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Determination of unreacted 2,4-toluene diisocyanate (2,4TDI) and 2,6-toluene diisocyanate (2,6TDI) in foams at ultratrace level by using HPLC-CIS-MS-MS

Sébastien Gagné,*[ab] Jacques Lesage,[a] Claude Ostiguy[a] and Huu Van Tra[b]

[a] *Institut de recherche Robert-Sauvé en santé et en sécurité du travail, 505 West De Maisonneuve Blvd., Montréal, Québec, Canada H3A 3C2. E-mail: sebgag@irsst.qc.ca*
[b] *Chemistry Department, Université du Québec à Montréal, Case Postale 8888, succ. Centre-Ville, Montréal, Québec, Canada H3C 3P8*

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Isocyanates can cause occupational asthma. By using available HPLC-UVF methods, isocyanates can be quantified only at levels above 1% of the Permissible Exposure Limits (PEL). Once sensitized, workers can react to concentrations below these limits of detection (LOD) making these methods insufficiently sensitive to adequately evaluate trace amounts of isocyanates present in air or in materials at safe levels for sensitized workers. This article describes a novel method for isocyanate analysis allowing the quantification of 2,4TDI and 2,6TDI monomers at very low concentrations using HPLC-CIS-MS-MS. The method's sensitivity increases with a decrease in the alkali radius. The LOD is 0.039 ng mL^{-1} for 2,4TDI and 0.100 ng mL^{-1} for 2,6TDI in solution when lithium is the alkali adduct, which is 20 times more sensitive than HPLC-UVF method. This new method allows determination in foam at levels of 0.078 ng g^{-1} for 2,4TDI and 0.200 ng g^{-1} for 2,6TDI respectively, for a 0.5 g foam sample. This is more than 100 times more sensitive than other methods for determining free monomers in solid materials. Analytical reproducibility and precision are better than 92% and 93% for both diisocyanate monomers. The use of HPLC-UVF conventional method failed to detect unreacted isocyanates in foam samples, but TDI monomers were quantified by HPLC-CIS-MS-MS.

Introduction

Isocyanates are powerful respiratory and cutaneous irritants and sensitizers whose most severe outcome is occupational asthma.[1–6] The literature reports that 5% to 10% of exposed workers could develop isocyanate sensitization during their professional lives.[7–11] When sensitized, workers can be affected by isocyanate concentrations much lower than the Permissible Exposure Limits (PEL).[12]

Adopted regulations in different countries are becoming more stringent.[13] As an example, the Quebec PEL for TDI monomers is 5 ppb[12] and air recirculation is prohibited in workplaces using isocyanates.

Diisocyanate compounds have reactive NCO functions that must be stabilized during or immediately after sampling. Secondary amines like 1-(2-methoxyphenyl)piperazine (MOPIP), 9-(*N*-methylaminomethyl)anthracene (MAMA) and dibutylamine (DBA) are commonly used for derivatization and the urea derivative compounds obtained are stable and quantifiable.[14] To reach low limits of quantification, current analytical methods use HPLC coupled with an ultraviolet (UV-DAD) detector for MOPIP urea derivative, an ultraviolet-fluorescence (UVF) detector for MAMA urea derivative and a mass spectrometric (MS) detector for DBA and MOPIP derivatives.[15–20] Current limits of detection (LOD)[15–20] are in the range of 50 ng mL^{-1} to 0.4 ng mL^{-1} in solution for 2,4TDI, and in the range of 50 ng mL^{-1} to 0.4 ng mL^{-1} for 2,6TDI.

Few studies have attempted to develop analytical methodology to quantify residual TDI in foams[21–23] and each one has important drawbacks: non-reproducibility, limited selectivity and limited sensitivity. Residual TDI monomers are expected in foams because of incomplete reactions or the use of a non-stoichiometric ratio of isocyanates to polyols.

