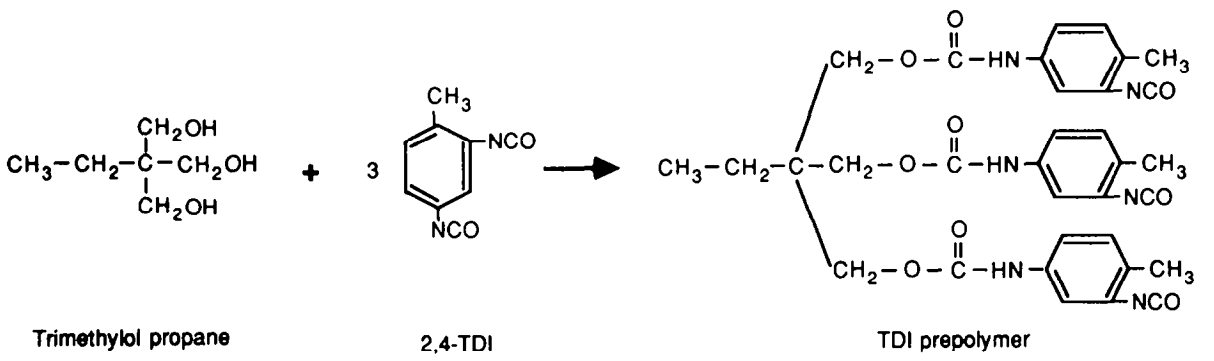

FIG. 1. Idealized chemical structure of most commonly used prepolymer of TDI that results from combination of a triol (trimethylol propane) with TDI. Resulting TDI prepolymer molecule has three functional isocyanate groups.

DISCUSSION

Isocyanate monomers are well documented as a cause of asthma.[1, 5, 6] Although isocyanate prepolymers are now widely used in the production of polyurethane compounds, it has never been firmly demonstrated that they can cause occupational asthma. Belin et al.[17] reported a subject with life-threatening asthma after exposure to a spray paint made of HDI prepolymer and HDI monomer. The subject had an increased level of IgE to HDI-HSA and MDI-HSA, but specific inhalation tests were not performed. Nielsen et al.[18] described asthma and systemic symptoms consistent with hypersensitivity pneumonitis that occurred in a man exposed to a spray paint containing both a TDI prepolymer (Desmodur L; Bayer AG, Leverkusen, Germany) and TDI monomer. Immunologic studies did not reveal the presence of specific antibodies (IgE and IgG) to TDI monomer and TDI prepolymer conjugated to HSA. The subject had occupational-type bronchoprovocation tests with the commercial product; therefore, it could not be ruled out that TDI monomer was the cause of asthma in this particular case. Séguin et al.[19] found an 11% prevalence of occupational asthma in spray painters exposed to various types of isocyanates, including a prepolymer of MDI (polymethylene polyphenyl diisocyanate). In the study by Séguin et al.,[19] the presence of isocyanate-induced asthma was confirmed by inhalation challenges with a paint containing both monomeric MDI and the prepolymer of MDI; therefore, it was not specifically assessed as to whether the prepolymer of MDI was the causative agent.

In our study, inhalation challenges were performed with each component of the commercial varnish separately, that is, TDI monomer, purified TDI prepolymer, and xylene-propylene glycol ether acetate. Both subjects developed late asthmatic reactions after exposure to the varnish and to purified TDI prepolymer but not after exposure to the other components of the system. We believe that gradual exposure to TDI monomer did not "prime" the subsequent positive reaction to the combination of TDI monomer and TDI prepolymer for the following reason: Between each series of tests, bronchial responsiveness to methacholine was assessed to ensure that no change had occurred. Second, reactions to the varnish containing TDI monomer and TDI prepolymer could not be due to the residual presence of TDI monomer. Indeed, we were unable to detect significant levels of isocyanates with our MDA 7100 monitor for the 2-hour intervals of exposure, except for subject No. 2 for whom 2 ppb recordings were obtained for three periods of 2-minute assessment. The temporal patterns of asthmatic reactions induced by the purified TDI prepolymer were similar to patterns induced by the commercial varnish. The prepolymer of TDI induced less intense bronchial reactions than the commercial varnish. This finding could be explained by the lower level of bronchial reactivity at the time the subjects were challenged with the prepolymer, as evidenced by the observed PC_{20} values. Another reason could be that the concentrations of prepolymer could have been different in the two last series of tests. We had no means to assess these concentrations because no on-line chromatographic assessments of prepolymer is available. Thus, specific inhalation tests convincingly demonstrated that the TDI prepolymer contained in the varnish was the cause of occupational asthma in our subjects.

