STUDY

Chemical Analysis of 2,4-Toluene Diisocyanate, 1,6-Hexamethylene Diisocyanate, and Isophorone Diisocyanate in Petrolatum Patch-Test Preparations

Malin Frick-Engfeldt, Erik Zimerson, Daniel Karlsson, Åsa Marand, Gunnar Skarping, Marléne Isaksson, and Magnus Bruze

Background: Isocyanates with the general formula R-(N=C=O) are theoretically contact sensitizers. However, allergic contact dermatitis (ACD) from isocyanates is seldom reported. In previous reports, patients reacted to their isocyanate-based work materials but not to commercial patch-test preparations of isocyanates. Therefore, we suspected that the low frequency of reported ACD from isocyanates was partly due to inadequate commercial preparations. A past study also showed the concentrations of diphenylmethane-4,4′-diisocyanate (4,4′-MDI) in petrolatum preparations to be much lower than declared.

Objective: In this study, 2,4-toluene diisocyanate (2,4-TDI), 1,6-hexamethylene diisocyanate (1,6-HDI), and isophorone diisocyanate (IPDI) were investigated in a similar fashion.

Methods: In preparations from 12 dermatology departments and two suppliers of patch-test allergens, we determined the isocyanate content as the isocyanate-dibutylamine derivative, using liquid chromatography and mass spectrometry. The preparations were considered stable if the ratio between the stated and found concentrations was within the range of 0.8 to 1.2.

Results: Although 28 of 36 investigated preparations had ratios outside of the stable range, they were in its vicinity, which indicates that preparations of 2,4-TDI, 1,6-HDI, and IPDI are more stable than are preparations of 4,4′-MDI where previously reported results showed ratios far outside of stable range.

Conclusion: As opposed to preparations of 4,4′-MDI, preparations of 2,4-TDI, 1,6-HDI, and IPDI can be considered to be stable.

ISOCYANATES are compounds that contain the functional group –N=C=O, which readily reacts with water, alcohols, amines, and thiols. Isocyanates are widely used in the plastics industry because they form polyurethane products such as soft and rigid foams, coatings, adhesives, elastomers, and lacquers upon addition reaction with multifunctional alcohols (polyols). Based on their molecular structure, isocyanates can be classified into two subgroups: aromatic isocyanates and aliphatic isocyanates (Fig 1). The production of the aromatic isocyanates toluene diisocyanate (TDI) and diphenylmethane diisocyanate (MDI) account for more than 95% of global isocyanate production. Aliphatic isocyanates such as isophorone diisocyanate (IPDI) and 1,6-hexamethylene diisocyanate (1,6-HDI) are generally more expensive to produce but are used when the performance of aromatic diisocyanates is inadequate (this is mainly because of their tendency to undergo oxidative discoloration on exposure to light and moisture).[1]

Exposure to isocyanates is irritating to the respiratory tract and can cause immunologically mediated outcomes (eg, hypersensitive pneumonitis and diisocyanate-induced asthma).[2] Compared to respiratory symptoms, delayed hypersensitivity and allergic contact dermatitis from isocyanates are less frequently reported.[3] Isocyanates are reactive, which makes them potential contact allergens as they easily react with nucleophilic groups in proteins within the skin. Patients in two studies reacted more frequently to patch tests with work materials containing MDI than to patch tests with commercial test preparations containing diphenylmethane-4,4′-diisocyanate (4,4′-MDI).[4,5] It was suspected that the low frequency of reports on contact allergy to isocyanates could partly be due to inadequate patch-test diagnostics when commercial isocyanate test preparations are used. Therefore, we obtained the isocyanate series used at eight European and four American dermatology

From the Department of Occupational and Environmental Dermatology, Malmö University Hospital, Lund University, Malmö, Sweden, and Work Environment Chemistry, Stockholm University, Hässleholm, Sweden.

Supported by the Swedish Council for Working Life and Social Research.