The objective of this study is to develop a new analytical method for laboratory analysis of very low concentrations of residual 2,4TDI and 2,6TDI monomers with a high level of selectivity and sensitivity. Analysis will be done by coupling HPLC with MS-MS with the use of an electrospray ionization interface (ESI). A previous study[24] showed the potential of such an approach when protonating with hydrogen substantially increased the sensitivity of the conventional HPLC method. This approach gives a fragmentation pattern where the charge is on the derivatizing agent fraction, and then measures the amine rather than the isocyanate. The objective of the present study and approach is to measure a specific fragment from the isocyanate monomer. To modify the fragmentation pattern, coordination-ionspray tandem mass spectrometry (CIS-MS-MS)[25] is considered. The different fragmentation patterns of protonated compounds and alkali-linked adducts are already reported in the literature for sugars, lipids and peptides.[26–29]

Methods

Chemicals

2,4TDI (96%) monomer, 2,6TDI (97%) monomer and 1-(2-methoxyphenyl)piperazine (MOPIP) 98% were obtained from Aldrich Chemical Company (Milwaukee, WI) and were used without any further purification. Acetonitrile (ACN), methanol and water from Fisher Scientific Co. (Pittsburg, PA), dimethylsulfoxide (DMSO) (99.8%) and toluene from EM Science (Gibbstown, NJ), acetic acid glacial (99.9%), dichloromethane and dimethylformamide from J.T. Baker (Phillipsburg, NJ) were all HPLC grade solvents. Sodium acetate trihydrate, ACS

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grade, came from Fisher Scientific Co. (Pittsburgh, PA), lithium acetate dihydrate (98%), potassium acetate (99+%), rubidium acetate (99.8%) and caesium acetate (99.9%) came from Aldrich Chemical Company (Milwaukee, WI). MRFA (Met-Arg-Phe-Ala) compound for the Finnigan TSQ 700 mass spectrometer calibration was supplied by Finnigan (San Jose, CA), and DMSO-d6 (99.9%) for ^{1}H-NMR by Aldrich Chemical Company (Milwaukee, WI).

Methods

Buffer preparation. 2 mM alkali acetate solutions were prepared in water and the pH was adjusted to 3.5 with glacial acetic acid. The resulting solutions were filtered under vacuum with a 0.2 μm CSC nylon filter.

Standard solution preparation. The procedure for TDI derivatization with MOPIP has already been described.[14] The TDI-MOPIP standard purities were checked by HPLC-UV-MS as described below and by ^{1}H-NMR on a Gemini 300BB operating at 300 MHz. A TDI-MOPIP stock solution was prepared by dissolving 25 mg urea derivative in dimethylformamide. Standard solutions were then prepared at concentrations up to 32.8 ng mL^{-1} for 2,4TDI and 31.3 ng mL^{-1} for 2,6TDI in 80% ACN/20% DMSO solvent.

Foam extraction procedure. Approximately 0.5 g of foam was weighed precisely and cut into small pieces. 100 mL of toluene was added and the suspension was shaken for 30 min at room temperature, then filtered on a Buckner funnel and washed with toluene. 1 mL of MOPIP solution (5 mg mL^{-1}) was added to the filtrate and shaken overnight. The toluene was evaporated with a rotary evaporator and the urea derivative was solubilized with 9.95 mL of desorption solution and transferred to a 10 mL volumetric flask. 0.05 mL of acetic anhydride was added to quench excess MOPIP.

Spiked foam procedure. Approximately 0.5 g of foam was weighed and cut into small pieces. A known amount of TDI in toluene was spiked on the foam piece and the toluene was evaporated at room temperature. 100 mL of toluene was then added and the foam extraction procedure was repeated from this point.

Instrumentation

Every parameter on the TSQ 700 was optimized to obtain a better signal-to-noise ratio. The different ESI interface parameters (capillary temperature, electrospray current and optimal buffer concentration to prevent clogging) and the collision cell pressure of the TSQ were optimized. Table 1 summarizes the experimental instrumentation used and Table 2 lists the optimal parameters for each alkali adduct.

Results and discussion

Analytical method

Analytical parameters

In two previous studies using a methodology with protonated species, a 0.4 ng mL^{-1} LOD[20] was established for 2,4 and 2,6 TDI and a 0.076 ng mL^{-1} LOD was established for 2,4TDI and a 0.115 ng mL^{-1} LOD for 2,6TDI.[24] Even if this approach has a better selectivity than conventional methods, this selectivity is nevertheless limited because the charge is located on the molecular compound in the first quadrupole (m/z = 559.3 for $[M + H]^+$), but after the collision cell, the detected daughter ion is not selective to the isocyanate but is selective to the reagent used for derivatization (m/z = 193 for $[M - TDIMOPIP + H]^+$). The isocyanate monomer is then indirectly analyzed and quantified.