The physiopathology of asthma induced by isocyanates is still unknown. The hazardous effect of diisocyanate has been related to the presence of the highly reactive NCO groups bound to the volatile monomers. Although the TDI prepolymers are less volatile than the monomers, they still contain functional NCO groups that can be inhaled when the prepolymer is generated in an aerosol form. It has been hypothesized that there could be a structure-activity relationship in the development of asthmatic reactions to low molecular weight agents.[20] It appears that at

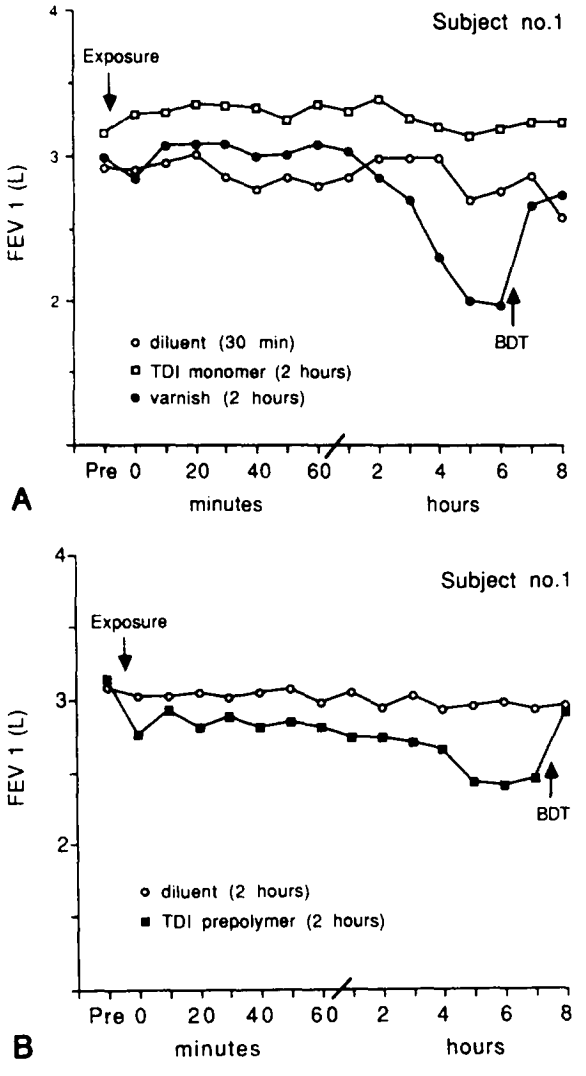

FIG. 2. A, Results of first and second series of specific inhalation tests in subject No. 1. Changes in FEV_1 after exposure to a control diluent (○), to TDI monomer (□), and to varnish made of TDI monomer and TDI prepolymer (●); *BDT,* bronchodilator (inhaled albuterol, 200 μg). **B,** Results of third series of specific inhalation tests in subject No.1. Changes in FEV_1 after exposure to a mixture of xylene and propylene glycol ether acetate as control substance (○) and to purified TDI prepolymer (■); *BDT,* bronchodilator (inhaled albuterol, 200 μg).