Address reprint requests to Malin Frick-Engfeldt, Department of Occupational and Environmental Dermatology, Malmö University Hospital, S-205 02 Malmö, Sweden; E-mail: malin.frick@med.lu.se

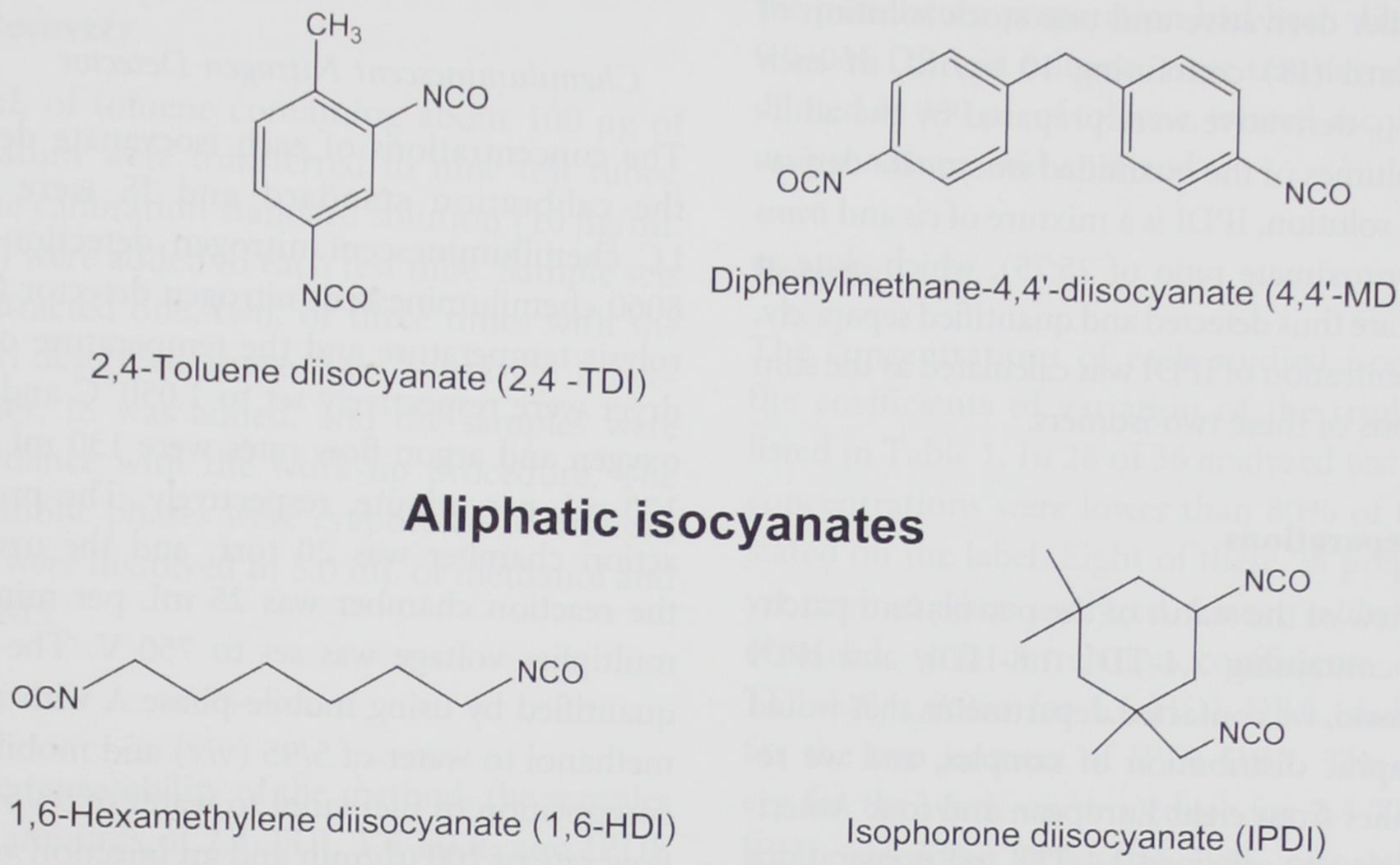


Figure 1. Molecular structure of the aromatic and aliphatic diisocyanates present in the isocyanate series.