To avoid this important drawback, the CIS-MS-MS method was developed and the results are presented in Table 3. With this approach, the selectivity level significantly increases because the measured daughter ion is a selective fragment from the isocyanate. Similar results were recently presented by our research team for hexamethylene diisocyanate (HDI).[30] HPLC-CIS-MS-MS is selective because chromatography will deliver the TDI derivative at a selective and relatively narrow time interval. Then, at the first quadrupole, a narrow m/z window limits substances ($[M + Cat]^+$) that can enter the collision cell, and finally, the detector measures a narrow m/z which is a fragment selective to the TDI-urea complex ($[M - MOPIP + Cat]^+$). Using the CIS rather than protonation, the fragment detected in the MS is selective to the isocyanate rather than to the complexing MOPIP amine. This approach substantially minimizes the possibility of interferences. As previously observed by other researchers and by our research team, the LOD increases with an increase in the alkali adduct radius.[29–30] We assume that this effect can be directly associated with the ease of fragmentation of the pseudo-molecular ion. Pearson's concept of hard and soft acids[31] suggests that lithium will coordinate with the oxygen of the carbonyl more strongly than caesium. This will allow the formation of a more stable coordination complex which will then fragment in a way where a MOPIP leaves the complex. This expected fragment will display more intensity with the use of the more stable coordination, *i.e.*, coordination with lithium. A smaller frag-

Table 1 Instrumentation

Apparatus	HPLC	Hewlett Packard series 1100
	UV detector	Hewlett Packard series 1050, 254 nm
	Column	Zorbax C18 (150 × 2.1, 5 μm)
	ESI	Finnigan
	Mass spectrometer	Triple quads, Finnigan TSQ 700
HPLC conditions	Mobile phase	45% (95% ACN + 5% MeOH)/55% alkali buffer
	Flow	0.200 mL min^{-1}
	Injection volume	10 μL
Infusion optimization	Flow	7 μL min^{-1}
	Solution concentration	2,6TDIMOPIP 379.5 ng mL^{-1}
	Nebulization gas	70 psi nitrogen
	Auxiliary gas	2 L min^{-1} nitrogen
	Scan time	0.23 s
	Electron multiplier	1200 V
HPLC analysis	2,4TDI retention time	12.20 min
	2,6TDI retention time	8.74 min
	Electron multiplier	1800 V

Table 2 Optimal parameters for each alkali adduct

Parameters	Li^+	Na^+	K^+	Rb^+	Cs^+
Ionization current/kV	4	4	4	4	4
Capillary temperature (°C)	280	320	260	260	280
Collision cell pressure/mTorr	2.5	2.5	2.5	3.0	3.0
Buffer concentration/mM	2	2	2	2	2

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mentation ratio [M − MOPIP + Cat]$^+$/[M + Cat]$^+$ resulting in less selective *m*/*z* ions going to the detector decreases the LOD as illustrated in Fig. 1. With the use of lithium as the alkali adduct, the method shows a sensitivity comparable to the one obtained with the protonated compound, but the selectivity is much better with the alkali adducts. This approach yields the most sensitive and selective method that actually exists. The reproducibility of [M − MOPIP + Li]$^+$ ion is calculated from 6 measurements at each of the six different concentrations on the calibration curve is between 94% and 98% for 2,4TDI, and 92% and 98% for 2,6 TDI, with a precision better than 93% for each TDI monomer. Precision is calculated from six different concentrations spread over the entire calibration curve and repeated six times for each measurement by the same person on the same instrument on three different days.

Residual TDI monomers in foam samples

Three foam samples were collected. These materials had been prepared from several weeks to several years earlier. The usual three-day postproduction aging follow-up was greatly exceeded, but two published studies out of three[21–23] report no residual TDI monomers after this period of time. The third study detects some residual TDI monomers but its selectivity is limited to the UVF detector response and chromatographic retention time. The LOD of the alkali adduct method is compared in Table 4 with the LOD of other published methods, and a substantial gain in sensitivity is observed with the lithium-linked method.

