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Validation of a diffusive sampling method for airborne low-molecular isocyanates using 4-nitro-7-piperazinobenzo-2-oxa-1,3-diazole-impregnated filters and liquid chromatography–tandem mass spectrometry

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Abstract

A diffusive sampling method for the determination of low-molecular isocyanates as their 4-nitro-7-piperazinobenzo-2-oxa-1,3-diazole (NBDPZ) derivatives using tandem mass spectrometry (MS/MS) after atmospheric pressure chemical ionisation (APCI) is presented. Isocyanic acid (ICA), methyl isocyanate (MIC), ethyl isocyanate (EIC) and phenyl isocyanate (PhIC) are collected on NBDPZ-impregnated polystyrene divinyl benzene (SDB) filter tapes. The method was validated for MIC, EIC and PhIC for concentrations between 0.5 and 50 ppb at relative humidity (RH) conditions from 10 up to 90%. Validation was carried out by active sampling using 1-(2-methoxyphenyl)piperazine (2-MP) as derivatising agent. Sampling periods applied were between 15 min and more than 8 h. The sampling rates were determined to be 21.0 mL/min for MIC with a relative standard deviation (RSD) of 9.0% for 184 samplers, 15.6 mL/min for EIC (RSD 11.6%; $N = 154$) and 11.5 mL/min for PhIC (RSD 8.4%; $N = 87$). The limits of quantification were 1.4 ppb for MIC and 1.3 ppb for EIC and PhIC applying 15 min sampling periods. Owing to high background signals, isocyanic acid could only be determined when it was present in concentrations in the high ppb range.

Keywords: Diffusive sampling; Isocyanic acid; Isocyanates; LC–MS/MS; NBDPZ; 2-MP

1. Introduction

Isocyanates are important compounds in the field of occupational hygiene. Besides their high acute toxicity, isocyanates also show strong sensitising properties, being considered as a major cause of occupational asthma in western countries. Sensitisation usually takes at least several weeks of exposure, but then even very low concentrations below existing occupational exposure limits (OEL) could trigger life-threatening asthma attacks [1–7]. Today, isocyanates have been regulated to some of the lowest levels in workplace air for any organic compound, with OELs of 5–20 ppb [8–10]. In the Netherlands, the existing exposure limits for individual isocyanates will probably be lowered during 2006, while, e.g. in Switzerland the 5 ppb exposure limit for single compounds was extended to be applied for free isocyanate groups in 2005 [11,12]. Diisocyanates are predominantly used in the polymer industries during manufacture of polyurethane (PUR) products or as components for adhesives, paints and lacquers. Monoisocyanates are mainly used as intermediates for synthesis of pharmaceutical and agricultural products, such as pesticides and herbicides. It is known that under high-temperature conditions (above 200–300 °C), isocyanates are released from usually stable compounds, such as PUR products. Conditions that are prone to cause the release of isocyanates are readily achieved during many work processes, e.g. welding, cutting and grinding. Isocyanates will also be set free during spray-painting and foam-blowing operations [13–17]. Additionally, it has been shown that low-molecular isocyanates were detected in significant concentrations when other nitrogen containing materials are thermally decomposed [18,19].

In the past, a large variety of analytical methods for the determination of isocyanates has been reported, employing mainly derivatisation procedures with secondary amines as reagents to stabilise the highly reactive analytes and to

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improve detection properties. The most common reagents include *N*-4-nitrobenzyl-*N*-*n*-propylamine ("nitro reagent") [20–22], 3-(2-aminoethyl)indole (tryptamine) [23–25], 1-(2-methoxyphenyl)piperazine (2-MP) [26–31], dibutylamine (DBA) [32–34], 1-(2-pyridyl)piperazine (2-PP) [35], 9-(*N*-methylaminomethyl)anthracene (MAMA) [36–38], 1-(9-anthracenylmethyl)piperazine (MAP) [39–41] and 4-nitro-7-piperazinobenzo-2-oxa-1,3-diazole (NBDPZ) [42–44]. After liquid chromatographic separation, quantification is performed by means of UV/vis absorbance, fluorescence, electrochemical (EC), mass spectrometric (MS) or tandem mass spectrometric (MS/MS) detection. The assessment of isocyanate exposure is challenging due to their varying occurrence in vapour form, as particles or aerosols, as well as monomers, oligomers and polymers with different number of free isocyanate groups. Therefore, method selection must be carefully matched to the individual situation. So far, no such thing as the best reagent for all purposes exists and new reagents are still currently being presented [45,46].

Regarding the determination of isocyanate concentrations in workplace atmospheres, up to now all routine and standard measurements are based on active (pumped) sampling methods. The latter are especially suited in all those cases where short-term peak concentrations have to be monitored, which are known to be a substantial contributor to the development of occupational asthma. In order to be better suited for personal sampling, solvent free methods are gaining importance [47–49].