departments as well as series from two major European suppliers of patch-test allergens in order to perform chemical analysis primarily on 4,4′-MDI. The analysis of 4,4′-MDI preparations showed that the concentration found in these preparations was much lower than was declared and thus lead to a high risk of false-negative test results.[6] We have now analyzed other isocyanates from the isocyanate series, namely, 2,4-toluene diisocyanate (2,4-TDI), 1,6-HDI, and IPDI. The method used is based on a method for monitoring isocyanates in air, where the highly reactive isocyanates are reacted with di-*n*-butylamine (DBA) to form stable isocyanate-DBA derivatives that do not react with their surroundings during the work-up procedure and analysis (Fig 2).[7]

Materials and Methods

Chemicals

Toluene and isooctane were obtained from Lab-Scan (Dublin, Ireland); methanol and ethanol, from Kemetyl (Stockholm, Sweden); DBA, from Aldrich Chemie (Steinheim, Germany); $^2H_{18}$-labeled di-*n*-butylamine (DBA-d_{18}), from C/D/N Isotopes (Pointe-Claire, Quebec, Canada); caffeine, from Sigma Chemical (St. Louis, MO); 2,4-TDI, from TCI (Tokyo, Japan); 1,6-HDI, from Acros Organics (Morris Plains, NJ); and IPDI, from Merck (Darmstadt, Germany).

Preparations of DBA and DBA-d_{18} derivatives of isocyanates (2,4-TDI, 1,6-HDI, and IPDI) to be used as calibration standards and internal standards, respectively, were prepared by placing about 15 mg of each isocyanate into test tubes. Double samples of each isocyanate were weighed in, and each isocyanate was dissolved in two different solutions of 10 mL of isooctane containing either 50 µL of DBA or 50 µL of DBA-d_{18}. DBA and DBA-d_{18} were added in excess to ensure that all isocyanate was reacted. The test tubes were shaken and placed in an ultrasonic bath for 20 minutes. The excess reagent and isooctane were then removed by evaporation of the samples. The residues were dissolved by adding 10 mL of methanol to each test tube.

The DBA and DBA-d_{18} derivatives of each isocyanate were quantified with an Antek 8060 chemiluminescent nitrogen detector (Antek Instruments Inc., Houston, TX),

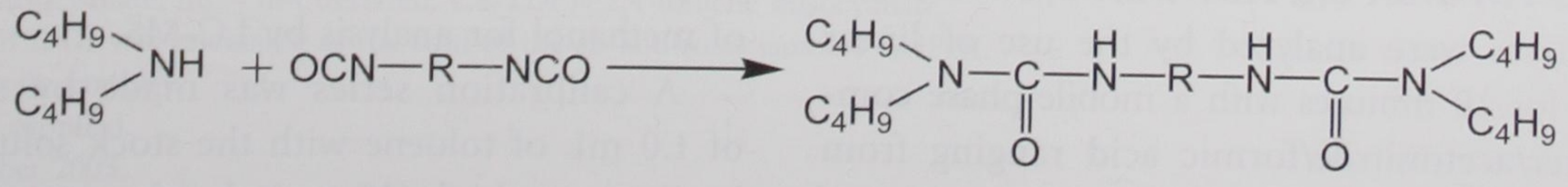


Figure 2. General reaction describing the conversion of reactive diisocyanate into a stable urea derivate by reaction of the diisocyanate with the secondary amine, di-*n*-butylamine (DBA).

with caffeine as an external standard. One stock solution of the calibration standard containing 10 μg/mL of each isocyanate-DBA derivative and one stock solution of the internal standard (IS) containing 10 μg/mL of each isocyanate-DBA-d_{18} derivative were prepared by the addition of different volumes of the quantified isocyanate derivatives to a methanol solution. IPDI is a mixture of *cis* and *trans* isomers (in the approximate ratio of 25:75), which elute at different times and are thus detected and quantified separately. However, the concentration of IPDI was calculated as the sum of the concentrations of these two isomers.

