Isocyanates, Amines and Alkanolamines
Sampling, Chromatography and Detection

Jakob B Riddar
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Jakob B Riddar

Doctoral Thesis
Department of Analytical Chemistry
Stockholm University
Abstract

Isocyanates, aromatic-, aliphatic- and alkanolamines are commonly used in the industry today. Millions of workers in Europe are exposed. The most frequent health symptoms are respiratory and dermal disorder. Due to the health risk most of the compounds in this thesis are regulated by authorities and have occupational exposure limits (OELs). Consequently, reliable and robust air sampling methods are urgently needed.

In this thesis dry samplers for isocyanates, aliphatic- and alkanolamines have been developed and evaluated. The isocyanate sampler is now a commercial product (ASSET EZ4-NCP Dry Sampler, Supelco). The samplers were based on a denuder with a filter in series. The denuder and filter were impregnated with di-n-butylamine for the isocyanate sampler and with sulphuric acid for the aliphatic- and alkanolamine sampler.

The robustness of the dry samplers was extensively evaluated. This was performed in a climate chamber containing a controlled atmosphere of the studied compounds.

New methods based on hydrophilic interaction liquid chromatography (HILIC) coupled with tandem mass spectrometry (MSMS) were developed for determination of aromatic-, aliphatic- and alkanolamines in aqueous solutions. Isocyanates were determined by reversed-phase liquid chromatography MSMS.

HILIC in combination with MS is a most powerful system, and highly sensitive determinations, several orders of magnitude below the OELs, of polar compounds present in the work environment can be accomplished.

The selected samplers enable sampling during short sampling times and for whole work shifts. The samplers can be stored for months before and after sampling. The performance of the samplers was unaffected by variation in temperature, humidity, flow-rate and pre- and post-sampling of ambient air.

Sampling for the compounds studied is now greatly simplified, and assessment of the work environment is facilitated.
List of Papers

The thesis is based on the papers listed below. References to papers in the text are assigned with roman numerals. All published papers are reproduced with permission of the publishers.


*The author was responsible for the evaluation of sampling pumps, planning and conducting some of the laboratory work and some of the writing*


*The author was responsible for developing the characterization methodology, planning and conducting most of the laboratory work, and most of the writing*


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The author was responsible for developing the characterization methodology, planning and conducting most of the laboratory work, and most of the writing


The author was responsible for developing the characterization methodology, planning and conducting most of the laboratory work, and most of the writing
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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-TDA</td>
<td>2,4-toluenediamine</td>
</tr>
<tr>
<td>2,6-TDA</td>
<td>2,6-toluenediamine</td>
</tr>
<tr>
<td>2-MP</td>
<td>1-(2-methoxyphenyl)piperazine</td>
</tr>
<tr>
<td>2-PP</td>
<td>1-(2-Pyridyl)piperazine</td>
</tr>
<tr>
<td>4’4-MDA</td>
<td>4’4-methylenedianiline</td>
</tr>
<tr>
<td>AA</td>
<td>allylamine</td>
</tr>
<tr>
<td>APS</td>
<td>Aerodynamic Particle Sizer</td>
</tr>
<tr>
<td>BCEC-Cl</td>
<td>2-(11H-benzo[a]-carbazol-11-yl) ethyl chloroformate</td>
</tr>
<tr>
<td>BCEOC</td>
<td>1,2-benzo-3,4-dihydrocarbazole-9-ethyl chloroformate</td>
</tr>
<tr>
<td>BSA</td>
<td>N,O-bistrimethylsilyllacetamide</td>
</tr>
<tr>
<td>BSC</td>
<td>benzenesulfonyl chloride</td>
</tr>
<tr>
<td>C18</td>
<td>octadecylsilica</td>
</tr>
<tr>
<td>CE</td>
<td>Capillary Electrophoresis</td>
</tr>
<tr>
<td>CHA</td>
<td>cyclohexylamine</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical ionization</td>
</tr>
<tr>
<td>CID</td>
<td>Collision Induced Dissociation</td>
</tr>
<tr>
<td>CLND</td>
<td>Chemiluminescent Nitrogen Detector</td>
</tr>
<tr>
<td>Dabsyl</td>
<td>4-dimethylaminoazobenzene-4'-sulfonyl chloride</td>
</tr>
<tr>
<td>DAN</td>
<td>1,8-diaminonaphthalene</td>
</tr>
<tr>
<td>Dansyl</td>
<td>5-(dimethylamino)naphthalene-1-sulfonyl chloride</td>
</tr>
<tr>
<td>DBA</td>
<td>di-n-butylamine</td>
</tr>
<tr>
<td>DEA</td>
<td>diethylamine</td>
</tr>
<tr>
<td>DEAA</td>
<td>diethanolamine</td>
</tr>
<tr>
<td>DEEAA</td>
<td>diethylethanolamine</td>
</tr>
<tr>
<td>DIPA</td>
<td>diisopropylamine</td>
</tr>
<tr>
<td>DIPAA</td>
<td>diisopropanolamine</td>
</tr>
<tr>
<td>DPEAA</td>
<td>diisopropylethanolamine</td>
</tr>
<tr>
<td>DMEA</td>
<td>dimethylethylamine</td>
</tr>
<tr>
<td>DMEA</td>
<td>Dimethylethanolamine</td>
</tr>
<tr>
<td>DNB</td>
<td>3,5-dinitrobenzoyl chloride</td>
</tr>
<tr>
<td>DNFB</td>
<td>1-fluoro-2,4-dinitrobenzene</td>
</tr>
<tr>
<td>EA</td>
<td>ethylamine</td>
</tr>
<tr>
<td>EAA</td>
<td>Ethylamine</td>
</tr>
<tr>
<td>EC</td>
<td>Electrochemical detection</td>
</tr>
<tr>
<td>ECD</td>
<td>Electron capture detection</td>
</tr>
<tr>
<td>ES</td>
<td>Electrospray</td>
</tr>
<tr>
<td>ESI</td>
<td>Electro Spray ionisation</td>
</tr>
<tr>
<td>ETCF</td>
<td>Ethyl chloroformate</td>
</tr>
</tbody>
</table>
PAC  9-anthracenylmethyl-1-piperazinecarboxylate
PAD  Pulsed Amperometric Detection
pCEC Capillary High-Performance Liquid Chromatography
PFBay pentafluorobenzaldehyde
PFPA pentafluoropropionic anhydride
PhI  phenyl isocyanate
PITC  phenyl isothiocyanate
pMDI  polymeric methylene diphenyl diisocyanates
PPIA  2-(2-phenyl-1H-phenanthro-[9,10-d]imidazole-1-yl)-acetic acid
PTR-MS Proton Transfer Reaction Mass Spectrometry
PUR  polyurethane
Q3  Triple Quadrupole
RH  Relative Humilitites
RP  Reversed Phase
SAMF  6-oxy-(N-succinimidyl acetate)-9- (2′-methoxycarbonyl) fluorescein
SDME  Single-drop Micro Extraction
SIFA  N-hydroxysuccinimidyl fluorescein-O-acetate
SIR  Selective Ion Recording
SMPS  Scanning Mobility Particle Sizer Spectrometers
SPE  Solid-Phase Extraction
SPME  Solid-Phase MicroExtraction
STEL  Short-Term Exposure Limit
TBCF  tertbutyl chloroformate
TCECF  trichloroethyl chloroformate
TDA  toluenediamine
TDI  toluene diisocyanate
TDS  Thermal Desorption System
TEA  triethylamine
TEAA  triethanolamine
TFAA  Trifluoroacetic anhydride
TLC  Thin Layer Chromatography
TLV  Threshold Limit Value
TMCS  trimethylchlorosilane
TMPAB-Osu  8-phenyl-(4-oxy-acetic acid N-hydroxysuccinimidyl ester)-4,4-
difluoro-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene
TRIG  Total Reactive Isocyanate Group
Tryptamine  3-(2-aminoethyl)indole
TSD  Therospecific Detector
TSIM  trimethylsilylimidazole
TWA  Time Weighted Average
UV  Ultraviolet (detection)
VOC  volatile chemical ionization
ZIC  Zwitterionic
1 Sammanfattning (in Swedish)

Isocyanater används främst för produktion av polyuretan-baserade plast, lack, lim m m. Exponering för isocyanater kan ge upphov främst luftvägsproblem som t ex astma. Isocyanaterna kan omvandlas till aminer och de motsvarande aromatiska aminerna kan ge cancer. Alifatiska aminer finns både i biologiska system och i plast-, medicin-, textil-, kosmetika- och metallindustrin. De är mycket flyktiga, har en skämd lukt och irriterar ögon och luftvägar. Alkanolaminer används i plast-, medicin-, textil-, kosmetika-, gasutvinning- och metallindustrin och exponering sker både mot hud och luftvägar vilket kan ge upphov till hudallergiska besvär samt astma.

Avhandlingen tar främst upp luftprovtagning av isocyanater, alifatiska- och alkanolaminer för att användas till kontroll av luften i arbetsmiljön. Tidigare har provtagningen skett med glassflaskor med vätskor vilket är opraktiskt i fält. En tidigare utvecklad torr provtagare där isocyanaterna skyddas genom att reagera dem med dibutylamin vidareutvecklades och testades utförligt för isocyanater. Den torra provtagaren anpassades för att kunna provta aminer genom att ersätta dibutylamin med svavelsyra som omvandlar aminerna till salt och därför mindre flyktiga. Aromatiska aminer bestämdes från mjukt skum som används i t ex madrasser, tvättvampar m m.


Kombinationen av provtagare och analysmetoder gav att lufthalter kunde mätas som var tio till hundra gånger under de gränsvärden som satts upp för lufthalter.
Bild över genererings- och exponeringskamrarna samt provtningsuppställning.
Bild över upparbetning av provtagare, samt analys av prov.
2 Introduction

2.1 Studied compounds

2.1.1 Isocyanates

In this thesis five of the most common diisocyanates in polyurethane (PUR) production and six monoisocyanates associated with decomposition of PUR were studied (Table 1).

Table 1. Aromatic amines associated with polyurethane-production, abbreviation, structure, molecular weight and vapour pressure.

<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviation</th>
<th>Structure</th>
<th>Molecular weight (g/mol)</th>
<th>Vapour pressure at 25°C (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isocyanic acid</td>
<td>ICA</td>
<td></td>
<td>43</td>
<td>90000</td>
</tr>
<tr>
<td>Methyl isocyanate</td>
<td>MIC</td>
<td></td>
<td>57</td>
<td>71000</td>
</tr>
<tr>
<td>Ethyl isocyanate</td>
<td>EIC</td>
<td></td>
<td>71</td>
<td>28000</td>
</tr>
<tr>
<td>Propyl isocyanate</td>
<td>PIC</td>
<td></td>
<td>85</td>
<td>11000</td>
</tr>
<tr>
<td>Butyl isocyanate</td>
<td>BIC</td>
<td></td>
<td>99</td>
<td>2600</td>
</tr>
<tr>
<td>Phenyl isocyanate</td>
<td>PhI</td>
<td></td>
<td>119</td>
<td>280</td>
</tr>
<tr>
<td>Hexamethylene diisocyanate</td>
<td>1,6-HDI</td>
<td><img src="image" alt="" /></td>
<td>168</td>
<td>2.2</td>
</tr>
<tr>
<td>Isophorone diisocyanate</td>
<td>IPDI</td>
<td><img src="image" alt="" /></td>
<td>222</td>
<td>0.34</td>
</tr>
</tbody>
</table>
2.1.2 Aromatic amines

Among the many aromatic amines that have industrial applications this thesis is limited to three aromatic amines mainly related with the production of isocyanates, namely 2,4- toluenediamine (2,4-TDA), 2,6-toluenediamine (2,6-TDA) and 4’4'-methyleneedianiline (4’4'-MDA) (Table 2).

