

# Validation of Transferability of DBA Derivatization and LC–MS/MS Determination Method for Isocyanates via an Interlaboratory Comparison

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An adapted method for the quantitative determination of isocyanates in air was implemented and validated in-house. The method was based on air sampling using an impinger flask containing di-*n*-butylamine (DBA) in toluene and a glass fibre filter in series. The DBA derivatives were determined using liquid chromatography and tandem mass spectrometry. Studied isocyanates were isophorone diisocyanate, isocyanic acid (ICA), methyl isocyanate, ethyl isocyanate, propyl isocyanate, hexamethylene diisocyanate (HDI), 2,6- and 2,4-toluene diisocyanate, 4,4'-methylene diphenyl diisocyanate (MDI), phenyl isocyanate (PhI), MDI oligomers and different HDI adducts. Monitoring of selected reactions resulted in quantifications with correlation coefficients >0.995, within-batch relative standard deviation (RSD) of repeatability was <13% for all analytes. Between-batch RSD (reproducibility) was determined for all the compounds with the exception of the adducts and oligomers and was also <13%. As an additional validation procedure, the method was evaluated by exchanging field (air) and standard samples between two laboratories. The RSDs observed by the two laboratories were comparable. The concentrations determined were between 80 and 120% of each other, depending on the analyte and the individual concentrations. The method was applied in a large field study on exposure of workers in car repair shops and industrial painters with >500 samples.

**Keywords:** DBA; interlaboratory method comparison; isocyanates; liquid chromatography mass spectrometry

## INTRODUCTION

Isocyanates are widely used in industry in the production and processing of polyurethane (PUR) products, such as soft and rigid foam, adhesives, elastomers, coatings and lacquers. PUR is one of the most commonly used plastics. In the year 2000, the total PUR market was 9.3 million tonnes (Thorpe, 2002). For industrial production of PUR, technical grade isocyanates are mainly used. These products contain a variety of different isocyanates and isomers with different number of isocyanate (NCO) groups, commonly

based on the monomers of hexamethylene diisocyanate (HDI), toluene diisocyanate (TDI), methylene diphenyl diisocyanate (MDI) or isophorone diisocyanate (IPDI). Isocyanate adducts of lower volatility than the monomeric isocyanates such as biuretes, isocyanurates or allophanates are frequently used in technical grades of the aliphatic diisocyanates HDI and IPDI to reduce exposure. Technical MDI products (i.e. polymeric MDI) contain several MDI isomers and oligomeric derivatives of MDI with increasing number of aromatic rings with a varying composition depending on the mix. The most commonly used technical mixes of TDI contain mixtures with different ratios (e.g. 80/20 and 65/35) of the 2,6- and 2,4-TDI isomers.

During the production and processing of PUR products, exposures to isocyanates have been described for

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a wide range of applications such as manufacturing of soft and rigid foam (Tinnenberg *et al.*, 1997; Kääriä *et al.*, 2001a,b), molding of elastomeres (Marand *et al.*, 2004), spray foaming (Crespo and Galan, 1999) and spray painting (Myer *et al.*, 1993; Rudzinski *et al.*, 1995; Maître *et al.*, 1996; Woskie *et al.*, 2004). Exposure to isocyanates has also been reported during work operations that involve thermal degradation of the PUR polymer such as processing of PUR-coated metal sheet in car repair shops, flame lamination of PUR with textiles and welding in district heating pipes (Karlsson *et al.*, 2000, 2001; Dahlin *et al.*, 2004). In addition to the complex mixture of isocyanates in both gas and particle phase that are generated during thermal degradation of PUR, other compounds such as amines, aminoisocyanates and anhydrides have also been reported previously (Karlsson *et al.*, 2002; Dahlin *et al.*, 2004). Monoisocyanates such as isocyanic acid (ICA) and methyl isocyanate (MIC) can also be emitted during thermal degradation of other nitrogen-containing polymers (Karlsson *et al.*, 1998, 2000).