Patch-Test Preparations

To get a general view of the status of the petrolatum patch-test preparations containing 2,4-TDI, 1,6-HDI, and IPDI used around the world, we contacted departments that would represent a geographic distribution of samples, and we received positive replies from eight European and four American departments. We also obtained 2,4-TDI test preparations directly from the two major European suppliers of patch-test allergens. Additional preparations of 1,6-HDI and IPDI were obtained from one of the suppliers.

Analytic Apparatuses

Liquid Chromatography Mass Spectrometry (LC-MS)

Analyses of the 2,4-TDI, 1,6-HDI, and IPDI content in the patch-test preparations were performed with a mass spectrometer (Platform LCZ; Micromass, Altrincham, Cheshire, UK) in the electrospray mode monitoring positive ions (ESI^+). The cone voltage was 40 V, and a capillary voltage of 3.5 kV was used. The temperature of the ion source was 110°C, and the desolvation temperature was 200°C. Quantifications were made by selected ion recording, monitoring the molecular ions. Quantitative measurements were made by calculating the response ratio between the analyte (eg, as a DBA derivative) and the DBA-d_{18}–labeled IS. The mass spectrometry (MS) instrument was connected to Shimadzu LC-10ADVP liquid chromatography (LC) pumps (Shimadzu, Kyoto, Japan), and 20 μL loop injections containing a 4 μL sample plug surrounded by 16 μL of water were made with a CTC-Pal LC autosampler (CTC Analytics, Zwingen, Switzerland). The TDI-DBA, HDI-DBA, IPDI-DBA, TDI–DBA-d_{18}, HDI–DBA-d_{18}, and IPDI–DBA-d_{18} derivatives were analyzed by the use of linear gradient elution for 10 minutes with a mobile-phase composition of water/acetonitrile/formic acid ranging from 45/55/0.05 (v/v/v) to 0/100/0.05 (v/v/v) and a flow rate of 100 μL per minute. The LC column used was an Ace C18 (Advanced Chromatography Technologies, Aberdeen, Scotland) column (50.0 mm × 1.0 mm, with 3 μm particles).

Chemiluminescent Nitrogen Detector

The concentrations of each isocyanate derivative used in the calibration standard and IS were determined by LC chemiluminescent nitrogen detection. On the Antek 8060 chemiluminescent nitrogen detector (CLND), the pyrolysis temperature and the temperature of the membrane dryer were respectively set to 1,050°C and 60°C. The inlet oxygen and argon flow rates were 130 mL per minute and 170 mL per minute, respectively. The pressure in the reaction chamber was 20 torr, and the ozone flow rate in the reaction chamber was 25 mL per minute. The photomultiplier voltage was set to 750 V. The derivatives were quantified by using mobile-phase A with a composition of methanol to water of 5/95 (v/v) and mobile-phase B with a composition of methanol to water of 95/5 (v/v) and with a flow rate of 100 μL/min and an injection volume of 200 nL. Analysis of 2,4-TDI and HDI derivatives was performed with isocratic elution at 75% mobile-phase B (B), and analysis of IPDI derivatives was performed with isocratic elution at 85% B.

Work-Up Procedure

Triple samples of each preparation were made. For each sample, about 100 mg of the petrolatum preparation were put into a test tube. The isocyanate in the petrolatum preparation (ie, 2,4-TDI, IPDI, or 1,6-HDI) was reacted with DBA in excess by the addition of 10.0 mL of 0.010M DBA in toluene, and the sample was treated in an ultrasonic bath for 30 minutes (see Fig 2). The samples containing 2,4-TDI and IPDI were diluted ×10 in toluene whereas the samples containing 1,6-HDI were not diluted. Then 1.0 mL of each sample was transferred into a new test tube, and 100 μL of isocyanate–DBA-d_{18} (10 μg/mL) serving as IS was added. Each sample was evaporated to dryness in a vacuum centrifuge, and extraction was performed by the addition of 5.0 mL of isooctane and 5.0 mL of methanol/water (9/1 [v/v]) and vigorous shaking for 10 minutes. The isooctane phase was discarded, and the methanolic phase was washed with 5.0 mL of isooctane, after which it was evaporated to dryness. The residue was dissolved in 5.0 mL of methanol for analysis by LC-MS.