Table 2. Aromatic amines associated with isocyanate-production, Abbreviation, structure, molecular weight and vapour pressure.

<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviation</th>
<th>Structure</th>
<th>Molecular weight (g/mol)</th>
<th>Vapour pressure at 25°C (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-Toluene diisocyanate</td>
<td>2,4-TDI</td>
<td><img src="image" alt="Structure" /></td>
<td>147</td>
<td>2.8</td>
</tr>
<tr>
<td>2,6-Toluene diisocyanate</td>
<td>2,6-TDI</td>
<td><img src="image" alt="Structure" /></td>
<td>174</td>
<td>3.2</td>
</tr>
<tr>
<td>4,4’- Methylene bisphenyl isocyanate</td>
<td>4,4’-MDI</td>
<td><img src="image" alt="Structure" /></td>
<td>250</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

2.1.3 Aliphatic amines

Aliphatic monoamines are extensively used in the industry and appear in various applications and locations. The aliphatic amines studied in this thesis are limited to those aliphatic monoamines that have Occupational Exposure Limits (OEL) in Sweden (Table 3).
Table 3. Aliphatic amines with OEL-regulation, Abbreviation, structure, molecular weight and vapour pressure.

<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviation</th>
<th>Structure</th>
<th>Molecular weight (g/mol)</th>
<th>Vapour pressure at 25°C (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylamine</td>
<td>EA</td>
<td>(\text{NH}_2)</td>
<td>45</td>
<td>150000</td>
</tr>
<tr>
<td>Isopropylamine</td>
<td>IPA</td>
<td>(\text{NH}_2)</td>
<td>59</td>
<td>81000</td>
</tr>
<tr>
<td>Allylamine</td>
<td>AA</td>
<td>(\text{NH}_2)</td>
<td>57</td>
<td>33000</td>
</tr>
<tr>
<td>N-Butylamine</td>
<td>NBA</td>
<td>(\text{NH}_2)</td>
<td>73</td>
<td>13000</td>
</tr>
<tr>
<td>Diethylamine</td>
<td>DEA</td>
<td>(\text{N} )</td>
<td>73</td>
<td>29000</td>
</tr>
<tr>
<td>Diisopropylamine</td>
<td>DIPA</td>
<td>(\text{N} )</td>
<td>101</td>
<td>9900</td>
</tr>
<tr>
<td>Dimethylethylamine</td>
<td>DMEA</td>
<td>(\text{N} )</td>
<td>73</td>
<td>66000</td>
</tr>
<tr>
<td>Triethylamine</td>
<td>TEA</td>
<td>(\text{N} )</td>
<td>101</td>
<td>7500</td>
</tr>
<tr>
<td>Cyclohexylamine</td>
<td>CHA</td>
<td>(\text{NH}_2)</td>
<td>99</td>
<td>1100</td>
</tr>
</tbody>
</table>

2.1.4 Alkanolamines

In this thesis a selection of alkanolamines was made based on OELs and industrial application (Table 4).

Table 4. Alkanolamines with OEL-regulation and/or industrial application, Abbreviation, structure, molecular weight and vapour pressure.

<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviation</th>
<th>Structure</th>
<th>Molecular weight (g/mol)</th>
<th>Vapour pressure at 25°C (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylalcoholamine</td>
<td>EAA</td>
<td>(\text{NH}_2)</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>N-Propylalcoholamine</td>
<td>NPAA</td>
<td>(\text{NH}_2)</td>
<td>75</td>
<td>23</td>
</tr>
</tbody>
</table>
2.2 Properties and Occurrence

2.2.1 Isocyanates

Isocyanates are characterised by the presence of at least one isocyanate group (\(-N=C=O\)). This makes most isocyanates strong electrophiles reacting easily with active hydrogen-containing nucleophiles. Reactivity is further dependent on structure and the number of functional groups, with aromatic isocyanates normally more reactive than aliphatic isocyanates due to electron resonance. Reactivity is also dependent on the hydrogen-containing nucleophile reacting with the isocyanate in the following order: aliphatic amine > aromatic amine > alcohol > phenols > thiols. An isocyanate compound containing more than one isocyanate group can undergo polymerisation in the presence of a nucleophile containing two or more active hydrogen groups. With diamine present the reaction leads to the formation of polyurea, if a dialcohol or diphenol is used polyurethane will be the result (Figure 1).
Isocyanates are manufactured by reacting amines with phosgene. Due to the severe hazards associated with phosgene the production requires special precautions; so far no viable alternative process has been found.

In 2000 the global market for diisocyanates was 4.4 million tonnes, dispensed between the different isocyanates as following: 61.3% methylene diphenyl diisocyanates (MDI), 34.1% toluene diisocyanates (TDI), 3.4% the total of hexamethylene diisocyanate (HDI) and isophorone diisocyanates (IPDI), and 1.2% the total for other isocyanates. The main use for MDI and TDI is in the production of flexible or rigid foam but also as coatings, sealants, binders and elastomers. Today MDI dominates due to lower vapour pressure compared to TDI. Aromatic isocyanates can be oxidized by ultraviolet light. HDI and IPDI are usually used in coatings as they are not so easily oxidized. In the production of PUR pure diisocyanate monomers can be used, as in the production of TDI based soft foam containing a mix of TDA isomers. In the production of MDI-based rigid foam a crude mix of monomeric isomers and oligomers from the MDI-manufacturing called polymeric MDI (pMDI) are used. In many cases the diisocyanates have been treated prior to PUR production. This is done mostly to change properties such as viscosity, reactivity and volatility for easier handling, improved quality and safety reasons. This can be achieved by adding a small amount of polyol to the isocyanate to prepolymerize it. Other methods are the reaction of isocyanates with urea or urethane to form adducts such as biurets, isocyanurates and allophanates or react the isocyanate with itself to form di- and trimers. Both methods are used to produce technical HDI and IPDI.

Compared to diisocyanates the volumes of monoisocyanates are small. Monoisocyanates are used as modifiers of polymers and in the production of pesticides and pharmaceutical products. Thermal degradation of polyurethane or phenol–formaldehyde–urea resins produces monoisocyanates as degradation products.
2.2.2 Aromatic amines

The three diamines are closely associated with the production of polymers and especially the production of their isocyanate analogues. The amines are usually the base for the synthesis/production of the corresponding isocyanates. The isocyanates are reacted with water releasing carbon dioxide as a blowing agent that results in PUR foam. The majority of the produced diamines are used in the production of PUR foam. Other areas of use are as curing agents in the production of PUR and epoxy resins.

2.2.3 Aliphatic amines

Aliphatic monoamines are classified as primary, secondary, tertiary or cyclic amines depending on how many alkyl-groups are attached to a single nitrogen atom with a lone electron pair. Hydrogen bonding makes most aliphatic amines soluble in water, with decreased solubility with increased length of carbon chains. The hydrogen bonding also influences the boiling point for mainly primary and secondary amines, although not to the same degree as for the corresponding alcohols. Aliphatic amines are weak bases. The basicity generally increases with additional alkyl groups but steric hindrance from the alkyl group or groups can decrease the basicity.

Aliphatic amines can be found in numerous biological systems, often as degradation products of amino acids resulting in a putrid smell.

Aliphatic amines are used in chemical, pharmaceutical, rubber, plastics, photography, dye-stuff, textile, cosmetics and metal industries. Ethylamine (EA) is a dye intermediate, a rubber latex stabilizer and is used in oil refining and pharmaceuticals. Allylamine (AA) is used in different industries as a solvent and also in the preparation of diuretics, sedatives and antiseptics. Isopropylamine (IPA) is used in the production of pesticides fertilizers and pharmaceuticals. N-Butylamine (NBA) is used as solvent and intermediate in the pharmaceutical, rubber, photography, plastics, dye-stuff and leather- and synthetic tanning industries and also as a pesticide. Diethylamine (DEA) is a solvent in the petroleum industry and a corrosion inhibitor in the metal industries and in the production of rubber, textile and flotation chemicals, synthetic resins, dye and insecticides. Cyclohexylamine (CHA) is used in the industrial processing of pharmaceuticals, plastics, paper, rubber, insecticides, textiles, dyestuff, petroleum, some synthetic sweeteners and as a corrosion inhibitor in steam lines and boilers. Triethylamine (TEA) is used as an accelerator for developers in the photography industry and as a catalyst in a reaction between resins and isocyanates in production of PUR foams and in PUR cold box in the foundry industry. TEA is also an intermediate in the production of ethanol amine, vulcanisation accelerators in rubber industry and herbicides. Diisopropylamine (DI-
PA) is used to adjust the pH of cosmetic formulations \(^{24}\). Dimethylethylamine (DMEA) is used to production of mold-cores and in polymerization of polyamides \(^{25,26}\) and in printing \(^{27}\).

Aliphatic amines frequently end up in the environment and due to their aqueous solubility most often in rivers and lakes water and bottom sediment as well as in the ground water \(^{28-30}\).

### 2.2.4 Alkanolamines

Alkanolamines contains at least one hydroxyl (-OH) and one amino (-NH\(_2\), -NHR, and -NR\(_2\)) functional group. With the most commonly used alkanolamines the amine has one or more alcohol groups connected as well as the possibility for alkyl groups. This makes most alkanolamines very polar with complete solubility in water and can appear both as vapour and as an aerosol. The dual functional groups also make several different reactions possible. All these properties make alkanolamines highly versatile and therefore are used in a variety of industrial applications.

In the production of urethane chemicals and foams diethanolamine (DEAA), triethanolamine (TEAA) \(^{31}\) and dimethylethanolamine (DMEA) \(^{32}\) are used as catalysts to promote stability during the reaction process and isopropanolamine (IPAA) and diisopropanolamine (DIPAA) \(^{33}\) provide higher tensile and tear strength, shorten pot time of the elastomer and aid in high temperature resistance. TEAA \(^{31}\) is used as an intermediate for chemicals used in the manufacture of rubber. Ethanolamine (EAA), DEAA and TEAA \(^{31}\) are used in cement and concrete production to enhance strength, reduce drying time and protect against the effects of freezing and thawing and TEAA is also used as cement grinding media during manufacturing.

EAA, DEAA \(^{31}\), IPAA \(^{33}\), DMEA and methyldeethanolamine (MDEAA) \(^{32}\) are used in the production of pharmaceutical products. EAA, DEAA, TEAA \(^{31}\), IPAA and DIPAA \(^{33}\) are used as components in herbicides, EAA, DEAA and TEAA \(^{31}\) are also intermediates in manufacturing of molluscicide, fungicides and algacide products.