In recent years, passive sampling methods have proven great effectiveness, reliability and cost-efficiency in personal air monitoring applications for a large variety of airborne analytes [50]. Especially their easy handling, i.e. the application of solvent-free sampling, the use of portable badges, or the rapid preparation of the sampler itself, has turned out to be a significant advantage when being compared with active sampling systems. However, owing to the inherently smaller volumes that are sampled, diffusive methods are hardly suited to be applied for peak-concentration monitoring. In practice, sampling intervals for diffusive sampling experiments range from 15 min up to 8 h. With respect to isocyanates, there are up to now only two fully validated passive methods for methyl isocyanate (MIC) known from the literature [43,51], as well as an early approach by Rando et al. [52] reporting a passive dosimeter for toluene diisocyanate (TDI) based on a modification of the colourimetric Marcali method [53]. Furthermore, Batlle et al. presented two methods for diffusion-controlled sampling of TDI and hexamethylene diisocyanate (HDI) using SPME devices [54,55]. The very low OEL for isocyanates cause strong requirements on the analytical methods, especially if diffusive sampling is used for collection. In this case, sample volumes are inherently small unless very long sampling periods are accomplished. Current research in the field of isocyanate analysis is more and more focussing on the development and application of highly sensitive mass spectrometric detection methods [28,32,56–58], which is compatible with applications that require high selectivity and sensitivity, such as diffusive sampling does. Recently, it has been shown that different filter materials as well as high and low relative humidity (RH) have a significant influence on diffusive sampling efficiency [59]. Furthermore, it could be shown that passive sampling for MIC, EIC and PhIC using NBDPZ-coated SDB filters is possible [59]. However, the method has not been validated yet and isocyanic acid as an important airborne pollutant has not been considered up to now.

The aim of this work was to develop a fully validated diffusive sampling method for the determination of airborne methyl (MIC), ethyl (EIC) and phenyl (PhIC) isocyanate, as well as isocyanic acid (ICA), using NBDPZ-coated polystyrene divinyl benzene filter tapes as collection material. For validation, an active sampling method based on the use of 2-MP impregnated filters as independent reference method was performed.

2. Experimental

2.1. Chemicals

1-(2-Methoxyphenyl)piperazine, cyanuric acid, ethyl and phenyl isocyanate (EIC, PhIC), formic acid and anhydrous toluene were purchased from Aldrich Chemie (Steinheim, Germany) in the highest quality available. Methyl isocyanate was obtained from Chem Service (West Chester, PA, USA) and caproic, valeric, isobutyric and acetic anhydride were delivered by Fluka (Buchs, Switzerland). Acetonitrile and water (both HPLC-S gradient grade) were obtained from Biosolve (Valkenswaard, The Netherlands). 4-Nitro-7-piperazinobenzo-2-oxa-1,3-diazole and its isocyanate derivatives were synthesised as described in reference [42]. 2-MP derivatives of isocyanates were synthesised according to reference [26].

2.2. Synthesis of isocyanic acid NBDPZ urea derivative

NBDPZ (50 mg) was dissolved in 200 mL of acetonitrile and placed in a gas-washing bottle that was connected to a round bottom flask containing cyanuric acid. A constant stream of nitrogen was led through the whole set-up passing the cyanuric acid and bubbled slowly through the NBDPZ solution. Cyanuric acid was then thermally decomposed to yield ICA by carefully heating with a Bunsen burner for about 30 min. In order to collect retrimerised cyanuric acid and to prevent it from entering the NBDPZ solution, about 1 m of wound and spiral shaped glass tubings were inserted before the gas-washing bottle. The latter was additionally secured with a glass wool plug. The decomposition of cyanuric acid was continued until no NBDPZ reagent was left unreacted in the gas-washing bottle, as monitored by LC with fluorescence detection. After completion, the reaction solution was evaporated to dryness, and the light orange solid ICA-NBDPZ urea derivative was recrystallised from acetonitrile for further purification. Identity and purity of the synthesised ICA-NBDPZ derivative was determined by LC, mass spectrometry and elemental analysis.

2.3. Generation of standard atmospheres

Isocyanate test atmospheres were dynamically generated by continuous evaporation of defined amounts of analyte standard solutions into a constant stream of humidified air. For

this purpose, a generation system was constructed based on the model of a similar set-up described in the literature [60,61]. The nebuliser was a TR-50-C1 (J.E. Meinhard, Santa Ana, CA, USA), and the syringe pump (KD Scientific, Holliston, MA, USA) was operated at flow rates between 1 and 10 μL/min with syringe volumes from 0.5 up to 2.5 mL (SGE, Darmstadt, Germany). Air flows were 0.4 L/min through the nebuliser, additional 4.6 L/min added at the bottom end of the evaporation chamber and further dilution with 35 L/min of humidified air. The Teflon®- and glass-made exposure chamber had dimensions of 7 cm × 5 cm × 100 cm and comprised six sliding doors to introduce the diffusive sampling badges and seven ports for active reference sampling. Dry air was delivered by a compressor model 2xOF302-40MD2 (Jun-Air, Nørresundby, Denmark). All air flows were set and controlled with mass-flow controllers (EL-Flow® series F-201C and F-201AC, Bronkhorst Hi-Tec, Ruurlo, The Netherlands). The part led through the nebuliser was additionally adjusted using a rotameter valve (Cole Palmer, Vernon Hills, Illinois, USA). The flow of 35 L/min was split into four parallel channels, three of which were led through gas-washing bottles that were filled with water and placed in a tempered water bath (25 °C). These four flows were later re-united and could be adjusted individually by means of needle valves to allow rapid control of relative humidity conditions between 10 and 100% inside the test chamber. All tubing was made of Teflon® and all connections and valves were from stainless steel (Swagelok, Waddinxveen, The Netherlands) to ensure maximum inertness.

2.4. Preparation of isocyanate standards

Standard solutions for generation of isocyanate test atmospheres (except for ICA) were made by dissolving the respective isocyanate in anhydrous toluene. The concentrations of these stock solutions were determined by LC–UV/vis, and the solutions were stored in the freezer. Diluted standards were made from stock solutions by further dilution with dry toluene to the required concentration range. As no stable solutions could be obtained in toluene for ICA, THF was used as solvent. In this case, the same procedure was applied as for the synthesis of the ICA-NBDPZ derivative, except that pure THF without addition of NBDPZ was added to the gas-washing bottle.