The first foam sample was obtained from seat padding, the second was from protection foam for shipping consumable

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Table 3 Analytical parameters for 2,4-TDIMOPIP and 2,6-TDIMOPIP

Compound	Parameters	Li$^+$	Na$^+$	K$^+$	Rb$^+$	Cs$^+$
2,4TDI-MOPIP	Selectivity MS-MS (*m*/*z*)	565–373	581–389	597–405	643–451	691–499
	Linearity/ng mL^{-1}	LOD–32.8	LOD–32.8	LOD–32.8	LOD–32.8	LOD–32.8
	LOD/ng mL^{-1}	0.039	0.074	0.285	1.42	5.89
	Reproducibility	> 94%	—	—	—	—
	Precision	> 95%	—	—	—	—
2,6TDI-MOPIP	Selectivity MS-MS (*m*/*z*)	565–373	581–389	597–405	643–451	691–499
	Linearity/ng mL^{-1}	LOD–31.3	LOD–31.3	LOD–31.3	LOD–31.3	LOD–31.3
	LOD/ng mL^{-1}	0.100	0.109	0.218	0.907	4.29
	Reproducibility	> 92%	—	—	—	—
	Precision	> 93%	—	—	—	—

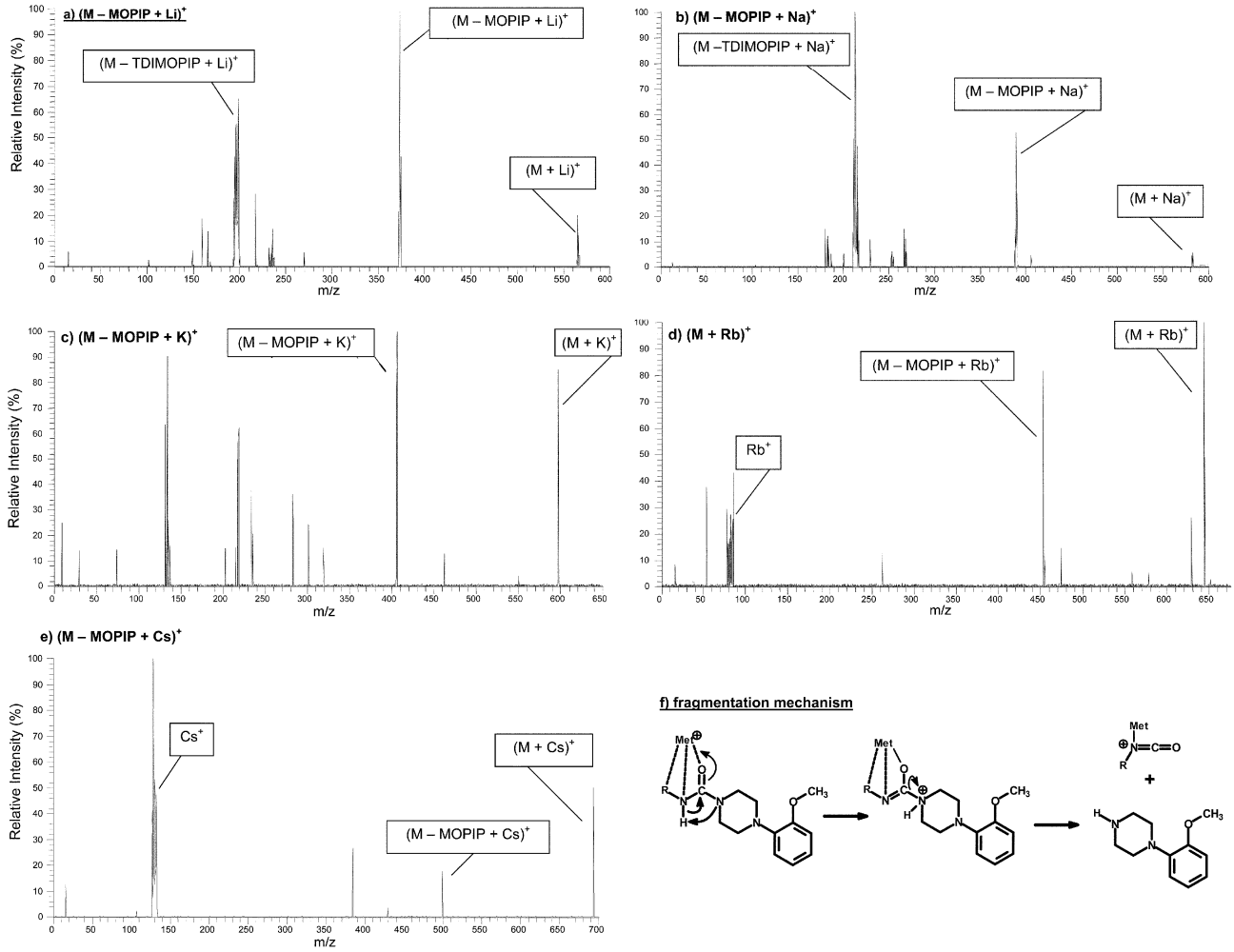

Fig. 1 CIS-MS-MS spectra for each [M − MOPIP + Cat]$^+$ and mechanism of fragmentation.