DEAA, TEAA \(^{31}\) and DIPAA \(^{33}\) are used in complex modern developing systems in photographic chemical industry. EAA \(^{31}\) is used as a pH control agent in the formulation of packaging and printing inks. IPAA and DIPAA \(^{33}\) are used in paint strippers to penetrate the paint and lift it from the substrate. TEAA \(^{31}\) and IPAA \(^{33}\) are used as intermediate for adhesive chemicals.

In treatment of sour natural gas EAA, DEAA \(^{34}\), DIPAA \(^{33}\) and MDEAA \(^{32}\) are used to remove acid gases such as H\(_2\)S. DMEAA \(^{32}\) is used in water treatment as a constituent of strongly basic anion exchange resins to adsorb solid and colloidal particles.
The basicity of alkanolamines is utilised as corrosion inhibition in a wide range of applications. Diethylethanolamine (DEEAA), DMEAA and IPAA are used as corrosion inhibitors in return-condensate steam and boiler systems. TEAA is used to prevent corrosion of drilling equipment for oil wells. DMEAA, DEEAA, and DIPAA are used in coatings as complexing agents, resin neutralizers, catalysts for hardening, corrosion inhibition, resin modifiers, and cross-linking aid. EAA, DEAA, TEAA, IPAA, and DIPAA are all used in metalworking fluids to improve corrosion protection, lubricates, foam suppression, and reduce friction in metal cutting applications.

Several alkanolamines are used in surfactants that are then used as emulsifying and dispersing agents. IPAA and DIPAA are used in personal care products ranging from hand lotions, cosmetic creams to hair products. DEEAA and DMEAA are used for water-resistant waxes and polishes. EAA, DEAA and TEAA are used in laundry detergents and fabric softeners and EAA, DEAA, TEAA, DMEAA and DIPAA as textile additives.

2.3 Exposure and health effects

2.3.1 Isocyanates

2.3.1.1 Exposure

The two main routes of exposure to isocyanates are through inhalation and/or dermal contact usually in an industrial environment. This has led to regulations regarding monitoring quantities in air and safety equipment when handling isocyanates and related PUR products.

The airborne exposures consist of isocyanates in vapour and/or as an aerosol. The gas can, depending on physical and chemical characteristics, condense on to particles. The particles grow in size through agglomeration or shrink through evaporation. The exposure from inhalation of isocyanate aerosol is greatly dependent on the sizes of the particles as well as the chemical structure. Larger particles and gas are deposited in the upper airways. All particles smaller than 10 µm have the potential of being biologically active, with the possibility of entering the lungs. Particles will generally be deposited depending on size, with smaller particles further into the lungs. Airborne isocyanate exposure can originate from production of PUR foam, from spray painting, spray application, from glues, medical casts. Another way to be exposed to airborne isocyanate is through thermal degradation of PUR from welding, cutting, grinding, fabric heat treatment, iron foundry moulding and core making, and fire.
Dermal exposures to isocyanates can be through direct handling of PUR products or by skin exposure to airborne isocyanates. Exposures have been reported for lacquers 56, glues 45, 57, paint or binders 57-59, foams 39, 40, 57, iron foundry moulding and core making 53, 60 and in the analysis of PUR 57.

Diisocyanates, such as HDI, TDI and MDI, dominate the air and dermal exposures in production and application operations. Exposure to TDI and MDI occurs mostly from manufacturing and treatment of PUR foam 38, 40. HDI-exposure happens typically in spray paint operations 41, 42.

Monoisocyanates commonly occur as an airborne products from thermal degradation of diisocyanate based PUR products 38, 48, 49, 51. Isocyanic acid (ICA) and methyl isocyanate (MIC) can be found in thermal degradation products from phenol-formaldehyde-urea resins. An accident in a carbide pesticide plant in Bhopal caused the worst exposure to MIC so far with a death toll of 2500–6000 and incapacitating over 200 000 people 61.

2.3.1.2 Health effects

The main health effects from isocyanate exposure are respiratory symptoms, primarily asthma from exposure to primarily monomers, oligomers and duct of polymeric isocyanates such as MDI 44, 47, 62, TDI 52, 63, 64, and HDI 41, 65, 66. Estimates of the prevalence of asthma amongst workers handling isocyanates range from 5-15% 67, 68. Deaths from isocyanate induced asthma attacks have been reported 44, 62. Other respiratory symptoms from isocyanate exposure are hypersensitivity pneumonitis 69-71, rhinitis 57, 72-74, and chronic obstructive pulmonary disease (COPD) 57, 75, 76. In recent time several reports of dermal exposure leading to respiratory effects, mainly occupational asthma, have been presented 77, 78.

Contact allergy from dermal exposure of isocyanate has been reported for HDI, TDI, and MDI 56, 57, 79. The symptoms of dermal isocyanate exposure can be mild, and the combination of false negatives from patch test and a negligence to ask workers about skin problems when being evaluated for isocyanate-asthma indicate an underestimation of contact dermatitis caused by isocyanate 57, 80.

The relation between isocyanates and antibodies is not clear with several reports of no antibodies present in symptomatic patients 45, 63 or that patients with antibodies show fewer symptoms 81. Antibodies for isocyanates have been reported both in association with occupational asthma 52, 70, 71, 77 and rhinitis 72 but in most cases only a minority of the patients had antibodies for isocyanates. An estimate of 10-30% of patients with occupational asthma had antibodies to diisocyanates 68. This makes monitoring of antibodies an unsuitable biomarker.
The health effects from exposure to diisocyanates are more thoroughly studied compared to exposure from monoisocyanates, mirroring the more extensive industrial use of diisocyanates. MIC is an exception as health effects of high concentration level exposure is thoroughly studied. Acute symptoms of MIC are vomiting and nausea, eye and throat injuries, unconsciousness, and pulmonary oedemas that can lead to death, while the chronic effects are ocular lesions, respiratory impairment, significant neurological, reproductive, neurobehavioral, and psychological effects. The effects of low levels occupational exposure of MIC are less clear. Phenyl isocyanate (PhI) is known to sensitize and cause asthma-symptoms in animals. Studies on animals exposed to thermal degradation products of PUR, indicated that the particle borne isocyanates have the more dominant toxic effects. Once in the body the isocyanates will react and can be found in urine and plasma; the corresponding amines have been used for biomarkers for isocyanate exposure.

2.3.2 Aromatic amines
2.3.2.1 Exposure
Occupational exposure to MDA and TDA occurs primarily in the production of PUR or when processing PUR-products. Welding in PUR-insulated steel pipes or flame lamination of soft PUR foam textiles causes thermal degradation of PUR and the formation of corresponding amines in air. Medical PUR-based material has been known to leak MDA, generally after different sterilization techniques. Studies of breast implants covered with PUR discovered them to be instable and leak TDA. Leakage of TDA and MDA from food packing material has been reported.

2.3.2.2 Health effects
Of the amines studied 4’4-MDA and 2,4-TDA are listed as possible carcinogenic to humans. Both are easily absorbed through the skin. MDA is known to cause acute liver damage, hepatitis, both through accidental ingestion and dermal exposure. Other symptoms that have been reported from dermal contact with MDA are jaundice, bile duct inflammation, suppression of bile excretion, allergic contact dermatitis, photosensitivity and yellow staining of the skin. Ingestion has been reported to cause jaundice and impaired visual acuity. If exposed to TDA the result may be ataxia, tachycardia, nausea, vomiting, convulsions, respiratory depression, and irritating of the eyes. Both TDA isomers and MDA have been shown to be mutagenic.
2.3.3 Aliphatic amines

2.3.3.1 Exposure

Rubber gloves have been suggested as a source for dermal exposure to DEA. Exposure to TEA and MDEA occurs primarily among cold-box core makers in the foundry industry and in PUR foam production.

2.3.3.2 Health effects

EA can cause severe irritation of exposed skin, eyes, and mucous membranes. In animal studies EA has been found to cause adverse effects and degenerative changes in heart, liver, kidney, and associated injury to the endocrine system in animals, and direct skin contact caused skin burns, scarring and necrosis. The vapour of AA is an irritant that has been shown to have effects on the heart and circulatory system in animals. Myocardial and vascular legions have been observed. Some of AA’s toxicity has been attributed to the formation of acrolein in vivo. There is also a definite risk of explosion over a wide range of concentrations in air. IPA vapour may be injurious to the eyes and respiratory tract. Transitory visual disturbances have been reported. DEA can possibly cause allergic contact dermatitis. Airborne exposure showed moderate to strong olfactory response and distinct nasal and eye irritation were observed. Chronic bacterial infection of the urinary bladder can convert DEA to the corresponding volatile N-nitrosamines by endogenous nitrosation and excreted in urine. NBA is the most important isomer commercially. It is irritating to the eyes and respiratory tract. NBA is readily absorbed through the skin. Any absorbed NBA is readily metabolized. Several reports of visual disturbances (haze and halos) and objective corneal oedema have been reported from exposure to TEA and MDEA. Uptake of DMEA through the skin is of far less importance than simultaneous uptake via the airways. CHA is mainly an irritant that may damage and sensitize the skin and is also a principal metabolite of cyclamate. Mutagenic, embryogenic, and tumorigenic potential in animal have been observed for CHA, but no carcinogenic effects.

2.3.4 Alkanolamines

2.3.4.1 Exposure

Exposure to alkanolamines occurs primarily with the use of various alkanolamine-containing products. Occupational exposures have been reported for EAA, DEAA, TEAA and MDEAA in metal working fluids (MWF), DMEAA in spray painting and printing, EAA in the beauty culture industry, and EAA and DEAA in cleaning products. Domestic exposure happens mainly with personal hygiene products, DEAA in skin lotion.
Health effects from alkanolamine exposure are mainly allergic contact dermatitis and respiratory symptoms such as asthma. Allergic contact dermatitis has been reported for alkanolamineborates, EAA, DEAA, TEAA, and IPAA. A study of patch-test data for EAA, DEAA and TEAA concluded that all three have a weak sensitization potential; nevertheless, the industrial use of EAA and DEAA in MWF and regular exposure can be assumed to cause occupational sensitization. Positive allergic reactions to TEA exposure seem to be caused by cosmetics and/or topical therapeutic preparations possibly on damaged skin. Occupational asthma has been reported for EAA, DEAA and TEAA. Massive ingestion of an EAA-containing alkaline detergent caused asthma-like symptoms followed by acute respiratory distress syndrome and death. Reports have also been presented of rhinitis caused by DMEAA and unyielding sneezing caused by TEAA with specific IgE antibody. DMEAA can cause reversible corneal opacity, with resultant decrements in visual acuity and contrast sensitivity. Exposure to DEEAA well below 200 ppm can cause nausea and vomiting. Secondary alkanolamines have been reported to form carcinogenic nitrosamines.

2.4 Classifications and exposure limitations

2.4.1 Isocyanates

The occupational exposure limits (OEL) in Sweden for monoisocyanates over an 8-hour time weighted average (TWA) are 5-10 ppb and with a 5 min threshold limit value (TLV) of 10-20 ppb. For disocyanates the TWA are 2 ppb with a TLV of 5 ppb. 2,4-TDI is classified as possibly carcinogenic to humans while 4’4-MDI, pMDI are not.