Exposure to isocyanate monomers is a well-known risk and is mainly associated with respiratory disorders, such as asthma, airway irritations and hypersensitivity pneumonitis (Bernstein, 1996; Wisniewski and Redlich, 2001). Also polyisocyanates are known to cause occupational asthma and other respiratory effects (Vandenplas *et al.*, 1992, 1993a,b; Eifan *et al.*, 2005).

Because of their importance, in the past decades several chromatographic methods for the determination of isocyanates in air have been described in the literature (Warwick *et al.*, 1981; Spanne *et al.*, 1996; Streicher *et al.*, 1996; Wu *et al.*, 1987; Vangrosveld *et al.*, 2003).

In 2003–2005, a large isocyanate exposure study in spray painting industries was performed at TNO in collaboration with the Institute for Risk Assessment Sciences. In addition to the assessment of exposure to isocyanates, related health effects and exposure–response relationships of workers were evaluated by Pronk *et al.*, 2006a,b and Pronk *et al.*, 2007. For this study, a method for determination of diisocyanates, isocyanates oligomers and adducts as well as thermal degradation products such as monoisocyanates, aminoisocyanates and amines was needed. The method should be specific, robust, easily implemented and reliable. Both quantitation and identification of the detected isocyanates should be achieved. Based on published results, the method based on liquid chromatography (LC)–mass spectrometry (MS/MS) determination of isocyanates as di-*n*-butylamine (DBA) derivatives described by Karlsson *et al.* (2000, 2005) was selected and implemented at TNO. In addition to isocyanates and their oligomers and adducts, also amines and aminoisocyanates could be determined as carbamate esters

by reacting the amine groups with ethyl chloroformate described by Karlsson *et al.* (2002). The method has recently been accepted as an International Organisation for Standardisation (ISO) method for determining isocyanates, aminoisocyanates and amines in work place air (ISO 7734–1, 2006a,b).

The purpose of this study was to perform a within-laboratory validation for isocyanate determination with the implemented method and to perform additional evaluation of the method by exchanging field and standard samples between two laboratories and comparing the results.

The validated method was applied to hundreds of field samples from task-related air sampling in car paint shops and industrial spray painters. Detailed results of the field studies were published elsewhere (Pronk *et al.*, 2006a,b, 2007).

## EXPERIMENTAL

### Chemicals

Acetonitrile, toluene, ethyl chloroformate, sodium hydroxide pellets, pyridine, formic acid and ethanol were all purchased from Merck (Darmstadt, Germany). DBA was purchased from Sigma (Zwijndrecht, The Netherlands) and LC–MS grade methanol from Biosolve (Valkenswaard, The Netherlands). Purified water used for *high performance liquid chromatography* (HPLC) was prepared by the ELGA system. Standards of the underivatized isocyanate standards 1,6-HDI, 2,6-TDI, 2,4-TDI and IPDI and 4,4'-MDI were purchased from Sigma and were of >97% purity.

### Standards and internal standards

Internal standard solutions containing (i) DBA derivatives of d3-MIC, d4-HDI, d3-2,4-TDI, d3-2,6-TDI and d2-4,4'-MDI ( $1 \mu\text{g ml}^{-1}$ ), (ii) d9-DBA derivatives of ICA, MIC, ethyl isocyanate (EIC), propyl isocyanate (PIC), phenyl isocyanate (PhI), HDI, 2,4-TDI, 2,6-TDI, IPDI and MDI ( $1 \mu\text{g ml}^{-1}$ ) and (iii) d9-DBA-derivatized HDI-biuret ( $1 \mu\text{g ml}^{-1}$ ), HDI-isocyanurate ( $1 \mu\text{g ml}^{-1}$ ), HDI-dibiuret ( $0.3 \mu\text{g ml}^{-1}$ ) and HDI-diisocyanurate ( $0.3 \mu\text{g ml}^{-1}$ ) were used for the validation of the method and analysis of the field samples.