A calibration series was made by spiking aliquots of 1.0 mL of toluene with the stock solution of the calibration standard (10 μg/mL isocyanate-DBA) to seven concentrations in the range of 0.0 to 3.0 μg/mL isocyanate,

after which they were treated according to the work-up procedure and analyzed.

Extraction Recovery

Aliquots of 1 mL of toluene containing about 100 µg of dissolved petrolatum were transferred to nine test tubes, and 250 µL of the calibration standard solution (10 µg/mL isocyanate-DBA) were added to each test tube. Sample sets of three were extracted one, two, or three times with the extraction system described above (see "Work-Up Procedure"). Thereafter, IS was added, and the samples were washed in accordance with the work-up procedure. The remaining methanolic phases were evaporated to dryness, and the residues were dissolved in 5.0 mL of methanol and analyzed by LC-MS.

Repeatability

To determine the repeatability of the method, the samples with the highest amounts of 2,4-TDI, 1,6-HDI, and IPDI, respectively, were used. In all cases, this referred to the preparations directly obtained from "Supplier 1" as listed in Table 1. Aliquots of 100 µL of the stock solution, wherein the petrolatum preparation had been diluted in 10.0 mL of 0.010M DBA in toluene, were transferred to 10 test tubes, diluted in 900 µL of toluene, treated according to the work-up procedure, and analyzed.

Results

The concentrations of each studied isocyanate as well as the coefficients of variation of the triplicate samples are listed in Table 1. In 28 of 36 analyzed test preparations, the concentrations were lower than 80% of the concentration stated on the label. Eight of these 28 preparations had not yet expired when analyzed. Linear calibration graphs were obtained, with correlation coefficients of 0.997 for 2,4-TDI–DBA, 0.953 for 1,6-HDI–DBA, and 0.934 and 0.999 for the two isomers of IPDI-DBA. The extraction recovery for the work-up procedure for 2,4-TDI, 1,6-HDI, and IPDI was 83%, 88%, and 79%, respectively, and it was shown that for a work-up procedure with two more

Table 1. Results of Analyses of Patch-Test Preparations of Diisocyanates in Petrolatum, July 2003