2.4.2 Aromatic amines

Both 2,4-TDA and 4’4-MDA are classed as carcinogenic. In Sweden no limits of exposure from 2,4-TDA and 4’4-MDA are specified, but their handling is restricted to authorised laboratories/companies. The PUR manufacturing industry has concluded that PUR material with up to 5 ppm poses no health risk and that the levels of TDA and MDA from manufac-
turing of PUR foam products appear to fall well within the acceptable health risk criteria \(^{161}\).

2.4.3 Aliphatic amines

The OELs in Sweden for aliphatic amines (EA, IPA, AA, DMA, DEA, DIPA, DMEA, TEA and CHA) over an 8-hour TWA are 2-10 ppm and with a 15-min Short-Term Exposure Limit (STEL) of 5-20 ppm \(^{159}\). For the four isomers of butylamine (NBA, IBA, SBA, TBA) the TLV during a reference time limit of 15 minute has been determined to 5 ppm \(^{159}\).

2.4.4 Alkanolamines

The OELs in Sweden for alkanolamines (EAA, DEAA, TEAA and DEEAA) over an 8-hour TWA are 0.8-3 ppm and with a 15 min STEL of 1.6-10 ppm \(^{159}\).
3 Aim of the thesis

• To investigate robustness of the dry sampler for isocyanates in air

• To investigate hydrophilic interaction liquid chromatography combined with tandem mass spectrometry for aromatic and aliphatic amines, as well as alkanolamines

• To develop an analytical method for the determination of free aromatic amines in flexible polyurethane foam in comparison to methods using derivatization

• To develop a new sampler and analytical methods to determine aliphatic amines and alkanolamines in air

• To investigate robustness of the new sampler for aliphatic amines and alkanolamines in air
4 Controlled atmosphere

4.1 Exposure chambers

To achieve reproducible measurements when evaluating a sampling method it is important to have stable temperature, humidity, and flow rate of in- and outlet air. The reactivity of the isocyanates has several implications on the design of the exposure chamber. Surface interaction cannot be totally avoided and are affected by temperature and the wall material. For isocyanates a partial steady-state will occur as well as interaction with humidity or contaminations \(^{162}\). To minimize the losses of isocyanates it is recommended to use high purity isocyanates, very clean pressurized air or a dry inert gas and good temperature control \(^{163}\). To gain better control over humidity and the concentration mixing ratio, and to reduce losses in the chamber, temperature-controlled ventilation and internal air circulation are recommended. A lower pressure then the ambient pressure outside the chamber will minimise the risk of leakage from the chamber.

Two differently sized exposure chambers were used. Sampling atmospheres were taken from the chambers by a glass tube (Ø = 4.94 mm, L = 28 cm) that passed through one of the exposure chambers’ openings leading outside where it had a bend with a ball joint in the end. To the ball joint forked glass connection (Ø = 4.94 mm, L = 9.0 cm) was attach with a socket joint. The glass connections had 2, 4, 5 or 8 forks, all ending the forks with ball joints. One 2-forked connection coupled with two 5-forked connections created a 10-forked glass connection. The up to ten samplers at the same time were attached in parallel, one sampler per fork ball joint.

In paper I, III, IV and V a smaller chamber was used. It had a volume of 0.3 m\(^3\), build of glass walls mounted in a stainless steel frame \(^{164}\) (Figure 2). It had five connections on the sides for inflow of air and introduction of standard atmosphere/generated compounds. The circular door had four connections for sampling. The incoming air was a mix of dry air and air humidified by bubbling through a water filled container with controlled temperature. The air mixing was provided with four computer fans of fixed speed. Laboratory exhaust ventilation in the ceiling kept the pressure slightly lower than the surrounding. The temperature ranged from ambient to 35°C.
The larger chamber was used in paper I. It was made of stainless steel with a volume of 0.85 m$^3$. One side had a front door equipped with manipulative gloves. The sides had over 30 connections in various sizes for connecting inlets for standard atmosphere/generated compounds or outlets for sampling equipment. The influent air was humidified in two steps. A controlled amount of water was added to heated air to be cooled to the preferred temperature. The air was then passed through a humidifier to maintain a constant humidity (between 10-90 \% relative humidity). The influent air could be regulated up to 200 l/min. Inside the chamber a mounted mixing fan unit could produce flow rates ranging over 0-90 l/s. The chamber exhaust ventilation was connected to a high-powered fan that kept the chamber pressure below the ambient pressure outside.

4.2 Generating standard atmospheres

The evaluation of a sampler’s performance requires stable generation of the desired analytes in air to create a standard atmosphere. Several methods can be used to achieve this; thermal degradation of sample material containing
chemicals of interests, direct injection, diffusion, permeation and vapour saturation 163, 165-170.

4.2.1 Generating gas phase

Gas-phase standard atmospheres were typically generated by membrane permeation. Permeation tubes of silicone rubber were attached to glass-vials. Different analytes was added to the vials to different heights depending on the vapour pressure for the analyte. When only the glass vial was filled only gas permeation occurred, when the silicone part was filled liquid permeation occurred. The silicon tubes were placed inside a metal permeation chamber with a volume of 0.77 l that had an adjustable flow of nitrogen (Figure 3). The permeation chamber was placed in a water bath to regulate the temperature. The flow of nitrogen in combination with the temperature of the water bath regulated the generated analyte concentrations.

![Figure 3. Schematic of liquid phase membrane permeation generation.](image)

In Paper I isocyanates were generated with mixed liquid-phase and gas-phase permeation. Isocyanates have been generated with membrane permeation previously 163, 166, 169. The generated average concentrations during the sampling periods were in the range of 52–205 µg/m for HDI, 11–118 µg/m³ for IPDI, and 5–154 µg/m for TDI. From PTR-MS data, the generated concentration varied <5% relative standard deviation (RSD) during a 24-h period and <2% RSD during a 6-h period.

In Paper V alkanolamines were generated by liquid-phase permeation. The generated average concentrations during the experiments was in the range of
0.38–1.7 mg/m³ for EAA, 0.78–3.2 mg/m³ for IPAA, 0.23–7.4 mg/m³ for DMEAA, 0.13–5.4 mg/m³ for DEEAA and 0.03–0.5 mg/m³ for MDEAA. From PTR-MS data, the generated concentration had RSD of 5.2 % (EAA), 5.7 % (IPAA), 9.4 % (DMEAA), 12.5 % (DEEAA) and 19.3 % (MDEAA) during a 12-h period and <4.9 % RSD during an 8-h period.

In (Paper III) all aliphatic amines were generated by gas-phase permeation, except for CHA that was generated with liquid-phase permeation, where the length of the silicone tubes were adjusted depending on vapour pressure to regulate the permeation rate (permeation length: AA; 3.5 cm, IPA; 0.5 cm, NBA; 6.0 cm, DEA; 1.5 cm, DMEA; 0.25 cm, TEA; 8.0 cm, CHA; 10.0 cm). Duplicate permeation tubes for all aliphatic amine, except for CHA which had one, were placed inside a glass bottle with a volume of 0.5 l with an adjustable flow of nitrogen through the bottle. The glass bottle was placed in a water bath to regulate the temperature that also affected the generated concentrations. The generated average concentrations were in the range of 2.0–5.3 mg/m³ for AA, 1.7–8.4 mg/m³ for IPA, 0.9–2.4 mg/m³ for NBA, 0.94–8.5 mg/m³ for DEA, 0.9–6.9 mg/m³ for DMEA, 0.5–5.6 mg/m³ for TEA and 5.7–15.4 mg/m³ for CHA. From PTR-MS data, the generated concentration varied <6.5 % RSD with exception for CHA that varied 17.3 %, during a 12-h period and <4.2 % RSD during an 8-h period.

4.2.2 Generating particles and gas phase

A technique not as precise as the method above is the generation of an aerosol using thermal degradation by heating material samples. The samples were placed between two glass wool plugs in a glass tube. Hot air (250-350°C) was blown through the glass tube into the exposure chamber. The material samples (usually polymers) decompose creating a complex mixture of gas and particles. This is more consistent with industrial work operations. The resulting aerosol may vary depending on chemical reactions, particle agglomeration, ventilation and deposition.

This method was used to produce airborne concentrations of ICA, MIC, EIC, PIC, PhI, HDI, IPDI, TDI and MDI in Paper I in the range of 1.4-500 μg/m³ with a RSD in the range of 0.5-11 %.

It was also used in paper IV to produce airborne concentrations of EAA, NPAA, IPAA, DMEAA, DEAA, DEEAA, MDEAA, TEAA, DIPAA or DIPEAA in the range of 0.09-4.0 mg/m with a RSD in the range of 1.2-37%.
5 Sampling

5.1 Reagents

5.1.1 Isocyanates

Since airborne isocyanates pose the most common exposure and airway disorders the most frequent health effect, the most studied methods to determine isocyanates are by air sampling. The high reactivity of isocyanates has made it necessary to derivatize them in a controlled manner during sampling to minimize the loss until analysis. The same high reactivity towards primarily amines and alcohols has been utilized to bind the isocyanates as a derivative for safe storage. Depending on reagent and sampler type it is either solved in a solution or coated on a filter or a sorbent media or a combination.

Isocyanates affinity for protic reactants formed the bases for the first reagent developed, acid hydrolysis with water in a glass flask bubbler sampler. Diazotization of the resulting amines of TDI made spectrophotometric detection possible \(^{172}\). The drawback was that TDI originating from air could not be distinguished from the presence of the corresponding amine in air.

Several more specific reagents targeted for isocyanates have been developed over the years (Table 5). Their properties reflect their intended sampling media, separation technique and detection method.

Table 5. Amine based reagents used for derivatization of airborne isocyanates.

| Name (Abbr- | Ref | N-4-nitrobenzyl-N-n-propyamine (Nitro) \(^{173}\) | 1-(2-Pyridyl) piperazine (2-PP) \(^{174}\) |
| Abreviation) | | | |
| Structure | | | |
| C\(_2\)H\(_5\)NH | | | |
| Name (Abbr- | Ref | 9-(N-methylaminomethyl)anthracene (MAMA) \(^{175}\) | 1-(2-methoxyphenyl)piperazine (2-MP) \(^{176}\) |
| Abreviation) | | | |
| Structure | | | |
| | | | |
The first reagent to separate isocyanate and corresponding amine was dimethylformamide in the presence of an aliphatic base. The resulting derivative can be diazotised for colorimeter or spectrophotometer detection.

Alcohols readily react with isocyanates to form stable urethane compounds, and the alcohol can be used as both a solvent and a reactant at the same time. Methanol, ethanol and butanol were all used in the earlier methods developed. Subsequent methods used ethanol with the addition of an acid or a base to increase the derivatization rate. The advantage of having the solution as reagent turns to a disadvantage when applying alcohols to dry sampling methods.
As amines are amongst the fastest reagents in reacting with isocyanates and are reasonable safe to handle, it is not surprising that most reagents are amine-based. The produced urea-derivates are usually stable, and the amines can be selected depending on which sampling, separation and detection technique that will be used. Secondary amines are stronger nucleophiles and reacts faster with isocyanates then primary amines and consequently most amine-based reagents are secondary amines. Even though aliphatic amines react faster with isocyanates, the most used amine reagents are aromatic, because of the need for an aromatic group for ultraviolet detection (UV). Below is a summary of the most commonly used reagents.