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products, and the last one was from a camping mat. Because low residual TDI levels were found in each of the three samples using the Li adduct method, it was important to establish the recovery efficiency. The results are presented in Tables 5 and 6 and compared to the results of GC-MS method.[22] The recovery reported in Table 6 was obtained from the difference between a spiked foam sample with a known TDI concentration and an unspiked foam sample considered as a blank. These recoveries are excellent, especially when very low concentrations are involved. In fact, a recovery of more than 80% was obtained and quantified at levels corresponding to the LOD of the most sensitive method already available.[22]

Fig. 2 shows the chromatogram obtained after the extraction from the foam sample from seat padding on which UV detection at 254 nm is compared to MS-MS detection. UV cannot detect at this level but MS-MS can specifically quantify the amounts of 2,4TDI and 2,6TDI. With the sensitivity of the lithium adduct method, residual TDI aging from any sample can be studied down to ultratrace levels. In this particular case, the decrease in concentration of free isocyanate monomers was measured from the first day the foam was exposed to ambient laboratory atmosphere until two consecutive samples gave the same concentrations. Fig. 3 shows the two different curves obtained

Table 4 Comparison of LOD of different methods used for residual TDI determination in foams

Method	LOD of 2,4TDI/ ng g^{-1}	LOD of 2,6TDI/ ng g^{-1}
GC-FID (without derivatisation)[21]	10,000	Not documented
GC-MS (methanol derivative)[22]	10	Not documented
HPLC-UVF (MAMA derivative)[23]	2700	2500
Lithium CIS-MS-MS method	0.078	0.200

Table 5 Reproducibility of blank foam extraction on the same day

n	2,4TDI	2,6TDI
3	2.9 ng g^{-1} ± 1.8%	7.2 ng g^{-1} ± 9.22%

Table 6 Recovery of spiked TDI in foams of polyurethane seat padding

	Concentration/ ng g^{-1}	*n*	% Recovery 2,4TDI	% Recovery 2,6TDI
GC-MS (methanol derivative)[22]	100	6	82 ± 6.64	Not documented
	200	6	88 ± 4.35	Not documented
Lithium CIS-MS-MS method	130	3	85 ± 3.4	101 ± 10.1
	10	3	81 ± 2.2	113 ± 13.4
	15	3	88 ± 2.3	107 ± 9.7