Different standard solutions used for quantification contained (i) DBA derivatives of ICA, MIC, EIC, PIC, PhI, HDI, 2,4-TDI, 2,6-TDI, 4,4'-MDI and IPDI-isomers with a concentration of  $1 \mu\text{g ml}^{-1}$ , (ii) DBA derivatives of HDI-biuret ( $1 \mu\text{g ml}^{-1}$ ), HDI-dibiuret ( $1 \mu\text{g ml}^{-1}$ ), HDI-isocyanurate ( $0.3 \mu\text{g ml}^{-1}$ ) and HDI-diisocyanurate ( $0.3 \mu\text{g ml}^{-1}$ ) and (iii) DBA derivatives of 4,4'-MDI ( $10 \mu\text{g ml}^{-1}$ ), 3-ring MDI ( $5.9 \mu\text{g ml}^{-1}$ ), 4-ring MDI ( $2.3 \mu\text{g ml}^{-1}$ ) and 5-ring MDI ( $0.74 \mu\text{g ml}^{-1}$ ).

The preparation of the standard and internal standard solutions has been described elsewhere (Dahlin *et al.*, 2004; Karlsson *et al.*, 2005).

#### Field sampling for airborne exposures

Task-based personal air samples were collected at 1000 ml min<sup>-1</sup> using midjet impingers, containing 10 ml DBA in toluene with a glass fibre filter in series, attached to the lapel (Karlsson *et al.*, 2001). More details about the sampling procedure were described elsewhere (Pronk *et al.*, 2006a,b). After sampling, the samples were transferred into vials, sealed and stored at 4°C until further processing. For samples where high concentrations of analytes were expected, also a 10-fold dilution with the internal standard solution was performed.

#### Sample preparation

*Air samples and samples of thermal degradation of PUR foams.* An aliquot of 2 ml of the derivatized sample solution was transferred into a vial and internal standard (10 µl of one or both) solutions were added; the toluene was evaporated and the sample was dissolved in 200 µl of acetonitrile, assisted by sonification. The sample was then transferred into an autosampler vial and stored at 4°C until further analysis. The concentration factor of the air sample preparation is 10; PUR thermal degradation samples were not concentrated.

*Technical products.* Derivatized solutions of two technical products (DuPont XK 205 and Standox HS 15-25, used for validation) were prepared by dissolving ~10 mg of the individual product in 50 ml of toluene. The 0.25 ml of this solution was diluted with 0.01 mol l<sup>-1</sup> solution of DBA in toluene to a final volume of 5 ml. The solvent was evaporated to dryness and the residue was reconstituted in 5 ml of acetonitrile. The 190 µl of the solutions and 10 µl of internal standards were added to autosampler vials. The vials were properly sealed and stored at 4°C until further analysis.

#### Calibration

Isocyanates were quantified using suitable internal standards (d2-d4-labelled derivatives) according to

Table 1. In addition, isocyanates were quantified using their d9-DBA-derivatized analogue as internal standard. The calibration range (six dilutions and one blank containing the IS solution) during the within-laboratory validation and the field study was (i) 11–420 ng ml<sup>-1</sup> for 1,6-HDI, 4,4'-MDI, 2,4-TDI and 2,6-TDI, (ii) 5.5–526 ng ml<sup>-1</sup> for ICA-DBA, MIC-DBA, EIC-DBA, PIC-DBA, Phi-DBA, IPDI-DBA and (iii) 4–227 ng ml<sup>-1</sup> for the IPDI-DBA isomers.

MDI oligomers (3-, 4- and 5-ring MDI) were quantified using dilutions (five dilutions and a blank with the IS) of a well-characterized DBA-derivatized technical mixture as an external standard solution. The range was 30–3000 ng ml<sup>-1</sup> for 3-ring MDI, 22–1000 ng ml<sup>-1</sup> for 4-ring MDI and 37–370 ng ml<sup>-1</sup> for 5-ring MDI.