		2,4-TDI					*1,6-HDI*					*IPDI**				
Dept		*Stated Conc (% w/w)*	*Found Conc† (% w/w)*	*Ratio Stated/ Found*	*CV (%)*	*Expiry Date (yr-mo)*	*Stated Conc (% w/w)*	*Found Conc† (% w/w)*	*Ratio Stated/ Found*	*CV (%)*	*Expiry Date (yr-mo)*	*Stated Conc (% w/w)*	*Found Conc† (% w/w)*	*Ratio Stated/ Found*	*CV (%)*	*Expiry Date (yr-mo)*
1	USA	2	1.52	1.3	3.8	1997–09	0.1	0.067	1.5	3.4	1996–05			‡		
2	EUR	1	0.96	1.0	5.8	2003–11			‡					‡		
3§	EUR	1	0.76	1.3	1.6	2003–08	0.1	0.073	1.4	4.9	2004–05	1	0.83	1.2	5.6	2004–04
4	USA	2	1.46	1.4	6.2	2003–05	0.1	0.063	1.6	8.9	2002–12	1	0.79	1.3	4.3	2003–04
5a‖	EUR	2	1.56	1.3	2.6	2004–07	0.1	0.063	1.6	4.3	2004–05	1	0.78	1.3	1.8	2004–04
5b‖	EUR	2	1.66	1.2	12.9	2004–07	0.1	0.071	1.4	6.8	2004–09	1	0.79	1.3	4.4	2004–04
6	EUR	2	0.064	31.4	39.7	nd	0.1	0.034	3.0	8.9	nd	1	0.76	1.3	2.8	nd
7	EUR	2	1.22	1.7	3.5	1998–08	0.1	0.052	1.9	7.9	1997–01	1	0.78	1.3	5.4	1998–08
8	USA	2	1.64	1.2	7.0	2003–10	0.1	0.067	1.5	4.0	1996–04	1	0.77	1.3	0.6	2004–04
9	EUR	nd	< 0.0005#	—	—	nd			‡					‡		
10	EUR	2	0.32	6.3	8.6	nd	0.1	0.022	4.6	30.3	nd	1	0.72	1.4	10.9	nd
11	EUR	1	1.03	1.0	18.0	2003–12			‡					‡		
12	USA	2	0.43	4.7	6.5	1997–01	0.1	0.050	2.0	4.8	1997–01	1	0.73	1.4	6.8	1997–01
Supplier 1		2	1.75	1.1	5.0	2005–01	0.1	0.112	0.9	43.6	2005–02	1	0.8	1.3	4.8	2005–03
Supplier 2		1	0.88	1.1	5.5	2003–09			‡					‡		

Conc = concentration; CV = coefficient of variation for triplicate samples; Dept = department; 1,6-HDI = 1,6-hexamethylene diisocyanate; IPDI = isophorone diisocyanate; nd = not declared; 2,4-TDI = 2,4-toluene diisocyanate.

*The concentration of IPDI was calculated as the sum of the *cis* and *trans* isomers of IPDI.

†Mean value of triplicate samples.

‡No preparation was supplied.

§Analyzed in September 2003.

‖Department 5 sent two isocyanate series (5a and 5b).

#Less than quantification limit for samples treated according to the work-up procedure and quantified in the calibrated range.

Table 2. Extraction Recovery and Repeatability for Diisocyanates in Petrolatum Patch-Test Preparations

	2,4-TDI	*1,6-HDI*	*IPDI*
Yield after 1 extraction (%)	83	88	79
Yield after 3 extractions (%)	99	99	96
Repeatability of 10 samples (CV)	4.4%	2.7%	4.4%

CV = coefficient of variation; 1,6-HDI = 1,6-hexamethylene diisocyanate; IPDI = isophorone diisocyanate; 2,4-TDI = 2,4-toluene diisocyanate.

extractions with methanol/water (9/1 [v/v]), the recovery increased to 99%, 99%, and 96%, respectively (Table 2). The coefficient of variation for the 10 samples of each isocyanate analyzed to determine repeatability for the determination of 2,4-TDI, 1,6-HDI, and IPDI, respectively, in petrolatum patch-test preparations are shown in Table 2.

Discussion

As previously mentioned, the most well-known health risks from isocyanate exposure are the adverse effects on the respiratory tract; delayed hypersensitivity and allergic contact dermatitis are less frequently reported.[3] In 2002, however, Goossens and colleagues[4] reported on 13 patients with positive patch-test reactions to isocyanate-based products; only one of these 13 patients reacted to any commercial preparation of isocyanate (in this case, 4,4′-MDI). In 2003, we reported a similar pattern of reactions when investigating five workers at a company that used a lacquer based on MDI. These patients reacted more frequently to their own MDI-based product than to a commercial patch-test preparation of 4,4′-MDI.[5] The above-mentioned studies caused us to investigate commercial patch-test preparations of 4,4′-MDI.[6] In the present study, preparations containing 2,4-TDI, 1,6-HDI, and IPDI were analyzed in a similar fashion. As with the analysis of 4,4′-MDI, the method of analysis was developed from a method used for monitoring airborne isocyanates,[7] modified to involve a system for extracting isocyanates from petrolatum. Because 2,4-TDI, 1,6-HDI, and IPDI readily dissolve in toluene, toluene could be used as solvent, and thus we could avoid using methylene chloride, the environmentally less suitable solvent used when analyzing 4,4′-MDI. An investigation of the recovery of extraction showed that the extraction procedures had a yield of 83%, 88%, and 79% for 2,4-TDI, 1,6-HDI, and IPDI, respectively. These were increased to 99%, 99%, and 96%, respectively, by repeated extractions. For practical reasons and because all losses from the extraction procedure are compensated for by the use of IS, we decided to perform just one extraction. An IS designates a known amount of a compound, different from the analyte, that is added to the unknown. In the detector, the signal from the analyte (ie, an isocyanate-DBA derivative) is compared with the signal from the IS (ie, an isocyanate–DBA-d_{18} derivative), and the amount of analyte is calculated as the response ratio between the analyte and the IS. Any losses during the work-up procedure will be the same for both the analyte and the IS, resulting in the same response ratio.