The first amine-based reagent for air sampling was N-4-nitrobenzyl-N-n-propylamine (Nitro)\textsuperscript{173}. Nitro is relatively unstable and sensitive to light\textsuperscript{189}. Although widely used in standard methods\textsuperscript{190} it has been superseded with more reliable reagents.

1-(2-Pyridyl) piperazine (2-PP)\textsuperscript{174} has been used as a base for standard method\textsuperscript{191,192} and is still in use\textsuperscript{193}.

9-(N-methylaminomethyl) anthracene (MAMA)\textsuperscript{175} is very sensitive to fluorescence detection (FL) due to anthracene backbone, and high molar absorptivities makes sensitive photometric detection possible. However, both the reagent and the derivates are unstable in light\textsuperscript{194}. MAMA doesn’t react instantly with isocyanates\textsuperscript{195}, and sample loss due to interfering reactions with amine and alcohol during sampling has been reported\textsuperscript{196}. It is nevertheless still in use\textsuperscript{197}.

1-(2-methoxyphenyl) piperazine (2-MP)\textsuperscript{176} achieved higher selectivity with two methods of detection in combination, UV and electrochemical detection (EC). 2-MP has since made the transition to MS\textsuperscript{198}. An analytical standard method based on 2-MP is available\textsuperscript{199}. Disadvantages with 2-MP is that isocyanate concentration can be underestimated during long-term sampling\textsuperscript{200,201} and that amines and alcohols cause interference during sampling resulting in sample losses\textsuperscript{196}. 2-MP has been used extensively for sampling airborne isocyanates\textsuperscript{202} but due to similar structure to recreational drugs it has recently been regulated\textsuperscript{203}.

3-(2-Aminoethyl)indole (tryptamine)\textsuperscript{177} is one of the few reagents that utilize a primary amine. Nonetheless the tryptamine reaction rate with isocyanates keeps up well when compared with 2-MP and provides much faster reactions rates then nitro and 2-PP\textsuperscript{204}. Interference from the matrix can disturb the low-wavelength ranges\textsuperscript{194}.

Di-n-butylamine (DBA)\textsuperscript{178} has the fastest reaction rates when comparing amine reagents mostly because much higher concentrations can be used than with aromatic-containing reagents\textsuperscript{205}. The lack of aromatic ring unfortunately makes UV detection for aliphatic isocyanates impossible, but DBA is very
suitable for MS detection. Amines or phenols don’t interact when sampling isocyanates. DBA has been used as a base for a standard method. DBA was used as a reagent in Paper I.

1-(9-Anthracenylmethyl) piperazine (MAP) is similar to MAMA with an anthracene group to enable detection with both FL and UV, but with more distance to the isocyanates groups to decrease interference. However detection with FL is not completely independent of the isocyanates structure. MAP has faster reaction rate then 2-MP, tryptamine and MAMA.

Total Reactive Isocyanate Group (TRIG), requires reagents that give an equal signal for all isocyanate groups independent of the structure of the isocyanates. This makes determination possible without the need for a standard for any of the analyzed isocyanates compounds. For determination of TRIG, however, mass spectrometric quantification is problematic, because only compounds for which standards are available can be accurately determined. The different OEL-levels for different isocyanates make TRIG’s lack of structural information unsuitable for OEL measurement.

MAMA has an UV response nearly independent of the isocyanate structure, well suited for TRIG analysis. The response for FL however, does depend on the isocyanate structure.

With oxidation of the methoxy-group on 2-MP reagent an EC-signal independent of the analyte backbone can be acquired thus enabling TRIG quantification of oligomeric isocyanates based on the use of the corresponding monomers.

The response for tryptamine is fairly independent of the isocyanate structure for both FL and EC detection, making TRIG identification of unknown isocyanate possible from their detector response ratios and with the use of a different isocyanate derivative for quantification. A TRIG standard method based on tryptamine has been developed.

MAP was developed for TRIG analysis and has become a standard method.

5.1.2 Aromatic amines

5.1.2.1 Acid Anhydride

Several acid anhydrides have been employed for amine derivatization. Since acid anhydrides can react with protic solvents amines in aqueous extraction solution or hydrolysed biological samples the amines are extracted to an organic solvent such as toluene. Both MDA and TDA have been derivatized with acidic anhydride. Heat is required due to the slow reaction rate between the aromatic amine and acidic anhydride.
Perfluorofatty acid anhydrides react readily with amines in organic solvent, and the acid derivate formed was easily extracted with buffer from the organic phase prior to analysis\textsuperscript{217}. Several different perfluorofatty anhydrides have been used for derivatization of aromatic amine, the first was trifluoroacetic anhydride (TFAA)\textsuperscript{218} followed by heptafluorobutylic anhydride (HFBA)\textsuperscript{188} and pentafluoropropionic anhydride (PFPA)\textsuperscript{219}. PFPA has been used for the derivatization of TDA and MDA from air sampling\textsuperscript{49}, PUR foam extraction\textsuperscript{220} and biological sampling\textsuperscript{217} (Table 6). PFPA was used in paper II.

5.1.2.2 Chloroformate

A Chloroformate reagent such as an aliphatic chloroformate reacts with amines to form carbamate ester derivates\textsuperscript{221, 222}. A two-phase system of water at a specified pH and the organic phase has the amines evenly distributed between the two phases. The reaction occurs in the organic phase with a catalyst present. The catalyst removes the acid formed, and as the amines are consumed in the organic phase the equilibrium shifts and amines move from the water phase into the organic phase. MDA has been derivatized with isobutylchloroformate (IBCF)\textsuperscript{223} and ethyl chloroformate\textsuperscript{49}. Ethyl chloroformate (ETCF) has been used to derivatize TDA\textsuperscript{49, 220, 224}. ETCF was used in paper II.

**Table 6. Anhydride and chloroformate based reagents used for derivatization of aromatic amines.**

<table>
<thead>
<tr>
<th>Name (Abbreviation)</th>
<th>Ref</th>
<th>Trifluoroacetic anhydride (TFAA)</th>
<th>Ethyl chloroformate (ETCF)</th>
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<td>Name (Abbreviation)</td>
<td>Ref</td>
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<td>Isobutylchloroformate (IBCF)</td>
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<td>Structure</td>
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</table>

5.1.3 Aliphatic amines

Derivatization of aliphatic amines is primarily performed to improve chromatography and or to facilitate detection with for example UV or FL. Most reagents used for aliphatic amines were first developed for biochemical
analysis with the intent of FL- and/or UV-detection; 1-fluoro-2,4-
dinitrobenzene (DNFB)\textsuperscript{225}, 5-(dimethylamino)naphthalene-1-sulfonyl chloro-
ride (Dansyl)\textsuperscript{226}, 2,2-dihydroxyindane-1,3-dione (ninhydrin)\textsuperscript{227}, 4-
chloronitrobenzoxadiazole (NBD-Cl)\textsuperscript{228}, o-phthalaldehyde (OPA)\textsuperscript{229}, 9-
fluorenylmethyl chloroformate (FMOC)\textsuperscript{230}, fluorescamine or fluram\textsuperscript{231}, p-
toluenesulphonyl chloride\textsuperscript{232} that led to benzenesulphonyl chloride (BSC)\textsuperscript{233},
fluorescein\textsuperscript{234}, 4-dimethylaminoazobenzene-4'-sulphonyl chloride (Dabsyl)
\textsuperscript{235}, 2-methoxy-2,4-diphenyl-3(2H)-furanone (MDPF)\textsuperscript{236}, benzyol chloride
\textsuperscript{237}, naphthalene-2,3-dicarboxaldehyde (NDA)\textsuperscript{238}, phenyl isothiocyanate
(PITC)\textsuperscript{239}, 3,5-dinitrobenzoyl chloride (DNB)\textsuperscript{240}, N-hydroxysuccinimidyl
fluorescein-O-acetate (SIFA)\textsuperscript{241}, and 1,2-benzo-3,4-dihydrocarbazole-9-
ethyl chloroformate (BCEOC)\textsuperscript{242}. All of these reagents have one or more
aromatic group to enable FL and/or UV-vis detection, similar to reagents
developed specific for aliphatic amines; 1-naphthalisothiocyanate (NITC)
\textsuperscript{243}, 2-(2-phenyl-1H-phenanthro-[9,10-d]imidazole-1-yl)-aceticacid (PPIA)
\textsuperscript{244}, 8-phenyl-(4-oxy-acetic acid N-hydroxysuccinimidyl ester)-4,4-difluoro-
1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (TMPAB-Osu)\textsuperscript{245}, 2-
(11H-benzo[a]-carbazol-11-yl) ethyl chloroformate (BCEC-Cl)\textsuperscript{246}, 3-(4-
fluorinebenzoyl)-2-quinoline carboxaldehyde (FBQCA)\textsuperscript{247}. There are some
reagents not intended for FL/UV detection, such as pentafluorobenzaldehyde
(PFBAY)\textsuperscript{248} and 4-nitrophenyl trifluoracetate (NPTFA)\textsuperscript{249} that were first
applied to bioamines and in organic synthesis respectively, and aliphatic
chloroformates such as tertbutyl chloroformate (TBCF) were developed for
primary and secondary aliphatic amines\textsuperscript{221,222}.

Several of the reagents are similar in structure and differ mostly in how they
react with the amino-group. To get the amine to react with the reagent several-
functional groups have been used, such as halogen with DNFB\textsuperscript{225} and
NBD-Cl\textsuperscript{228}, sulphonylchloride with BSC\textsuperscript{233,250}, dabsyl chloride\textsuperscript{30} and dansyl
chloride\textsuperscript{250}, chloroformate with FMOC\textsuperscript{251}, TBCF/ IBCF\textsuperscript{221,252}, DBCEC-Cl
\textsuperscript{253}, DBCPC-Cl\textsuperscript{254}, trichloroethyl chloroformate (TCECF)\textsuperscript{251}, BCEOC\textsuperscript{255},
BCEC-Cl\textsuperscript{246}, isothiocyanate with NITC\textsuperscript{256}, FITC\textsuperscript{257}, aldehydes with NDA
\textsuperscript{258}, OPA\textsuperscript{259}, PITC\textsuperscript{260}, PFBAY\textsuperscript{261}, DNB\textsuperscript{262}, FBQCA\textsuperscript{247}, and benzoyl chloro-
ride/benzoate with SIBA\textsuperscript{263} and DNB\textsuperscript{264}.

Since most reagents interact with the nitrogen atom they usually only can be
used for primary aliphatic amines or primary and secondary aliphatic
amines. FBQCA\textsuperscript{247}, OPA\textsuperscript{229}, and fluorescamine\textsuperscript{231} can only derivatize pri-
mary aliphatic amines. The other listed reagents can derivatize both primary
and secondary aliphatic amines. Tertiary amines have been determined as
quaternary ammonium salts\textsuperscript{265} or as complex with m-dinitrobenzene\textsuperscript{266}. 