2.5. Diffusive sampler

The diffusive sampling badge used in this study is schematically described in reference [43]. The housing, with dimensions of 86 mm × 28 mm × 9 mm, was made of polypropylene. Two impregnated filters were placed beneath a 2.9 mm thick screen. The part of the screen covering the sampling filter comprised 112 diffusion channels (tubes) within a total area of 20 mm × 20 mm and with an orifice diameter of 1.0 mm for each hole, increasing slightly towards the collector surface. When the sampler was not in use, the diffusion channels were sealed by a sliding cover. The second filter (control filter) was used to quantify the isocyanate blank. The sampler is commercially available as UMEx 100 (with coated filters for sampling of formaldehyde and amines) from SKC (Eighty Four, PA, USA).

2.6. Coated filters for diffusive sampling

NBDPZ (10 mg) was dissolved in 10 mL of acetonitrile (4 mmol/L). Empore SDB-XC extraction disks, diameter 90 mm (3 M, St. Paul, MN, USA) were cut into 20 mm × 20 mm squares, put onto a glass surface and impregnated with 250 μL of the reagent solution. The filters were subsequently allowed to dry for 20 min under reduced pressure. One filter was placed under the sampling part of the badge and another under the control part. For some experiments, glass fibre filters (type A/E, diameter 37 mm, SKC, Inc., PA, USA) were prepared the same way, except that 200 μL of the reagent solution were applied to the filter. For passive sampling experiments with 2-MP as reagent, filters were prepared the same way using a solution of 100 mg 2-MP in 10 mL of acetonitrile for impregnation (52 mmol/L).

2.7. Coated filters for active reference sampling

Round glass fibre filters (GFB, diameter 25 mm, Whatman Ltd., Maidstone, UK) were placed onto a glass surface and impregnated with 400 μL of a solution containing 500 mg of 2-MP in 50 mL of acetonitrile (52 mmol/L). Afterwards, the filters were dried under reduced pressure and finally stored in a refrigerator. The same procedure was also applied to obtain NBDPZ-coated filters, using a reagent solution of 50 mg NBDPZ in 50 mL of acetonitrile instead (4 mmol/L).

2.8. Diffusive sampling experiments

The NBDPZ diffusive sampling experiments were performed mainly according to EN 838 [62]. The concentrations covered during this validation ranged from approximately 0.1 up to 10 times the threshold-limit value, which resembles isocyanate concentrations between 0.5 and 50 ppb. For most experiments, five or six diffusive samplers were simultaneously exposed to test atmospheres of MIC, EIC and PhIC. Some experiments were done with isocyanate atmospheres containing only one compound; but typically all three analytes were evaporated from one standard mixture to allow simultaneous diffusive sampling experiments of MIC, EIC and PhIC. To control the homogeneity of the test atmospheres inside the exposure chamber and to determine the variation between the single sampler badges, one experiment was carried out with 15 samplers in parallel. The sampling periods were mainly selected between 15 min and 8 h, and relative humidity was varied between 10 and 100%. Additionally, 2-MP diffusive sampling experiments were performed on a smaller scale with a reduced quantity of parallel diffusive samplers of each kind (equipped with either SDB or GF filters). Sample and control filters of exposed diffusive samplers were transferred into separate vials and extracted with 2 mL (for SDB filters) or 3 mL (for GF filters) of acetonitrile. The glass fibre filter samples had to be centrifuged prior to analysis for 5 min at 5000 rpm (Labofuge A, Heraeus Sepatech, Osterode, Germany) in order to settle loose filter particles.

2.9. Reference method

A pumped filter method described by Henriks-Eckerman et al. [63] was modified and applied to determine the isocyanate concentrations of generated test atmospheres. Two 2-MP-impregnated filters were placed on top of each other in a Swinnex 25 filter cassette (Millipore, Milford, MA, USA). Three or four filter cassettes were connected in parallel to the active sampling ports of the exposure chamber with a second filter cassette connected in series as backup. For a period of 10–30 min, samples were taken at pump flow rates between 0.3 and 0.5 L/min, using an air sampling pump (Thomas Diaphragm, H/D Pump, Environmental Monitoring Systems, Charlston, SC, USA). Parallel sampling was achieved by splitting the tubing into several parallel pathways, each provided with glass-capillary tubes (inner diameters between 0.45 and 0.6 mm) in order to maintain a constant pressure drop during sampling. The pump flow was adjusted with a needle valve, placed between pump and "splitting tree". The flow through each cartridge was determined prior and subsequent to the sampling using a DryCal DC-Lite flow calibrator (Bios, Butler, NJ, USA). For short-time exposure experiments, the active reference method was executed simultaneously with diffusive sampling. For longer experiments, it was carried out several times during the generation of the test atmosphere to verify its stability.

Exposed filters from one filter cassette were placed together in 4 mL LC vials and extracted with 4 mL of acetonitrile. The filter particles were allowed to settle down using a centrifuge for 5 min at 5000 rpm and analysed by means of LC–MS/MS.

The sampling procedure employing cartridges including two backup cassettes equipped with NBDPZ coated filters remained the same, except that in addition to LC–MS/MS detection, UV/vis and fluorescence detection were applicable as well.

2.10. HPLC instrumentation and analysis

2.10.1. NBDPZ spectroscopic methods

The chromatographic system for LC–UV/vis and LC–fluorescence analysis of NBDPZ urea derivatives was delivered by Shimadzu (Duisburg, Germany) and consisted of the following parts: two LC-10AS pumps, GT-104 degasser unit, SIL-10A autosampler, sample loop with variable injection volume of up to 50 μL, SUS mixing chamber (0.5 mL), CTO-10ACvp column oven, SPD-M10Avp diode-array detector, RF-10AXL fluorescence detector, CBM-10A controller unit and Class LC-10 software Version 1.63.