The results show that the preparations containing the aliphatic isocyanates 1,6-HDI and IPDI appear to be more stable than the previously analyzed preparations of 4,4′-MDI,[6] whose concentrations were much lower than declared. Isaksson and colleagues[8] stated that according to personal communications with the manufacturers, the prerequisite for stability of the content of the preparations from TRUE Test (Mekos, Hillerød, Denmark) and patch-test allergens from Hermal (Hermal, Reinbek, Germany) is ± 20% of the concentration stated on the label. This corresponds to an acceptable variation in ratio of 0.8 to 1.2 between stated and found concentrations. Although 28 of 36 investigated preparations of 2,4-TDI, 1,6-HDI, and IPDI have ratios outside of the acceptable range, they still are within the range's vicinity. When the same analysis was done for 4,4′-MDI, only one preparation directly obtained from one of the suppliers came close to the acceptable range (it had a ratio of 1.5). In all other cases, the ratios were far from the range; in the worst cases, the concentrations were more than 1,000 times lower than declared.[6] A possible explanation for the differences between 1,6-HDI and IPDI when compared with 4,4′-MDI is that aliphatic isocyanates are considered to be less reactive than are aromatic isocyanates such as 4,4′-MDI.[9] Because 2,4-TDI also is an aromatic isocyanate with about the same reactivity as 4,4′-MDI, results similar to those obtained when analyzing 4,4′-MDI were expected. However, the results indicate that the preparations of 2,4-TDI are considerably more stable than the preparations of 4,4′-MDI. The reason for this contradictory result remains unknown, and the result cannot be explained by differences in expiry dates because all preparations had about the same variation in age.

Yet another difference between the two studies is that the concentration of the preparations of 4,4′-MDI was shown to vary within the triplicate samples, as opposed to the analyses of the other isocyanates. As the repeatability trials when investigating 4,4′-MDI showed that the coefficient of variation between 10 samples from the same stock solution was less than 3%, it was suggested that the variation within the triplicate samples was due to inhomogeneous preparations rather than to methodologic

deficiencies.[6] As summarized in Table 1, the triplicate samples varied much less when 2,4-TDI, 1,6-HDI, and IPDI were being analyzed. This could be because the ground solid flakes of 4,4′-MDI were more difficult to disperse in petrolatum than were the liquid solutions of 2,4-TDI, 1,6-HDI, and IPDI.