HDI-isocyanurate, -diisocyanurate and -biuret were quantified using a well-characterized DBA-derivatized technical mixture as an external standard solution; the range was 20–700 ng ml<sup>-1</sup> for isocyanurate and biuret and 6–90 ng ml<sup>-1</sup> for diisocyanurate (five dilutions and a blank containing IS were used for calibration).

#### Within-laboratory validation

Linearity, instrumental within-batch and between-batch relative standard deviations (RSDs) were determined. For the 'monomeric' compounds, standard dilutions (15 and 100 ng ml<sup>-1</sup>) of all compounds with the exception of IPDI isomer (8 and 40 ng ml<sup>-1</sup>) and 1,6-HDI, 4,4'-MDI, 2,4-TDI and 2,6-TDI (30 and 200 ng ml<sup>-1</sup>) were prepared and used as validation samples. Linearity was determined in the ranges described above (see Calibration). Instrumental within-batch RSD (repeatability) was determined by analyzing five replicates of the two validation samples. Between-batch RSD (reproducibility) was determined by analyzing three individual batches, each with five replicates of the validation samples. Between-batch RSD was then calculated using analysis of variance.

For the MDI oligomers and HDI adducts, only the within-batch RSD of the method was determined using dilutions of derivatized technical products with

Table 1. Determined concentrations (ng ml<sup>-1</sup>) in the exchanged control samples

Isocyanate	Laboratory 1	RSD (%)	Laboratory 2	RSD (%)	Lab 1/Lab 2 (%)
2,4-TDI-DBA	667	6	670	2	100
2,6-TDI-DBA	805	3	671	1	120
1,6-HDI-DBA	643	3	663	1	97
4,4-MDI-DBA	552	4	664	2	83
2,4-TDI-DBA	23	4	24	1	97
2,6-TDI-DBA	27	4	23	2	117
1,6-HDI-DBA	21	3	22	2	94
4,4-MDI-DBA	23	4	24	3	95

the oligomers and adducts present at unknown concentrations. Linearity of the method was determined using characterized derivatized technical mixtures that were used as calibration solutions (see Calibration).

The instrument limit of detection (LOD) was defined as signal to noise ratio of 3. The limit of quantification (LOQ) of the monomers in the impinger liquid was set equal to the lowest calibration standard corrected for the concentration factor and corrected for the blank signal, if present.

Not all analytes were available as non-derivatized standards, the recovery was therefore determined only for 4,4'-MDI, 1,6-HDI, 2,4-TDI, 2,6-TDI and IPDI. DBA solution in toluene was spiked with these compounds at a concentration level of 100 ng ml<sup>-1</sup>. These samples were further processed as described in sample preparation. The recovery was determined in two separate batches, in each batch in duplicate.

#### *Between-laboratory evaluation*

In order to evaluate the performance of the implemented method, several types of samples were exchanged: (i) several different samples from thermal degradation of MDI and TDI PUR foams, (ii) several dilutions of a field sample containing HDI adducts and (iii) two dilutions of a standard containing 2,4-TDI-DBA, 2,6-TDI-DBA, 4,4'-MDI-DBA and 1,6-HDI-DBA (control samples). All samples used for the interlaboratory evaluation were prepared at Laboratory 2, shipped to Laboratory 1 together with the corresponding IS and calibration solutions and were analyzed by both laboratories. In order to distinguish between the comparison of the instrumental performance at both laboratories and the sample processing procedure, Laboratory 1 received aliquots of both the original sample (in DBA solution) and an aliquot of the sample processed by Laboratory 2 (addition of IS, evaporated and redissolved in acetonitrile).

*Thermal degradation of PUR foams.* Duplicate air samples were collected during thermal degradation of MDI and TDI-based PUR foam. The PUR foam was thermally degraded using a heating gun. The procedure was repeated six times and the amount of foam was varied to obtain samples containing different amounts of isocyanates. Aliquots of the collected samples ( $n = 12$ ) were analyzed by Laboratories 1 and 2.