For determination of the phenyl isocyanate NBDPZ urea derivative from diffusive sampling experiments, the following method was used: The column was a ProntoSIL® 120-3-C18 ace-EPS; particle size 3 μm; pore size 120 Å; column dimensions 150 mm × 4.6 mm (Bischoff Chromatography, Leonberg, Germany). The injection volume was 10 μL, and the column was run with a flow rate of 1 mL/min in a water/acetonitrile gradient (with 0.05% (v/v) formic acid in the aqueous phase). Starting conditions were 20% acetonitrile, followed by a linear gradient to 70% acetonitrile at 15 min and 100% acetonitrile at 16 min. After 1 min, the starting conditions were re-established within another minute. Total analysis time was 25 min including re-equilibration. Conditions for fluorescence detection were: $\lambda_{ex} = 471$ nm and $\lambda_{em} = 540$ nm. Absorption was measured at 480 nm.

For simultaneous analysis of all isocyanate NBDPZ urea derivatives from active sampling experiments, the following method was used: The column was a ProntoSIL® 120-5-phenyl; particle size 5 μm; pore size 120 Å; column dimensions 250 mm × 3 mm (Bischoff Chromatography). The injection volume was 10 μL, and the column was run with a flow rate of 0.8 mL/min applying a water/acetonitrile gradient (with 0.05% (v/v) formic acid in the aqueous phase). Starting conditions were 20% ACN. Five minutes of isocratic elution were followed by a linear gradient to 80% ACN at 20 min and back to the starting conditions within another minute. Total analysis time was 25 min including re-conditioning of the column.

2.10.2. MS/MS methods

For LC–MS/MS analysis, a system comprising a binary gradient HPLC pump (HP1100 model GF1312A), an autosampler (HP1100 model G1313A) and a diode-array UV detector (HP1100 model G1315B; all Agilent, Waldbronn, Germany) was connected to the mass spectrometric detector.

For separation of both the 2-MP and NBDPZ derivatives, a ProntoSIL® 120-5 phenyl column with dimensions of 2 mm × 250 mm, particle size of 5 μm and pore size of 120 Å was selected (Bischoff Chromatography).

For mass spectrometric detection, an Esquire 3000+ ion trap mass spectrometer (Bruker Daltonics, Bremen, Germany) was used, equipped with an ESI interface (for analysis of 2-MP derivatives) or an APCI source (for NBDPZ derivatives). All MS measurements were performed in the positive ion mode. The analytes were quantified by 6-point external calibrations run with each series of measurements. The resulting data were analysed using DataAnalysis software Version 3.1 (Bruker Daltonics).

2.10.3. MS method for NBDPZ

The injection volume was 5 μL, and the sample was eluted with 0.45 mL/min of a water/acetonitrile gradient (with 0.05% (v/v) formic acid in the aqueous phase). Starting conditions were 30% acetonitrile, followed by a linear gradient to 40% acetonitrile within 5 min and subsequently to 100% acetonitrile within another 5 min. After 1 min, a steep gradient for 1 min back to the starting conditions was applied. The total time for the analysis was 21 min, including re-equilibration. Tandem mass spectra were recorded in the manual MS/MS mode, scanning from *m/z* 100 to *m/z* 700 employing the APCI-MS parameter settings as shown in Table 1. Detection was performed as selected-reaction monitoring (SRM) on the transitions from the protonated pseudomolecular ion of the isocyanate derivative $[(IC\text{-}NBDPZ) + H]^+$ (*m/z* 293 for ICA; 307 for MIC; 321 for EIC and 369 for PhIC) to $[NBDPZ + H]^+$ (*m/z* 250), and data were collected as constant neutral loss scans of (*m/z* 43, 57, 71 and 119, respectively) with a maximum accumulation time of 200 ms. Time segments were programmed based on UV/vis retention times, in which different precursor ions were selected:

Table 1
List of APCI-MS parameters for Esquire 3000+

Parameter	Settings
Nebuliser gas (N_2) pressure (psi)	50
Dry gas (N_2) flow (L/min)	5
Dry gas (N_2) temperature (°C)	350
Vaporiser temperature (°C)	450
Corona current (nA)	4500
Capillary high voltage (V)	3115
Capillary exit voltage (V)	109.4
Skimmer voltage (V)	40.0
Octopole 1 voltage (V)	12.0
Octopole 2 voltage (V)	1.7
Octopole amplitude (Vpp)	150.0
Lens 1 voltage (V)	−5.0
Lens 2 voltage (V)	−60.0
Trap drive level	35.0

from 0 to 4 min, the eluent was diverted into waste; from 4 to 5.4 min, *m/z* 293.1 (NBDPZ-ICA) was selected; from 5.4 to 6.7 min, *m/z* 307.1 (NBDPZ-MIC); from 6.7 to 8.2 min, *m/z* 321.1 (NBDPZ-EIC); from 8.2 to 9.6 min, *m/z* 335.1 (NBDPZ-iPIC); from 9.6 to 12 min, *m/z* 369.1 (NBDPZ-PhIC); and from 12 to 20 min the eluent was again diverted into waste. The NBDPZ-iPIC signal was used as internal standard in some experiments.