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5.1.4 Alkanolamines

Derivatization of alkanolamines is primarily done to improve chromatography and/or to facilitate detection with for example UV or FL. The methods of derivatization either focus on the amine groups or the hydroxyl groups. The limitation of reagents that targets the amine group is that they usually do not work on tertiary amines. Reagents derivatizing the hydroxyl group lack this limitation. Since alkanolamines are relative stable compounds their derivatization usually is preformed after sampling, the exception being naphthyl isothiocyanate. Amine derivatization reagents are dansyl chloride, naphthyl isothiocyanate, fluorenyl methyl chloroformate, 6-oxy-(N-succinimidyl acetate)-9-(2’-methoxycarbonyl) fluorescein (SAMF), and FBQCA. Many amine derivatization reagents were first used for sampling ordinary primary and secondary amines (aliphatic amines). Reagent derivatizing the hydroxyl groups are trifluoroacetic anhydride and reagent based on silylation such as N,O-bis trimethylsilyllacetamide (BSA), hexamethyldisilazane (HMDS) / trimethylchlorosilane (TMCS) / anhydrous pyridine, trimethylsilylimidazole (TSIM) and trimethylsilylimidazole / trimethyl chlorosilane.

5.2 Air sampling

Air contains a gas-phase (vapour) and to various degrees airborne particles (aerosol). When collecting air samples it is either the vapour or the aerosol that is collected, occasionally both at the same time. Vapour molecules diffuse to a surface of a sampler when passing through and are the collected. Vapour molecules are collected either by absorption by a liquid, adsorption onto a solid surface or by reaction with the medium or a reagent in the medium. Filtration or inertial impaction is commonly used to collect an aerosol. To collect both vapour and aerosol the sampler usually consists of two steps. The exact combination of sampling methods depends on chemical and physical characteristics and on the particle size of the.

5.2.1 Impinger glass flask air sampler

The impinger glass flask is partly filled with aqueous or organic solutions usually with a reagent. The reagent solution collects the gas phase and larger particles (>1.5 µm) that are impacted onto the bottom due to the high velocity jet outlet. The high reagent concentration that mixes with the particles results in effective derivatization. The impinger flask can be coupled in series with a glass fibre filter for more efficient particle phase collection. The disadvantages of impinger flask sampling are that the impinger flask is made of glass and filled with organic sampling solvent (toluene or acetonitrile) that
is volatile. This limits sampling time due to vaporization. The flammable organic solutions with impinger are not the ideal contraption to fasten on workers when performing exposure measurement during hot work operations.

5.2.1.1 Liquid based methods of air sampling for isocyanates

Most of the early reagents, such as water, acid alcohol, alkalic alcohol, Nitro, 2-PP, MAMA, 2-MP, Tryptamine, DBA and MAP, were developed for wet air sampling. To improve the collection of particles the impinger flask has been coupled with a filter with DBA, 2-MP and MAP reagent. The high volatility of DBA means that the filter gets a continuous addition of reagent that derivatizes the smaller particles (<1.5 µm) that don’t impact but follows the air stream through the fluid. The impinger flask sampling method with DBA for isocyanates is described in ISO 17734.

Impinger flasks were used as a reference method in paper I and contained toluene and 0.01 M of DBA (5.2.2.3 Evaluation of the dry sampler for isocyanates). The flow rate through the sampler was 1.0 l/min.

5.2.1.2 Liquid based methods of air sampling of aromatic amines

The impinger flask has been used in numerous methods usually with simultaneous collection of isocyanates. The isocyanates reacts instantaneously with either the solvent in the impinger flask, such as water or ethanol, or with a reagent dissolved in toluene. The impinger flask solvents are usually made acidic or alkaline. The amines were either derivatized or determined as free amines. If the impinger flask solvent is water the isocyanates reacts to corresponding amines, and the total amine concentration is determined.

5.2.1.3 Liquid based methods of air sampling for aliphatic amines

Air sampling of aliphatic amines has been performed with glass flask bubblers containing sulphuric acid and with impinger flasks containing hydrochloric acid.

5.2.1.4 Liquid based methods of air sampling for alkanolamines

Air sampling of alkanolamines has been performed with impinger flask containing acid aqueous solution.

In paper IV an impinger flask containing 10 mL aqueous acetic acid (0.2 %) was demonstrated for the collection of airborne alkanolamines during 20 minutes. The flow rate through the sampler was 1.0 l/min. A linear increase of air concentrations of alkanolamines was observed with correlation efficiencies of > 0.96 (Figure 4). Compared with the calculated theoretical air concentrations, lower concentrations were measured.
**Figure 4.** 20 min sampling of alkanolamines in a controlled atmosphere with an impinger glass flask containing midget impinger 0.2 % acetic acid in water (v/v) with sampling flow rates of 1.0 l/min. Linear relationship (Impinger vs theoretical concentration :3.33, 5 and 6.78 mg/m$^3$); DIPEAA ($\bigcirc$) $y = 0.63x-0.27$, $R^2 = 0.99$, DIPAA (■) $y = 0.10x-0.25$, $R^2 = 0.98$, IPAA (▲) $y = 0.21x+0.36$, $R^2 = 0.97$, NPAA (□) $y = 0.38x-0.19$, $R^2 = 0.96$, DEEAA (●) $y = 0.63x-0.39$, $R^2 = 0.99$, DMEAA (◇) $y = 0.52x+0.18$, $R^2 = 0.99$, MDEAA (◇) $y = 0.08x-0.19$, $R^2 = 0.98$, TEAA (△) $y = 0.49x-0.48$, $R^2 = 0.99$, DEAA (+) $y = 0.14x-0.29$, $R^2 = 0.99$, EAA (○) $y = 0.20x-0.47$, $R^2 = 0.96$.

5.2.2 Dry methods for air sampling

In paper I, III and V a dry-sampler (Figure 5) consisting of a cylindrical polypropylene tube (L = 70 mm, ID = 8.2 mm) attached to a polypropylene filter holder (ID = 13 mm). Binder-free glass-fibre filters (pore size 0.3 µm) were used for collection of the analytes, impregnated with DBA for isocyanates or sulphuric acid for aliphatic- and alkanolamines. To retain the DBA from evaporating, an ion pair was formed with acetic acid on the glass fibre filter. The cylindrical denuder part was lined with a filter (25 × 57 mm) and an end filter (D = 13 mm) was placed in the filter holder to collect the particle fraction. The above description represents the first presented version of the sampler\(^1\). To enhance the collection efficiency a “V”-folded filter (14 mm
× 57 mm) was placed in the cylindrical denuder thus dividing the denuder in three passages and increasing the surface area by 112%. When prepared the sampler was sealed with caps in both ends. The recommended flow rate through the sampler was 200 ml/min.

Figure 5. Schematics of the dry sampler. Glass fibre filter impregnated with DBA/Acetic acid or sulphuric acid; A: Cylindrical filter (Denuder), B: V-shaped filter (Denuder) and C: End filter (Particle).

5.2.2.1 Denuder diffusion efficiency theory

The gas-phase diffusion efficiency for isocyantes in a cylindrical denuder primarily depends on a stable laminar gas flow and viscosity and temperature distributed homogeneously in the gas flow. A flow-subduction zone prior to the filters facilitates a laminar flow. The analyte diffusion coefficient will also greatly affect the diffusion efficiency. A decrease of flow rate and increase of the length of denuder tube improves the diffusion efficiency for gas phase analytes. The distance at which particles begin to deposit on the tube walls limits the denuder tube length. Contrary to the diffusion efficiency for gas phase analytes, the particle penetration is unaltered by the diameter of denuder tubes for a given volumetric flow.
To calculate the diffusion efficiency for gas phase analytes the Gormley and Kennedy equation (eq. 1) can be used for a cylindrical denuder and for a rectangular denuder, like the V-folded filter part, eq. 2 can be utilised.

Eq. 1.

$$\frac{C}{C_0} = 0.819e^{-\frac{3.6568\pi DL}{F}}$$

Eq. 2.

$$f = 1 - 0.91e^{-\frac{7.54wDL}{Qs}}$$

where

- $C = \text{the concentration of analyte penetrating the tube}$
- $C_0 = \text{the concentration of analyte in the entering air}$
- $D = \text{the diffusion coefficient of the analyte vapour}$
- $L = \text{the length of the denuder tube/channel}$
- $F = \text{the volumetric air flow rate applied to the tube}$
- $f = \text{the efficiency}$
- $w = \text{the channel width}$
- $Q = \text{the volumetric flow}$
- $s = \text{the channel height}$

The sampler’s theoretical denuder efficiency can be calculated from equation 1 and 2 with an assumption of laminar airflow. The theoretical denuder efficiency was also calculated for the sampler designed by Marand et al., 2005 that lacked the “V”-folded filter in the cylindrical denuder part. The “V”-folded filter divided the cylindrical tube into three narrower channels and consequently improves the collection efficiency. The additional 112% filter area improves the load capacity of the sampler.

5.2.2.2 Dry methods for air sampling of isocyanates

Nitro-coated glass-fibre filters have been analysed and compared with impinger glass flask methods and displayed equal or higher air concentrations. Nitro has also been used with coated glass powder and coated glass wool.

XAD-2 coated with MAMA showed good agreement with glass flask bubbler. For fractionated sampling with MAMA two method have been published, the first with dual Teflon-/fibre glass-filter where the second filter is impregnated with MAMA and the first filter is plain and derivatized after sampling with 2-MP and the second with impregnated denuder and filter in series.
Samplers with 2-PP-impregnated glass fibre filters have been used with the drawback that it fails when sampling air with saturated air humidity. The 2-PP glass fibre filter has been used for fractionated sampling in series after two unimpregnated teflon filter. The use of 2-PP coated sampling tubes has also been reported.

Sampling with a glass-fibre filter coated with 2-MP has been evaluated in comparison with impinger flasks and has been found to be all of superior, equal and inferior. To minimize breakthrough a dual filter in series has been proposed. The limited amount of reagent can with long-term sampling pose a risk of reagent depletion with high particle concentrations resulting in loss of isocyanates and underestimates of air concentrations.

Other proposed dry sampling methods are extraction columns, sintered glass, PUR sponge and two PUR foam based size selective samplers with filter back-up. Tryptamine-coated XAD-2 has been compared with impinger flasks with unsatisfactory results. A glass fibre filter coated with MAP displayed a good agreement with the impinger flask.

Dry sampling with DBA is problematic. DBA is highly volatile and evaporates quickly when air is drawn through the sampler. Two methods for denuder sampling with DBA have been proposed. The first method used DBA with a cylindrical denuder prepared with a chemisorptive stationary phase to fixate the DBA and when compared with impinger flask a reasonable agreement was found for most of the common isocyanates. The second method uses a cylindrical filter-coated denuder with an end-filter, all coated with DBA bound as an ion-pair with acetic acid. A further developed method of this sampler was used in paper I. Fractionated sampling with DBA has been performed with rectangular parallel denuders in series with a cascade impactor.

In paper I the sampling efficiency for gas-phase isocyanates in the sampler’s denuder section was assessed for five different flows. The breakthrough from denuder to end-filter was calculated from separate analysis of the denuder and end-filter. For the tested flow rates no breakthrough to the end-filter could be detected. Comparisons of the sampler’s denuder collection efficiency from the experimental data with the theoretically calculation for “V”-filter containing denuder are presented in Figure 6.
Figure 6. Sampling of standard atmosphere of HDI (◇), IPDI$_1$ (□), IPDI$_2$ (△), 2,4-TDI (⊗) and 2,4-TDI (⊙) from an exposure chamber with the dry sampler to determine the denuder collection efficiency for flow rates ranging from 100 to 500 ml/min.