Field samples containing HDI adducts consisted of two air samples collected during a spray painting operation. The samples were diluted 10 and 100 times and the dilutions were treated as separate samples. Aliquots of the samples were analyzed by Laboratory 1 and 2.

*Control samples.* These samples were prepared by Laboratory 2 by diluting two standard solutions of

2,4-TDI-DBA, 2,6-TDI-DBA, 4,4'-MDI-DBA and 1,6-HDI-DBA (at two concentration levels, ~20 and 600 ng ml<sup>-1</sup>, 10 replicates each). Five replicates were analyzed by Laboratory 2; 5 aliquots were shipped to Laboratory 1.

#### *Analysis*

*Laboratory 1.* The compounds were separated by Alliance HPLC (Waters, Altrincham, Cheshire, UK) using a Waters XTerra RP18, 150 × 2.1 mm, 3.5 μm particles HPLC column with a Waters XTerra, RP18, 10 × 2.1 mm × 5 μm guard column. The injection volume was 10 μl, and the autosampler temperature was maintained at 10°C. A water, acetonitrile, methanol and formic acid gradient was used, with a flow of 0.3 ml min<sup>-1</sup>. The analysis time was 20 min including the conditioning of the column. The mobile phase was composed of A: 5/95/0.05 acetonitrile/water/formic acid (v/v/v), B: 5/70/25/0.05 water/acetonitrile/methanol/formic acid (v/v/v/v) and C: 100/0.05 acetonitrile/formic acid (v/v). Gradient elution was performed from 30 to 90% B in 12.5 min and then 100% C in 0.1 min followed by isocratic elution with 100% C during additional 7 min.

The compounds were detected using a Quattro Ultima triple quadrupole mass spectrometer equipped with the Micromass ESI source in the positive ion mode (Waters). The capillary voltage was 3.5 kV, the vaporizer temperature was 250°C, the temperature of the source was 130°C, sheath gas flow was 132 l h<sup>-1</sup> and auxiliary gas flow was 612 l h<sup>-1</sup>. For quantification, selective reaction monitoring was used. Collision induced dissociation was performed using argon as collision gas and the pressure in the collision cell was 4 × 10<sup>-3</sup> mbar. Cone voltage and collision energies were optimized for each monitored reaction. MS/MS spectra and collision energies were similar to those described in the literature (Karlsson *et al.*, 2005). The most abundant reactions were selected for monitoring, one for each analyte.

*Laboratory 2.* The method of Laboratory 2 was published elsewhere by Karlsson *et al.* (2005).

## RESULTS AND DISCUSSION

#### *The method*

The method as described in the literature by Karlsson *et al.* (2005) was implemented by Laboratory 1. By adding methanol to the mobile phase, a change in selectivity was achieved and a reduction of acetonitrile adduct formation on the instrument used by Laboratory 1. A total of 16 compounds (excluding internal standards) were analyzed by a single injection per sample. During method development for the HDI adducts, in addition to the standards, two

products commonly used by the Dutch car repair shops included in this study were also analyzed.

Examples of chromatograms of two positive samples from a car paint shop (A) and a welding shop (B) are shown in Figure 1.

IPDI oligomers were not included in the study as they were of no relevance to the field study to which the method was applied.

#### Validation of the method in Laboratory 1

**Monomers.** For the monomers, the method was validated using standard solutions and field samples. The instrumental limits of detection for the studied compounds were comparable to previously presented results (Karlsson *et al.*, 2005) and ranged from 1 to 5 pg absolute on column. The LOQ ranged from 5 to 10 ng ml<sup>-1</sup>.