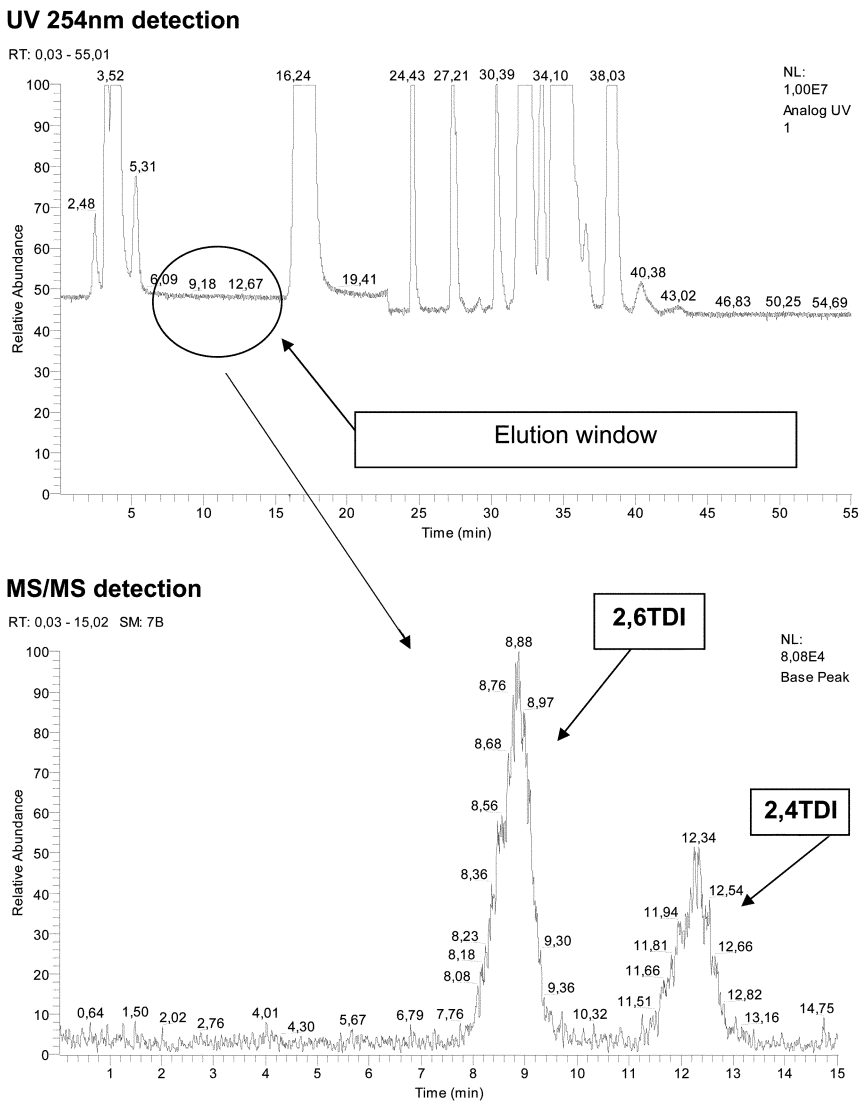

Fig. 2 Chromatogram of extraction of seat padding.

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for 2,4TDI and 2,6TDI. On the same figure, the limits of detection and quantification of the GC-MS method for 2,4TDI (the most sensitive method available) have been added. This study did not report any result for 2,6TDI. From all the samples analyzed, GC-FID, GC-MS and HPLC-UVF methods would not have detected or quantified the TDI monomers which have been selectively quantified by the lithium adduct HPLC-CIS-MS-MS method.

Table 7 shows the concentration of residual TDI for all three samples of different origins after 23 days of exposure to ambient atmosphere in the laboratory. All the concentrations found were below the LOD of conventional methods, and the measured concentrations of 2,6TDI were higher than for 2,4TDI as expected from previous studies.[32–33] The concentration from the camping mat sample was below the LOQ of the lithium adduct method but above the LOD, so it was seen, but the noise level was too high for quantification.

Conclusion

A novel method using HPLC coupled with CIS-MS-MS using lithium, has been developed for the determination of trace amounts of 2,4TDI and 2,6TDI. This method has limits of detection of 0.039 ng mL^{-1} and 0.100 ng mL^{-1} in solution, respectively, for 2,4TDI and 2,6TDI. When applied to the analysis of polyurethane foams, the proposed method has an LOD of 0.078 ng g^{-1} and of 0.200 ng g^{-1} respectively for 2,4TDI and 2,6TDI.

This sensitivity allows the study of residual monomeric TDI in foams at trace levels that cannot be evaluated by any other published analytical method. The method is not only very sensitive, but also with the selectivity level given by the chromatographic retention time and the alkali metal linked fragmentation pattern, the possibility of interferences is very low.

The proposed method allows incomparable LOD and precision with a matchless selectivity that is not achieved by any published method. This analytical method can be used successfully to determine trace amounts of isocyanates in material analysis since it could be extended to workplace environment samples. The same approach could be applied to any aliphatic or aromatic isocyanate.

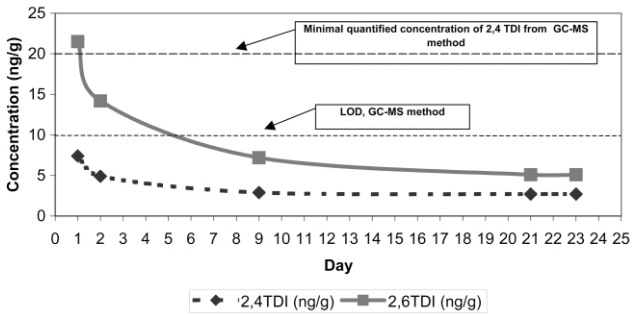

Fig. 3 Residual TDI from chair padding exposed to atmospheric air.

Table 7 Residual TDI found in different samples

Seat padding		Camping mat		Shipping protector	
2,4TDI/ ng g^{-1}	2,6TDI/ ng g^{-1}	2,4TDI/ ng g^{-1}	2,6TDI/ ng g^{-1}	2,4TDI/ ng g^{-1}	2,6TDI/ ng g
2.7	5.1	< LOQ	< LOQ	7.2	16.5

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