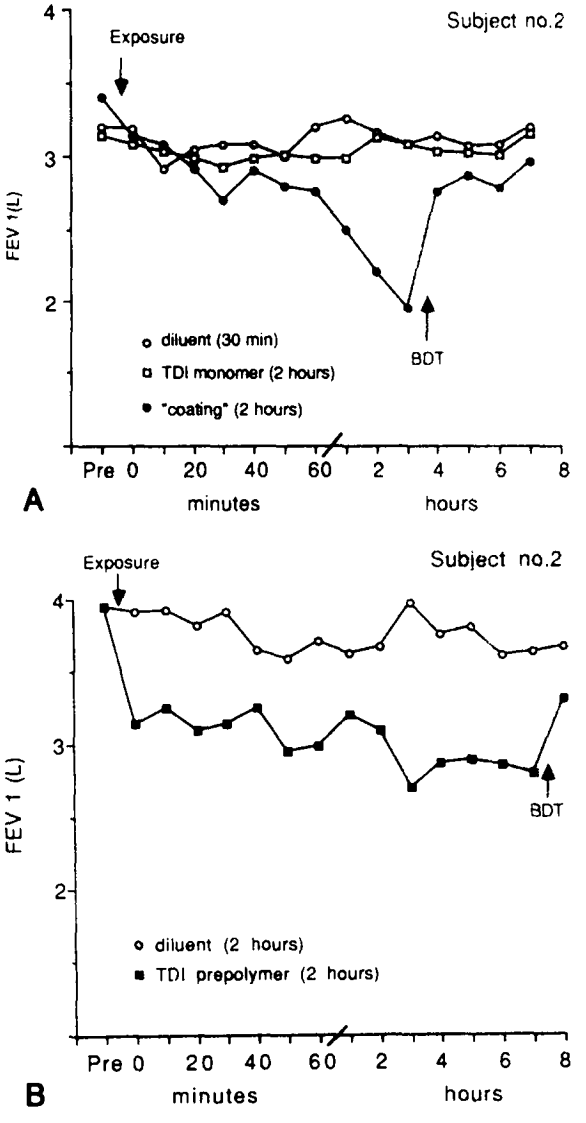

FIG. 3. A, Results of first and second series of specific inhalation tests in subject No. 2. Same legend as for *Fig. 2, A.* **B,** Results of third series of specific inhalation tests in subject No. 2. Same legend as for *Fig. 2, B.*

least two free radicals are required to cause such reactions. This feature is shared by both monomers and prepolymers of isocyanates. If this hypothesis is true, prepolymers are as likely to cause asthmatic reactions as monomers. Several investigators have described asthmatic[21-23] and immunologic cross-reactivity[22, 24, 25] between different types of isocyanate monomers. This cross-reactivity may result from the formation of new antigenic determinants induced by the interaction of the highly reactive isocyanates with human proteins. In our study, no crossed asthmatic reaction between the monomer and prepolymer forms of TDI was observed during the inhalation tests. Immunologic studies were nonconclusive because the subjects did not demonstrate specific antibodies either to TDI monomer HSA or to TDI prepolymer HSA. This study indicates that asthmatic reactions caused by TDI prepolymers, but not to the parent monomer, can occur in some subjects. This finding is relevant to the diagnostic evaluation of TDI-induced asthma. Inhalation challenges are most often performed by exposing the subjects to the vapors of monomeric TDI generated from pure TDI because it allows for a more satisfactory control of exposure levels compared with procedures with commercial compounds.[12, 13, 23, 26-28] It should therefore be kept in mind that challenge tests with TDI monomer may be negative if the worker develops selective asthmatic reactions to a derived

prepolymer. In our experience, such falsely negative inhalation challenges appear to be uncommon and can be easily prevented by taking a detailed occupational history.

Isocyanate-induced asthma has been observed in workers exposed to the highly volatile monomer of TDI.[1] It was initially claimed that isocyanates with higher vapor pressure, such as prepolymers, should be less hazardous than monomers. Although the TDI prepolymers are less volatile than the monomers, they still contain functional NCO groups that can be inhaled when the prepolymer is generated in an aerosol form.[29] It is interesting to note that our subjects had never sprayed the TDI prepolymer varnish. This observation suggests that brush application of this kind of varnish generates enough prepolymer, perhaps in the form of respirable droplets, to induce occupational asthma.

We conclude that TDI prepolymers per se are a potential cause of occupational asthma. However, the prevalence of occupational asthma caused by prepolymers in exposed workers remains to be documented. Some subjects can develop asthmatic reactions when they are exposed to prepolymers but not to the parent monomer. Inhalation challenge tests should therefore be performed with the specific type of TDI to which the subjects are exposed at work.

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