This study shows that commercial petrolatum patch-test preparations of 2,4-TDI, 1,6-HDI, and IPDI can be considered stable in most cases. However, we still recommend that patients be additionally tested with their own isocyanate-based work material because the technical products with which the patients come into contact are complex and can contain several more oligomers and isomers besides the monomeric isomers that are used in commercial isocyanates series (ie, 4,4′-MDI, 2,4-TDI, 1,6-HDI, and IPDI). The most frequently used TDI products used in industry consist of the two monomeric isomers 2,4-TDI and 2,6-TDI in mixtures of 80:20 or 65:35. Furthermore, technical products of HDI and IPDI are produced by reacting the monomeric isocyanates either with themselves or with urea or urethane compounds to form isocyanate adducts such as isocyanurates, biurets, and allophanates, and the monomer content of these products is generally very low.[10] It is possible that patients working with isocyanates become sensitized to monomeric isomers and/or oligomers that are present in their isocyanate-based products but are not represented in the isocyanate series. This is in accordance with a study in which cutaneous sensitization to polyisocyanate prepolymers was investigated with the Buehler test.[11] The authors found that technical products consisting of isocyanurates and biurets of HDI and TDI induced dermal sensitivity in guinea pigs whereas a product containing IPDI isocyanurate did not. They concluded that since the amount of residual monomer in the polyisocyanate products was very low, it was possible that skin sensitization was induced by the prepolymer itself and not by the presence of residual monomer.[11]

Conclusion

False-negative test results are less likely to occur when patch-testing with 2,4-TDI, 1,6-HDI, and IPDI than when patch-testing with 4,4′-MDI. However, we still recommend patch-testing with the patients' own isocyanate-based work materials since these often consist of complex mixtures that contain oligomers and/or monomeric isomers that are not represented in the commercially available isocyanate series.

Acknowledgments

The authors thank Marianne Dalene and Viveca Bursius at Work Environment Chemistry, Stockholm University, Hässleholm, Sweden, for valuable assistance. We also thank Prof. Donald V. Belsito, Dr. Francisco M. Brandão, Prof. Derk P. Bruynzeel, Dr. C. J. Le Coz, Prof. P. J. Frosch, Dr. Riita Jolanki, Prof. Howard I. Maibach, Dr. Francisco Javier Ortiz de Frutos, Prof. Frances J. Storrs, and Dr. James Taylor for providing patch-test preparations.

References

1. Ulrich H. Diisocyanates. In: Ulrich H, editor. Chemistry and technology of isocyanates. 1st ed. Chichester/NewYork/Brisbane/Toronto/Singapore: Wiley; 2001. p. 315.
2. Klees JE, Ott MG. Diisocyanates in polyurethane plastics applications. Occup Med 1999;14:759–76.
3. Estlander T, Kanerva L, Jolanki R. Polyurethane resins. In: Kanerva L, Elsner P, Wahlberg JE, Maibach HI, editors. Handbook of occupational dermatology. Berlin, Heidelberg, New York: Springer; 2000. p. 597–601.
4. Goossens A, Detienne T, Bruze M. Occupational allergic contact dermatitis caused by isocyanates. Contact Dermatitis 2002;47:304–8.
5. Frick M, Isaksson M, Bjorkner B, et al. Occupational allergic contact dermatitis in a company manufacturing boards coated with isocyanate lacquer. Contact Dermatitis 2003;48:255–60.
6. Frick M, Zimerson E, Karlsson D, et al. Poor correlation between stated and found concentrations of diphenylmethane-4,4′-diisocyanate (4,4′-MDI) in petrolatum patch-test preparations. Contact Dermatitis 2004;51:73–8.
7. Karlsson D, Dahlin J, Skarping G, et al. Determination of isocyanates, aminoisocyanates and amines in air formed during the thermal degradation of polyurethane. J Environ Monit 2002;4:216–22.
8. Isaksson M, Gruvberger B, Persson L, et al. Stability of corticosteroid patch test preparations. Contact Dermatitis 2000;42:144–8.
9. Thorpe D. Isocyanates. In: Lee S, editor. The Huntsman polyurethanes book. 1st ed. Chichester, UK: Wiley; 2002. p. 63–88.
10. Marand A, Dahlin J, Karlsson D, et al. Determination of technical grade isocyanates used in the production of polyurethane plastics. J Environ Monit 2004;6:606–14.
11. Zissu D, Binet S, Limasset JC. Cutaneous sensitization to some polyisocyanate prepolymers in guinea pigs. Contact Dermatitis 1998;39:248–51.