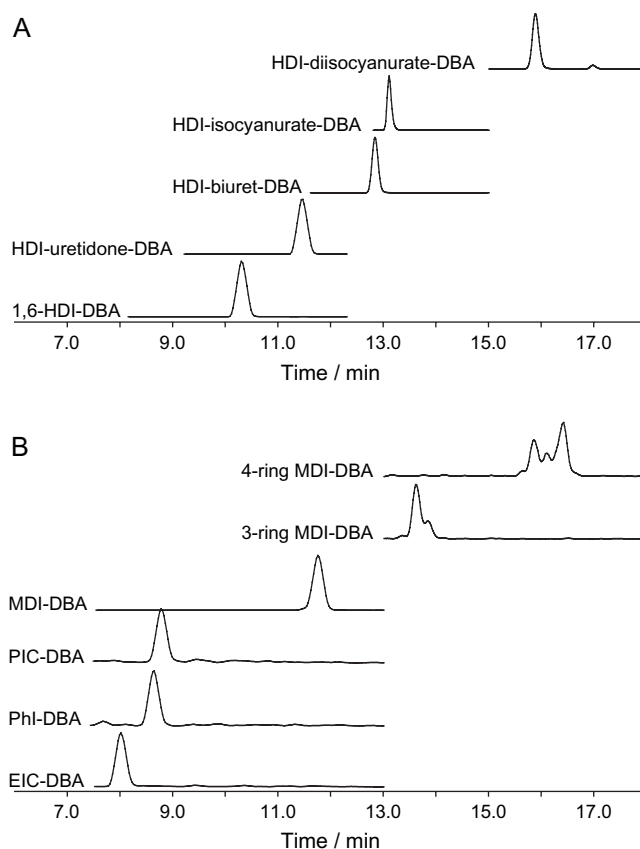
The method is linear in the studied range for all the compounds with  $r^2$  ranging from 0.995 to 0.999. However, for samples containing >500 ng ml<sup>-1</sup>, saturation of the peaks was observed.

For both within- and between-batch instrumental RSD, the criterion of 20% was met for all the analytes. The within-batch variations of the entire sample preparation procedure were determined for a number

of compounds present in a field sample and were comparable to those observed when a derivatized standard sample was used. The RSD varied from 1% for IPDI-DBA to 10% for 2,6-TDI-DBA.

Due to the limited availability of underderivatized standards, recoveries were determined only for 1,6-HDI (97%), 2,6-TDI (92%), 2,4-TDI (96%), IPDI (94%) and 4,4'-MDI (86%). The recoveries were determined as described in the literature (Karlsson *et al.*, 2002). The determined recoveries were partly affected by the purity of the used isocyanates (97–98%) and the lower recovery of MDI is probably caused by polymerization of the product.

**Adducts and oligomers.** Validation was performed with DBA-derivatized solutions of two products commonly used by the companies involved in the field study (one HDI-based and one MDI-based product) and the available standards. For this purpose, only relative concentrations (with respect to an internal standard) were used. The absolute concentrations of the individual adducts and oligomers were not determined. For the adducts and oligomers, the criteria for the within-batch RSD (repeatability) were met for all the analytes. Between-batch RSD (reproducibility) was not determined.



**Fig. 1.** Examples of chromatograms of positive isocyanate exposure samples from a car paint shop (A) and a welding shop (B).

Linearity was determined by analyzing the calibration solutions. In the studied range, the method was linear for all analytes with  $r^2$  ranging from 0.998 to 0.999. The instrumental LOD of the oligomers and the adducts, ranging from 200 to 500 pg, is much higher than the LOD determined for the monomeric compounds, if expressed in weight. If LOD is corrected for molar weight of the monomers and oligomers, the LOD of both groups is similar.

#### Between-laboratory evaluation

All performed experiments showed a good correlation of the concentrations determined by both laboratories.

For the control samples, the concentrations of 2,4-TDI-DBA, 2,6-TDI-DBA, 4,4'-MDI-DBA and 1,6-HDI-DBA in a standard dilution determined by Laboratory 1 were 80–120% of those determined by Laboratory 2 and the results are shown in Table 1. The differences can be explained by differences in the calibration.