The sampler’s 13-mm flow subduction zone prior to the filter seemed theoretically sufficient to achieve laminar flow, but the comparison with experimental data suggests non-laminar flow through the denuder. The complex geometry created by the added “V”-filter does make a theoretical calculation of the denuder collection efficiency challenging. The ratio between the sampler’s experimentally estimated denuder collection efficiency compared to the theoretical calculated for a plain cylindrical denuder equivalent to the one presented by Marand *et al.*, 2005[^164] is presented in Figure 7. The increase in the range of 5-51% with the presence of “V”-folded filter indicates a clear improvement of the denuder collection efficiency and load capacity over the lack of said filter.
Figure 7. The ratio between the experimentally determined denuder efficiency with "V"-filter versus theoretically calculated denuder efficiency without "V"-filter in percent for HDI (◊), IPDI₁ (□), IPDI₂ (△), 2,4-TDI (×) and 2,4-TDI (○) with flow rates ranging from 100 to 500 ml/min.

The precision for collecting gas-phase isocyanates was < 5.7 %. No breakthrough was observed for sampling during 120 minutes or for flow rates up to 500 ml/min during 30 minutes sampling. The isocyanate derivates on the sampler were stable in a refrigerator for up to 21 days. The sampler was not affected by exposure of clean air-flows for up to 10 h, either pre-, or post-exposed to isocyanates.

The sampler could perform sampling of gas-phase isocyanates for up to 32 hours with maintained capacity. An approximately linear relationship for the sampling times for each isocyanate could be established with intercepts close to the origin and correlation coefficients > 0.998.

The performance of the sampler for collection of gas-phase isocyanates with sampling flows rates in the range of 200 and 800 ml/min was investigated. A near linearity between amounts of sampled isocyanate plotted against flow rates was observed with correlation coefficients > 0.984 and intercepts close to the origin.
The influence of diffusion flux for gas-phase isocyanates during active sampling was investigated for a duration of 2 hours with flow rates in the range of 25-200 ml/min. The contribution from diffusion sampling was substantial for the two lower flow rates but decreased and stabilised for flow rates from 100 ml/min and (Figure 8).

**Figure 8.** Air concentrations of HDI (◊), IPDI\(_1\) (□), IPDI\(_2\) (△), 2,4-TDI (×) and 2,4-TDI (○) in standard atmospheres determined with dry sampler in duplicates with flow rates in the range of 25-200 ml/min (n = 5) during a sampling period of 2 hours.

The performance of the dry sampler was compared twice to DBA-impinger-filter method, the first during thermal degradation of PUR products under varied relative humilities (RH), and the second with standard atmospheres containing gas-phase isocyanates.

When comparing the sampling of isocyanates in the gas phase without the presence of thermal decomposition products, the concentration ratios between dry sampler and impinger glass flask-filter sampler were in the range of 1.03-1.44 (Figure 9). The results were in good agreement between the two methods with the exception of IPDI, probably due to adsorption in the glass tubing in the impinger flask.
Figure 9. Ratios of sampling using dry samplers and impinger-filter samplers for the collection of isocyanates from a standard atmosphere. A total of 12 dry samplers and 12 impinger-filter samplers have been compared in series of three.

Performing comparative sampling of thermal degradation products of PUR the dry sampler demonstrated general agreement with the impinger-filter method for all isocyanates except ICA and TDI (Figure 10). For TDI and ICA, there were considerable differences in the sampling. The derivatization chemistry for ICA was greatly affected by the humidity and ICA is possibly consumed by side reactions occurring in the impinger flask during sampling. TDI showed slightly higher levels (about 20%) in the impinger flask. The nature of TDI in the gas phase is not known in detail. This could indicate that there is a presence of TDI compounds that form TDI-DBA derivatives during sampling or storage of samples in toluene and that these reactions do not occur to the same extent in the dry sampler. The agreement between the two methods for IPDI is most likely due to particle-borne IPDI that does not adsorb on the surfaces in the glass line in the impinger flask.
Figure 10. Ratios of sampling using dry samplers and impinger-filter samplers for the collection of isocyanates generated during thermal degradation of polyurethane polymers at RH of 20% (1st bar), 40% (2nd bar), 60% (3rd bar), and 90% (4th bar). A total of 48 dry samplers and 48 impinger-filter samplers have been compared in three series for each RH.

5.2.2.4 Dry methods for air sampling of aromatic amines

Several methods for sampling of airborne aromatic amines using acid treated glass fibre filter exist. Most methods use sulphuric acid but phosphoric acid has also been used. Determination as free amine has been done, but in most case the amines are derivatized prior to analysis.

5.2.2.5 Dry methods for air sampling of aliphatic amines

Air sampling of aliphatic amines has been performed both with derivatization and as free aliphatic amines. Direct derivatization has been done with NITC impregnated filters, sampling tubes containing NITC coated XAD-2 resin, or NBD-Cl coated XAD-7 resin, or with NPTFA- or PFBAY-coated SPME. Derivatization after sampling has been performed with dansyl, after sulphuric acid impregnated glass fibre filter.
sampling, and with IBCF\textsuperscript{326}, after ion-pair extraction with bis-2-ethylhexylphosphate.

Air sampling of free aliphatic amines have been performed with sampling tubes containing silica gel\textsuperscript{15,327}, silica gel with sulphuric acid\textsuperscript{328}, silica gel with hydrochloric acid\textsuperscript{25}, phosphoric acid coated XAD-7 resin\textsuperscript{329,330}, activated charcoal filled glass tubes\textsuperscript{331}, and jumbo aluminum tube\textsuperscript{332}. Other dry methods that have been used are the dry cartridge sampler\textsuperscript{333}, SPME\textsuperscript{334}, cryogenic integrative air sampler\textsuperscript{335}, and film of non-peripherally substituted copper(II)\textsubscript{1,4,8,11,15,18,22,25}-octabutoxy-29H,31H-phthalocyanine-(nCuPc(Obu)\textsubscript{8})\textsuperscript{336}.

In paper III the sampler developed for isocyanates was used for aliphatic amine sampling with the change that the filters were treated with 1.6 ml of 0.1 M sulphuric acid solved in methanol that was evaporated to dryness prior to sampling.

5.2.2.6 Evaluation of the dry sampler for aliphatic amines

The extraction efficiency of aliphatic amines from the filters was on average 102 %. The precision for collection of gas phase aliphatic amines was on average 4.9% and the collection efficiency at 200 mL/min > 99.9 % with no breakthrough. Major breakthroughs at 800 mL/min were observed for TEA and DMEA and collection efficiencies of 82 % and 90 %. Minor breakthroughs were observed for DEA, NBA, IPA, and AA, and the collection efficiencies were > 97 %. The distribution of aliphatic amines in the denuder was very similar to the distribution of alkanolamines. For sampling flow rates of 200 mL/min a majority of the aliphatic amines was collected in the first quarter of the denuder and then declining throughout the denuder. The end-filter collected about a tenth of the aliphatic amines. At 1100 mL/min the highest collected amount of aliphatic amines was on the end-filter. The sampler, pre-, or post-exposed to aliphatic amines, could be in storage at ambient temperatures for up to 45 days. The sampler was not affected by exposure to clean air flows for up to 10 h, either pre-, or post-exposed to aliphatic amines. Linear relationships between five different air concentrations of IPA, DEA and TEA, measured with the sampler and the PTR-MS signal, were obtained with correlation coefficients > 0.994.

Sampling times up to eight hours were investigated for collection of gas-phase aliphatic amines. Linear relationships between the collected amount of amines and the sampling times were observed with correlation coefficients >0.997 (Figure 11).
Figure 11. Sampling with varied sampling times. Six series (sampling times: 0 – 480 min) of 5 samplers exposed to gas phase IPA, DEA and TEA (200 mL/min, 25 °C, RH = 50 %). Linear relationship (sampler amount vs sampling time 0-480 min): TEA (△): y = 0.077x+0.60, \( R^2 = 0.997 \); DEA (□):y = 0.14x+0.06, \( R^2 = 0.999 \); IPA (○):y = 0.13x+0.76, \( R^2 = 0.997 \).

Different sampling flow rates between 50–800 mL/min were investigated for collecting gas-phase aliphatic amines. A reduced sampling efficiency at sampling flow rates below 200 mL/min was observed (Figure 12), but more in-depth studies are needed to explain the phenomenon. Linear relationships between the collected amount of aliphatic amines and the sampling times were observed with correlation coefficients >0.977.
Figure 12. Sampling with various sampling flow rates. Six series (Sampling flow rates: 50–800 mL/min) of 5 samplers exposed to gas phase AA (○), IPA (–), NBA (+), DEA (△), DMEA (□), CHA (X) and TEA (◇) (30 – 60 min, 25 °C, RH = 50 %). Sampler concentration vs sampling flow rates 0–800 mL/min.

5.2.2.7 Dry methods for air sampling of alkanolamines

Air sampling of alkanolamines has been performed with sampling tubes containing silica gel or XAD-2 resin containing naphthyl isothiocyanate for derivatization and glass fibre filter, both plain and impregnated with sulphuric acid.

In paper V the sampler developed for isocyanates was used for alkanolamine sampling with the change that the filters were treated with 1.6 ml of 0.1 M sulphuric acid solved in methanol that was evaporated to dryness prior to sampling.

5.2.2.8 Evaluation of the dry sampler for alkanolamines

The extraction efficiency of alkanolamines from the filters was on average 99 %. The precision for sampling and work-up from collection of gas phase alkanolamines was < 4.8 %. At sampling flow rates of 200 mL/min the collection efficiency for the alkanolamines was > 99.9 % with no breakthrough. At sampling flow rates of 800 mL/min very minor breakthroughs were observed for DEEAA and MDEAA with collection efficiencies > 99.4 %. The sampler, pre-, or post-exposed to alkanolamines, could be stored at ambient temperatures for up to 45 days. The sampler was not affected by exposure to clean air flows for up to 10 h, either pre-, or post-exposed to alkanolamines.
Linear relationships between five different air concentrations of DMEAA and DEEAA, measured with the sampler and the PTR-MS signal, were obtained with correlation coefficients > 0.991. Linear relationships with correlation coefficients > 0.998 were observed for the collected amount of gas-phase DMEAA and DEEAA during varied sampling times between zero and eight hours.

After collection of gas-phase alkanolamines the denuder was dissected into eight parts to study the distribution of the analytes. For sampling flow rates of 200 mL/min nearly a tenth of the alkanolamines were collected in the first part of the sampler without the filter as a carrier for the acid (Figure 13). The second part of the denuder was collecting the highest amount of alkanolamines. The collected amounts then decline throughout the denuder. The end-filter collected between a tenth and a twentieth of the gas phase alkanolamines, demonstrating that the denuder is too short to collect all alkanolamines and the presence of the end filter is necessary to efficiently collect the alkanolamines. The denuder was more effective for alkanolamines with lower mass.

**Figure 13.** The distribution of alkanolamines in the sampler at a flow rate of 200 ml/min from entrance to end-filter. Bar order: DEEAA, DMEAA, IPAA and EAA.