2.10.4. MS method for 2-MP

The injection volume was 5 μL, and the sample was eluted with 0.3 mL/min applying a water/acetonitrile gradient (with 0.05% (v/v) formic acid in the aqueous phase). Starting conditions were 25% acetonitrile, followed by a linear gradient after 1 min to 85% acetonitrile within 3 min. After 2 min, the starting conditions were re-established within 1 min. The total time for the analysis was 15 min, including re-equilibration. Tandem mass spectra were recorded in the same way as described for the NBDPZ method, employing the ESI-MS parameter settings as shown in Table 2. The selected precursor segments were in this case: from 0 to 4.1 min into waste; from 4.1 to 5.6 min, *m/z* 250.0 (2-MP-MIC); from 5.6 to 7.6 min, *m/z* 264.0 (2-MP-EIC); from 7.6 to 10.1 min, *m/z* 312.0 (2-MP-PhIC); and from 10.1 to 15 min again into waste.

Table 2
List of ESI-MS parameters for Esquire 3000+

Parameter	Settings
Nebuliser gas (N_2) pressure (psi)	40
Dry gas (N_2) flow (L/min)	10
Dry gas (N_2) temperature (°C)	365
Capillary high voltage (V)	5000
Capillary exit voltage (V)	109.8
Skimmer voltage (V)	40.0
Octopole 1 voltage (V)	12.0
Octopole 2 voltage (V)	1.7
Octopole amplitude (Vpp)	142.5
Lens 1 voltage (V)	−5.0
Lens 2 voltage (V)	−60.0
Trap drive level	27.7

2.11. Nano-electrospray-Fourier transform ion cyclotron resonance-mass spectrometry

All nano-ESI-FTICRMS experiments were carried out using a LTQ FT Fourier transform ion cyclotron resonance hybrid mass spectrometer (Thermo Electron, Bremen, Germany), equipped with a 7.0 T actively shielded superconducting magnet and nano-ESI source. The instrument was operated in the positive ionisation mode. Ion transmission into the linear trap and signal intensity was automatically optimised for maximum ion signal of the EIC-NBDPZ. The parameters were: source voltage 0.8–1.0 kV, capillary voltage 26 V, capillary temperature 200 °C, and tube-lens voltage 100 V. Full scan FTICR mass spectra in the mass range *m/z* 100–500 were acquired with an automated gain control (AGC) of 2×10^5. The resolving power of the FTICR mass analyser was set to 200,000 (FWHM at *m/z* = 400). Accurate mass measurements were carried out by a zoom scan in a narrow mass window (±5 Da at AGC = 5×10^4 and a resolving power of 50,000). The instrument was calibrated externally using 0.01% solution of 85% phosphoric acid in water/methanol (1/1; v/v).

3. Results and discussion

3.1. NBDPZ method

Earlier it has been shown [43] that MIC can be analysed using diffusive sampling and fluorescence detection. In the present study, we have developed a method for PhIC. Acetic anhydride was found to be suitable for reagent excess deactivation, thus diminishing the interfering tailing of the NBDPZ peak. Fig. 1 shows the analysis of eluted sample and control filters from a diffusive sampler exposed to 30 ppb PhIC for 45 min. In that concentration range, fluorescence detection can well be applied, but owing to tailing problems and matrix interferences, both related to the reagent excess, the use of mass spectrometry for detection is much more favourable.

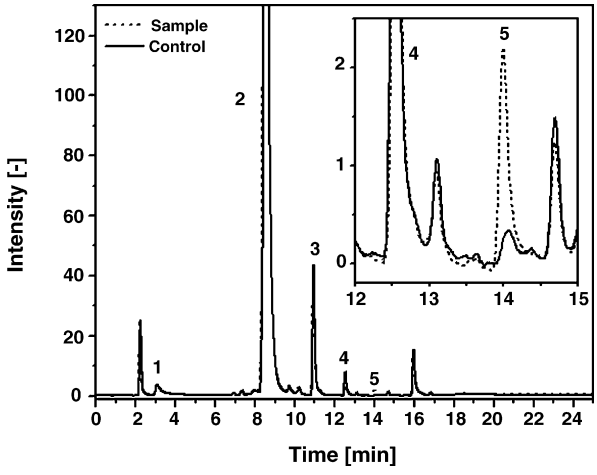

Fig. 1. Fluorescence analysis of a diffusive sampler exposed for 45 min to 30 ppb of PhIC; peak assignment: isocyanic acid background signal (1), acetylated NBDPZ excess (2), propionylated NBDPZ (3), unknown reaction product from anhydride impurity (4) and PhIC-NBDPZ derivative (5).

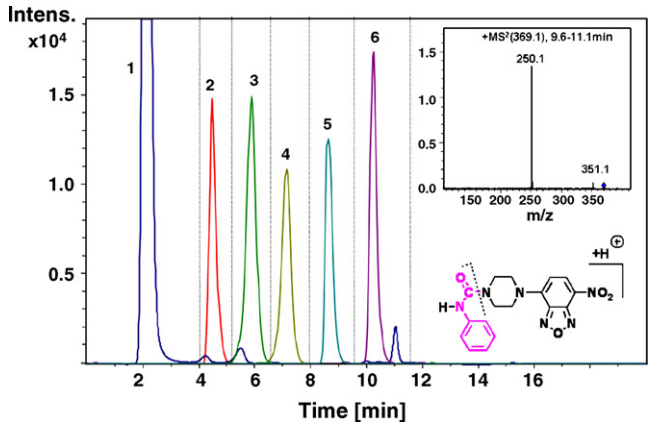

Fig. 2. Chromatograms of a typical separation of a mixture showing the NBDPZ reagent excess (1; UV trace at 480 nm) and mass traces of ICA (2), MIC (3), EIC (4), iPIC (5) and PhIC (6). The MS^2 fragmentation pattern and mass spectrum for the PhIC derivative is shown as an example. Vertical lines illustrate segment borders for precursor ion selection.