Figure 2 shows the correlation of the results obtained by analyzing the PUR thermal degradation sample where ICA, PHI, 2,4-TDI, 2,6-TDI and 4,4-TDI were detected (top) and the field sample containing HDI adducts (bottom). The concentrations determined by both laboratories show a very good correlation, independent of where the sample processing took place.

No difference in the correlation of the results was observed when using d9-DBA-derivatized isocyanates as internal standards compared to d2-4-labelled isocyanates DBA derivatives.

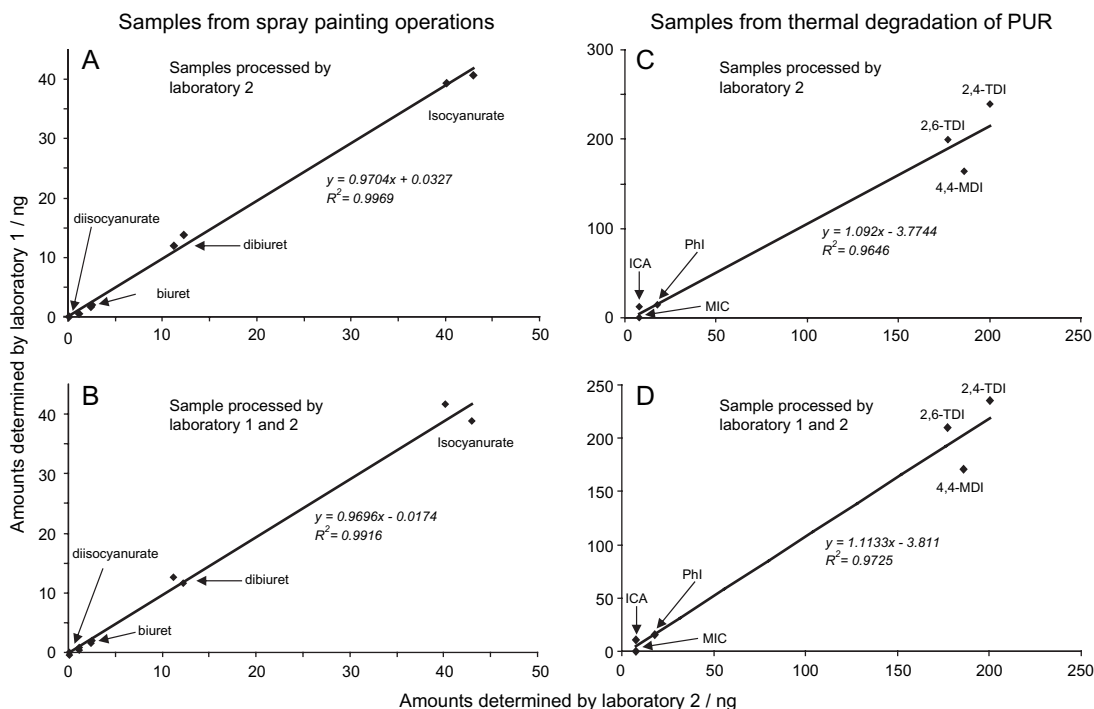
#### Field samples

More than 500 task-based air samples were taken for different tasks in Dutch car body repair shops and industrial painters and were analyzed by the implemented method. The design and results of the study for all compounds with the exception of amines have been described by Pronk *et al.* (2006a,b).

### CONCLUSIONS

The method described in the literature and in the recently accepted ISO standards was adapted and validated in-house. The validation results showed performance characteristics similar to those described in the literature. As an additional evaluation of the method, samples and standards were exchanged between two laboratories. The determined concentrations of several isocyanates and HDI adducts show very good correlation, demonstrating the robustness of the method.

The implemented and validated method was applied in a large field study in The Netherlands. Hundreds of samples were successfully analyzed.



**Fig. 2.** Interlaboratory evaluation: correlation of determined concentrations of isocyanates in a PUR degradation sample and HDI adducts in a field respiratory exposure sample. Samples were prepared by Laboratory 2.

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