The LC method applying optical detection, which was developed for the determination of phenyl isocyanate had an analytical limit of detection (LOD) of 1.8×10^{-8} mol/L for fluorescence and 5.9×10^{-8} mol/L for UV/vis detection, determined as a signal intensity of three times the noise. The limit of quantification (LOQ), determined as a signal intensity of 10 times the noise, was 6.0×10^{-8} (for FLD) and 2.0×10^{-7} mol/L (for UV/vis), respectively. The calibration function had a correlation coefficient of linear regression (R) of 0.99986 and a linear range of more than three decades above the LOQ. The fluorescence LOQ is equivalent to a concentration of about 10 ppb PhIC in air collected by 60 min diffusive sampling at an estimated uptake rate of 10 mL/min.

When tandem mass spectrometry was applied, the tailing of the reagent excess that caused a severe drawback in fluorescence detection became negligible. Only the large reagent excess must not be allowed to enter the mass spectrometer in order to avoid an overload and a contamination of the system. It was not necessary to add any anhydrides for reagent excess deactivation, as the addition of formic acid to the LC eluent sufficiently shifted the retention time of the reagent well in front of its derivatives. The first chromatographic window (0–4 min) was directed to the waste using a six-port switching valve, thus allowing only the analyte derivatives to enter the mass spectrometer. Baseline separation of the different analytes is favourable, as for every analyte, a different precursor ion is selected for fragmentation to obtain the best sensitivity (Fig. 2).

To investigate the influence of ion suppression or other matrix effects on the analysis result, isocyanate standard solutions with and without the addition of a reagent-impregnated blank filter have been analysed. No difference between the two data sets was observed, which means that the diffusive sampler analysis results are not influenced by any background signal (data not shown). The limits of quantification and limits of detection were determined by assessment of the signal-to-noise ratios of 3:1 for the LOD and 10:1 for the LOQ (Table 3). The calibration functions always had correlation coefficients of linear regression (R) of 0.99975 and better. The linear range comprised more than three decades starting at the LOQ. The NBDPZ quantification limits corresponded to concentrations of about 1.5 ppb PhIC in air collected by 15 min diffusive sampling at an estimated sampling rate of 10 mL/min; of about 1.3 ppb EIC (15 min at 16 mL/min); and of about 1.5 ppb MIC (15 min at 20 mL/min).

Table 3
MS/MS limits of detection and quantification

Derivative	NBDPZ		2-MP	
	LOD	LOQ	LOD	LOQ
ICA	6.0×10^{-9}	2.0×10^{-8}	–	–
MIC	2.8×10^{-9}	9.3×10^{-9}	8.7×10^{-10}	2.9×10^{-9}
EIC	1.9×10^{-9}	6.3×10^{-9}	1.5×10^{-9}	5.1×10^{-9}
PhIC	1.3×10^{-9}	4.3×10^{-9}	1.4×10^{-9}	4.6×10^{-9}

3.2. 2-MP method

The use of 2-MP in combination with tandem mass spectrometry as described in this paper is a modification of a method presented by Vangronsveld and Mandel [57]. However, in their work, quantitative method performance data was only provided for the analysis of the most common diisocyanates, while ICA, MIC and PhIC were only treated qualitatively or semiquantitatively. In the present paper, MS parameters have been optimised for the analysis of the MIC-2-MP derivative, and LODs for MIC-2-MP, EIC-2-MP and PhIC-2-MP have been determined in the same way as described for the NBDPZ method (data also shown in Table 3). Correlation coefficients of linear regression (R) were 0.999 and better, and a linear range of more than three decades starting at the LOQ was obtained. The sensitivity was in the same range as described by Vangronsveld and Mandel [57] for 2-MP diisocyanate derivatives.

4. Active sampling results

4.1. 2-MP reference method

The active 2-MP method was very robust for methyl and ethyl isocyanate, as the analysis results from 3 to 4 simultaneously taken samples from different positions in the test chamber showed average standard deviations of 2.5% for MIC and 2.3% for EIC, respectively. Initial experiments with up to six parallel samples showed no significant improvement compared to experiments with three to four samples, meaning that the reduced number was sufficient to obtain reliable results. These results also demonstrate that the test-atmosphere composition was homogeneous inside the whole exposure chamber. The overall recovery was 92% of the calculated concentration for MIC, and 98% for EIC. The test atmospheres were stable over a period of several hours, as air sampling at different points in time gave identical results within the above mentioned standard deviations. The concentrations of MIC and EIC determined by the 2-MP reference method were generally taken as basis for the calculation of the respective diffusive sampling rates.

While the standard deviation for one series of filters that were simultaneously exposed to phenyl isocyanate was 3.2%, PhIC test-atmosphere concentrations varied from 50 up to 120% of the calculated value. As active sampling based on the use of NBDPZ showed significantly better recovery, the high variations for PhIC obtained by the 2-MP method could not be explained by insufficient atmosphere generation. This failure of the active 2-MP reference method for PhIC has not been reported yet and needs a more in-depth elucidation in the future. As the results of the active NBDPZ method came much closer to the calculated value than the 2-MP method, this method was supposed to be better suited as a reference for PhIC.

4.2. Active NBDPZ method

Active sampling using NBDPZ-impregnated filters was applied the same way as with 2-MP except that the amount of reagent was about a factor of 10 smaller. This was due to the fact that NBDPZ coating solutions were lower in concentration because the solubility of NBDPZ in acetonitrile is limited. Quantitative collection was obtained only for PhIC, and no breakthroughs into the backup filter were seen. The mean deviation between the samplers at different sampling positions was 2.7%. For aliphatic isocyanates, significant breakthroughs had been detected even in a second backup filter. The amount of MIC collected on the backup filters was between 26 and 50% of the sample filter value, and on the second backup between 15 and 48%. For EIC the results showed breakthroughs of 11–39% for the first backup and 4–33% for the second. This means that the active NBDPZ method is only suitable for the determination of airborne phenyl isocyanate.

5. Diffusive sampler validation

5.1. Methyl isocyanate

In order to determine the diffusive sampling rate for methyl isocyanate, 36 series of experiments were conducted using

Table 4
NBDPZ diffusive sampling results of MIC on SDB filters

Experiment	*c*(MIC) (ppb)	*t* (min)	RH (%)	SR (mL/min)	RSD (%)	*N*	Reference yield (%)	RSD (%)
1	0.4	815	L	21.21	5.9	6	95.3	2.4
2	0.7	300	H	19.62	7.7	6	96.9	2.1
3	1.2	200	H	21.12	6.2	5	81.7	1.0
4	1.7	370	H	21.67	5.6	2	80.2	2.3
5	1.8	240	L	21.69	7.8	4	81.9	3.2
6	1.9	920	H	20.51	3.0	2	90.9	3.0
7	2.0	80	H	20.35	7.2	5	92.3	1.6
8	2.2	30	L	21.30	7.9	5	100.5	1.7
9	4.1	40	L	21.90	4.8	5	95.1	1.9
10	4.2	60	L	21.71	7.5	4	77.0	1.7
11	4.5	93	H	19.51	4.3	5	82.5	1.5
12	5.3	240	H	21.76	8.1	4	81.5	5.3
13	5.6	90	L	19.79	5.3	5	91.3	5.6
14	5.7	30	L	21.53	6.7	6	93.6	2.3
15	6.2	30	L	21.42	5.5	5	95.9	1.9
16	7.4	60	L	22.95	10.7	7	94.0	5.9
17	8.5	280	L	19.27	3.6	5	88.5	1.1
18	8.8	20	L	22.45	4.4	4	80.1	2.2
19	9.6	30	H	21.86	6.3	5	88.7	1.8
20	10.0	30	L	20.77	13.4	4	99.9	3.3
21	10.6	30	L	20.16	7.9	5	97.7	3.0
22	11.0	30	L	20.33	5.9	4	113.1	0.8
23	11.9	253	L	21.92	4.5	6	98.4	2.2
24	13.3	45	L	20.62	4.3	4	82.1	3.5
25	15.4	15	L	21.95	8.4	5	94.7	1.7
26	17.5	180	L	18.76	7.3	15	90.6	2.1
27	18.6	120	H	21.28	5.3	6	85.1	1.6
28	20.0	15	H	20.43	6.7	4	109.9	2.5
29	20.1	30	L	20.20	2.6	4	103.5	1.2
30	20.9	60	H	23.17	3.6	6	95.9	0.9
31	26.1	20	L	23.36	7.6	3	85.9	3.9
32	26.4	35	L	21.93	2.3	4	86.8	5.0
33	29.9	60	L	19.46	2.5	3	100.0	3.2
34	30.0	90	H	24.05	4.0	6	91.4	2.5
35	30.1	47	H	21.95	11.5	6	86.5	3.1
36	31.0	120	L	19.30	5.4	9	95.7	0.9
Mean				21.15			91.8	2.5
SD				1.25				
RSD (%)				5.89				

Table 5
NBDPZ diffusive sampling results of EIC on SDB filters

Experiment	*c*(EIC) (ppb)	*t* (min)	RH (%)	SR (mL/min)	RSD (%)	*N*	Reference yield (%)	RSD (%)
1	0.5	815	L	16.33	4.41	6	92.7	2.59
2	1	300	H	14.89	11.25	6	103.8	4.09
3	1.6	200	H	14.27	8.64	5	88.0	0.70
4	2.4	370	H	15.29	7.97	3	89.0	5.61
5	2.5	80	H	18.22	3.31	5	103.0	1.38
6	2.6	240	L	15.10	7.53	4	97.0	5.48
7	2.7	920	H	13.61	0.60	2	99.0	2.32
8	3.1	30	L	14.49	11.88	5	115.7	0.56
9	5.6	90	H	17.22	6.49	5	92.0	2.03
10	5.8	40	L	14.51	10.40	5	108.1	2.79
11	6	60	L	16.20	3.57	4	88.9	1.84
12	7.4	240	H	15.60	6.89	4	91.3	5.16
13	7.9	280	L	12.65	6.99	5	98.9	1.54
14	8.7	30	L	13.82	10.28	5	108.3	2.44
15	10.1	30	L	14.04	5.18	4	123.0	1.29
16	12	60	L	14.11	11.12	7	81.8	0.79
17	12.1	20	L	18.22	3.91	4	89.4	1.90
18	12.2	30	H	18.71	4.06	5	100.0	1.02
19	14.2	30	L	14.76	2.02	5	105.8	0.88
20	15.5	250	L	15.17	5.12	6	105.2	3.68
21	17.2	30	L	13.91	6.65	4	105.4	1.15
22	18.1	45	L	16.79	2.43	4	89.8	1.98
23	20.8	15	L	15.64	4.71	5	103.3	1.56
24	23.1	180	L	15.95	3.38	15	96.3	1.30
25	23.5	120	H	16.32	5.90	6	86.8	1.82
26	26.2	60	H	15.90	7.68	6	96.6	0.78
27	37.1	90	H	18.74	4.39	6	86.0	3.38
28	37.4	45	H	15.60	8.29	6	93.8	2.29
29	40.6	20	L	16.80	3.75	3	96.3	4.08
30	41.1	35	L	15.70	6.50	4	97.7	3.87
Mean				15.62			97.8	2.3
SD				1.55				
RSD (%)				9.92				

NBDPZ-impregnated SDB filters. MIC concentrations were varied between 0.4 and 31 ppm, which were determined with the active 2-MP filter method. For all 36 experiments, the average diffusive sampling rate was determined to be 21.2 mL/min with a relative standard deviation (RSD) of 5.9% (Table 4). If all single samplers from all experiments were considered, the mean sampling rate was 21.0 mL/min with a standard deviation of 9.0% ($N = 184$). The RSD of the individual samplers within one experiment averaged 6.2%. One experiment was carried out using 15 parallel samplers, in which the standard deviation was determined as 7.3%, demonstrating the good reliability and reproducibility of the passive method.

5.2. Ethyl isocyanate

As the respective diffusion rates are directly depending on the size of the analyte molecules, it is expected that the sampling rate for ethyl isocyanate is smaller than the one for MIC. For experimental determination of the sampling rate, 30 experiments were carried out in this case, covering a concentration range between 0.5 and 41.1 ppm of EIC in the exposure chamber. The overall passive sampling rate for EIC was found to be 15.6 mL/min with an RSD of 9.9% for the mean values of each experiment, and 15.6 mL/min ± 11.6% for all 154 individual samplers. The standard deviation within each experiment was 6.2% in average, while the one experiment of 15 simultaneously exposed samplers gave an RSD of 3.4% (Table 5).

5.3. Phenyl isocyanate

Based on sampling using the active NBDPZ reference method, the sampling rate for PhIC was determined to be 11.5 mL/min, while the standard deviation was 8.4% (Table 6). This would be quite acceptable for diffusive sampling applications. Six additional experiments with a total number of 29 diffusive samplers were carried out using LC–fluorescence for analysis. In these experiments, the PhIC concentration was varied between 2 and 30 ppb and sampling periods ranged from 45 min up to 8 h. The sampling rates obtained by this procedure gave an average result of 10.7 mL/min (RSD = 7.4%; $N = 29$), which was in the same range as the results obtained by MS/MS detection if the error margins are considered.

5.4. Isocyanic acid

Due to background interferences, the quantification of isocyanic acid (ICA) derivatives is problematic. For the 2-MP

Table 6
NBDPZ diffusive sampling results of PhIC on SDB filters; concentrations from NBDPZ reference method

Experiment	SR (mL/min)	RSD (%)	*N*	Reference yield	RSD (%)
1	12.20	7.2	6	104.0	1.5
4	13.40	6.0	4	113.4	5.3
5	12.76	4.5	4	96.3	2.6
9	10.38	2.4	5	100.0	×
10	10.74	4.8	4	95.0	4.0
11	12.42	3.5	5	102.1	14.7
12	10.72	2.3	5	92.7	3.0
13	11.84	3.5	5	95.8	4.2
18	12.00	6.7	6	100.0	×
19	12.03	4.2	4	94.7	3.4
21	12.18	9.4	4	118.1	3.8
22	11.17	5.1	6	133.4	1.2
23	11.38	7.0	6	86.4	2.9
24	10.44	4.5	4	95.1	3.9
25	11.19	3.5	4	136.2	2.5
29	9.85	8.6	15	131.3	3.6
Mean:	11.54	5.2		105.9	4.0
SD	0.97				
RSD (%)	8.40				

method, a large amount of ICA derivative was already found in the reagent solution that had been used for filter impregnation. Although there was almost no ICA background seen in the reagent solution, there was a similar problem observed for the NBDPZ method, too. After impregnation of both SDB and GF filters with NBDPZ, a background peak appeared that co-eluted with the ICA-NBDPZ peak and revealed the same fragmentation pattern in the MS/MS mode. The background signal was equivalent to a detector response from concentrations greater than 10 ppb for ICA collected by 120 min diffusive sampling at an estimated uptake rate of 25 mL/min. This makes reliable quantification in that range very difficult.

To verify the nature of these interfering compounds, nano-ESI-FTICRMS experiments were carried out for the determination of exact masses of these compounds. The experiments revealed that the interferences were indeed the respective ICA-2-MP and ICA-NBDPZ derivatives, as no compounds with different elemental composition could be detected. This was quite unexpected and demands a closer examination in the future.

Owing to these findings, only one diffusive sampling experiment was performed for ICA, exposing the samplers to a very high concentration of about 650 ppb for 1 h in order to obtain a sample peak that was very large in comparison to the background signal. In that experiment, a sampling rate of 25.7 mL/min was determined for isocyanic acid, and the standard deviation between the six samplers was 2.9%. This is to be considered as a preliminary result, since no reference method was applied. The ICA standard concentration was determined using the NBDPZ fluorescence method directly before the atmosphere was generated. The experiment showed that diffusive sampling also works for ICA, with a larger sampling rate than methyl isocyanate. However, prior to a full validation for ICA sampling, the reason for the interference has to be elucidated and minimised.

6. Conclusion

NBDPZ-coated polystyrene divinyl benzene (SDB) filters can be applied for the diffusive sampling of vapour-phase MIC, EIC and PhIC. A validation of passive sampling has been carried out for all three analytes. The determined sampling rates are independent of analyte concentration and relative humidity conditions; the rates are decreasing with increasing size of the analyte molecule, which fully complies with expectations from diffusion theory. Regarding the MS/MS method presented in this study, the LOQ was 1.5 ppb for the individual isocyanates when 15 min sampling periods were accomplished. For 8-h measurements, this corresponds to concentrations of below 50 ppt, which is 1% of the existing occupational exposure limit (OEL). Generally, the use of mass spectrometry is strongly recommended because of higher sensitivity and better selectivity. The fluorescence method for phenyl isocyanate showed a significantly higher LOQ and was not suitable for unrestricted application with passive sampling at concentrations below the OEL because of interferences resulting from the large reagent excess.

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