For sampling flow rates of 1100 mL/min nearly none of the alkanolamines were collected in the first part of the sampler (Figure 14). The second part of the denuder collected a twentieth of the alkanolamines, the highest amount on the denuder. The collected amounts then declined throughout the denuder. The highest amount of alkanolamines in the sampler was on the end-filter, about half of the collected gas phase alkanolamines, because of drastically reduced collection efficiency for the denuder at higher sampling flow rates.
rates. This also indicates the necessity for laminar air flow through the denuder to achieve effective denuder diffusion. The efficiency of the denuder mainly depends on whether the flow through is laminar or turbulent, but also temperature, diffusion rate and if the adsorption is efficient or if transport in the denuder is occurring. Collecting alkanolamines at more varied sampling flow rates and under other atmospheric conditions is necessary to clarify the mechanisms present in the denuder.

**Figure 14.** The distribution of alkanolamines in the sampler at a flow rate of 1100 ml/min from entrance to end-filter. Bar order: DEEAA, DMEAA, IPAA and EAA.

Sampling flow rates between 50 and 800 mL/min were used to collect gas-phase alkanolamines. At sampling flow rates below 200 mL/min a reduced efficiency down to 80% was observed, but the phenomenon requires more investigation. Linear relationships between the collected amount of alkanolamines and the sampling times were observed with correlation coefficients >0.974 (Figure 15).
Figure 15. Sampling with various sampling flow rates. Six series (Sampling flow rates: 0–800 mL/min) of 5 samplers exposed to gas phase alkanolamine (30 – 60 min, 25 °C, RH = 50 %). Linear relationship (sampler amount vs sampling flow rates 0–800 mL/min); MDEAA (◇): \( y = 0.0003x, R^2 = 0.997 \), DEEAA (□): \( y = 0.003x+0.12, R^2 = 0.974 \), DMEAA (△): \( y = 0.010x+0.02, R^2 = 0.997 \), IPAA (⊙): \( y = 0.016x+0.32 R^2 = 0.990 \) and EAA (＊): \( y = 0.009x+0.09 R^2 = 0.992 \).

5.2.3 Passive sampling

5.2.3.1 Isocyanates

Passive samplers only collect the gas phase as it is based on diffusion. Particles are not collected. Exposure to airborne isocyanate typically consists of both vapour and aerosol and all presented methods have problems differentiating particles and gas so the research has been limited. Diffusion sampling of MIC with 2-MP \(^{340}\) and NBDPZ \(^{341}\) has been presented. DBA has been used with solid-phase microextraction (SPME) \(^{342,343}\) and active single-drop Micro Extraction (SDME) \(^{344}\).

In paper I passive sampling was investigated for the dry sampler. The diffusion of isocyanates during 15 – 120 minutes sampling periods without active airflow indicated a diffusion sampling flow rate of 29 - 45 ml/min (Figure 16). Pronounced variations of the results can be expected due to the strong dependence on the strength and direction of the ventilation when performing passive sampling.
Figure 16. Passive sampling of HDI (◇), IPDI₁ (□), IPDI₂ (△), 2,4-TDI (×) and 2,4-TDI (○) in standard atmospheres using dry samplers (n = 4) during exposure periods in the range of 15-120 min.

5.3 Aqueous extraction

5.3.1 Aromatic amines

Extraction of amines from PUR flexible foam with methyl-tert-butyl ether, toluene, and diluted aqueous acetic acid has been performed previously. All methods found TDA and in some cases MDA, but there have also been studies that could not find the presence of amines. That the concentrations of TDA and MDA rapidly decline in newly produced PUR foam products could be an explanation. Heat prior to sampling can affect the presence of amine, as can the extraction procedure depending on extraction media, temperature and duration.

In paper II TDA and MDA were extracted from flexible PUR foam according to the method developed by Marand el al 2004. In the initial step the amines was extracted with 3 ml 0.1% acidic acid solution from 0.2g flexible PUR foam pieces in a 10 ml syringe. Next the piston squeezed the foam sample 20 times before filtration into a new test tube.
5.3.2 Aliphatic amines

The most common way of extract aliphatic amines prior to derivatization is with solid-phase extraction (SPE) that has been performed with PFBAY on urine \(^{348}\), FMOC on urine \(^{349, 350}\), benzoyl chloride on waste water \(^{351}\), DNB on tap and river waters \(^{264}\), dansyl chloride on environmental water samples \(^{352}\), and irrigation ditch, residual and fountain waters \(^{353}\), SAMF on lake water, cheese and red and white wine \(^{13}\), and fluorescamine on rain and tap water \(^{354}\). Headspace SPME has been used with PFBAY on wastewater \(^{325}\) and SIBA on lake water \(^{263}\), headspace single-drop micro extraction with PFBAY on wastewater \(^{355}\), and SPME coated with Dibenzo-18-crown-6 for subsequent derivatization with TFBza-sue on lake water and human urine \(^{356}\). Other extraction techniques for aliphatic amines are ion-pair extraction of water and sediment followed by derivatization with IBCF IBCF \(^{326}\) and liquid-liquid extraction (LLE) of surface and waste waters derivatized with FMOC-CL \(^{251}\).

Various forms of SPE have also been used to extract free primary, secondary and tertiary aliphatic amines from different aqueous solutions such as SPE with beer and tuna \(^{14}\), SPME with wastewater \(^{357}\) and urine \(^{334}\), headspace microextraction with tap and river water samples \(^{358}\), and static headspace preconcentration of urine \(^{359}\). Other methods are extraction of free tertiary aliphatic amines from water and bottom sediment with distillation flask and bas/acid \(^{28}\) and the use of a minicolumn fild with C18 on wastewater and surface water to sample free primary aliphatic amines \(^{360}\).

5.3.3 Alkanolamines

Extraction of alkanolamines has been performed on soil and groundwater samples \(^{361, 362}\), plant extracts \(^{363}\), skin rinsing \(^{141}\) and steam condensates from pH correction, and corrosion protection additives in oil and gas treatment \(^{364-366}\).

In paper IV the content of alkanolamines in metal-working fluids (MWF) was analysed. The analysis of three different MWFs suggested that the content of alkanolamines were as specified or slightly higher than what was specified for the products. In addition, for two of the products additional alkanolamines than what was specified could be determined.
6 Analysis

6.1 Work-up

6.1.1 Isocyanate

The work-up procedure of dry-sampled isocyanates in paper I was improved compared to a previously presented method \(^{164}\). To improve extraction the denuder tube was washed with toluene after removal of the filters.

In paper I the work-up consisted of a toluene extraction of the filters in the denuder tube and in the filter cassette. A dual extraction of the toluene containing derivates from the reagent was performed with the addition of 1 mM sulphuric acid and methanol. The toluene phase was evaporated to dryness and dissolved in acetonitrile prior to LC-MSMS analysis.

6.1.2 Aromatic amine

TDA and MDA can be determined as free amines but different sample matrixes usually make some work-up with derivatization necessary. The derivatization of amines protects them from oxidation but can also provide improved chromatography and lower detection levels. Two methods based on derivatization have been used in paper II for comparison to free amine determination, one based on periflourofatty acid anhydrides and the other on chloroformate esters.

Methods for free aromatic amines that utilise acid solvent or acid filters for sampling use alkaline solution for desorption \(^{283, 284, 367}\) and vice-versa for alkaline sampling with acid desorption \(^{95, 283}\). This was in most cases followed by toluene extraction \(^{284, 320, 367}\), filtering \(^{320}\) if necessary, and a suitable solvent for the selected separation method. Work-up from urine was more complicated but achieved with the urine made alkaline, hydrolysed, an addition of phenylene-1,3-diamine followed by liquid-liquid extraction, toluene extraction and acidified with phosphoric acid in preparation for ion-suppression and ion-pair separation \(^{368}\).

In paper II the stability of aromatic amines in PUR foam extraction solution matrix was examined. The composition of the PUR foam extraction solution matrix varied considerably between different foams. This affected the stabil-
ity of mainly TDA but to some degree also MDA (Figure 17). Both TDA and MDA were stable in the extraction solution without the presence of the matrix.

![Figure 17](image)

**Figure 17.** The degradation of 2,4-TDA in three different PUR foam extraction solutions (□, ◊, △) and TDA standard solutions (○).

In paper II flexible PUR foam was derivatized with PFPA and ETCF according to Marand et al., 2004 \(^{217}\). Comparison between the methods using reagents and the free aromatic amines was performed and found a good agreement between free amine and ETCF but no correlation with PFPA that showed overall higher concentration (Figure 18). If the foam was treated with heat prior to extraction all three methods showed similar higher concentrations. It is known that heat releases TDA from foam, but neither the extraction time nor amount added PFPA affects TDA concentrations \(^{217}\). PFPA derivatization of different TDA/TDI urea or urethane derivates to determine if the degradation of the derivates caused the formation of free was performed but derivates showed no signs of degradation.
Figure 18. Derivatized TDA with PFPA (□) and ETCF (◊) versus free TDA. PFPA’s linear regression: $y = 8.4x + 2.03; R^2 = 0.322$. ETCF’s linear regression: $y = 0.997x - 0.043; R^2 = 0.889$.

The highly irregular instability of TDA and MDA in extraction solution does make determination of free amine a somewhat unreliable method since the analysis must be performed immediately after extraction.

6.1.3 Aliphatic amine

Work-up of amines sampled with aluminum tubes was done with sulphuric acid or deionized water for desorption to then neutralized to pH 7. Sampling tubes with phosphoric acid coated XAD-7 was desorbed with methanol/deionized water for 30 minutes of shaking then added to a solution of NaOH/methanol or desorbed with ammonium hydroxide in methanol with 30 minutes of shaking. A sulfuric acid-treated silica gel tube has been desorbed with methanol and neutralized with KOH. Sampling tubes containing silica gel have been desorbed with sulphuric acid.

In paper III after air sampling the filters were carefully removed from the denuder and end filter using tweezers. The filters were folded and placed in test tubes with screw caps. To the test tubes, volumes of 5 ml of a 50/50 water-acetonitrile (v/v) solution were used for desorption of the aliphatic amines from the filters. The extraction solution was then ultra-sonicated...
treated, shaken and centrifuged before one ml of extraction solution was transferred to a new test tube with 50 μl of IS added. After shaking 100 μl were transferred to a LC-vial.

6.1.4 Alkanolamine

In several methods alkanolamines are collected without reagents using impinger-flask sampling \(^{288}\) and filter sampling \(^{141, 146, 338, 339}\) and with wet sampling methods \(^{362, 363, 365, 369}\). Impinger flasks have been used hexanesulfonic acid \(^{288}\) for collection of alkanolamine and desorption from the filters has been done with methanol \(^{141}\), methanol with quinolone and NaOH \(^{146}\), aqueous sodium hydroxide solution \(^{339}\), and 1-octanol in acetone \(^{338}\).

In paper V after air sampling the filters were carefully removed from the denuder and end filter using tweezers. The filters were folded and placed in test tubes with screw caps. To the test tubes, volumes of 5 ml of a 50/50 water-acetonitrile (v/v) solution were used for desorption of the alkanolamines from the filters. The extraction solution was then ultra-sound treated, shaken and centrifuged before one ml of extraction solution was transferred to a new test tube with 50 μl of IS added. After shaking 100 μl were transferred to a LC-vial.

6.2 Standards

To compensate for possible losses during work-up a known concentration of a substance with similar physical and chemical characteristics as the analyte can be added to the sample solution at the start of work-up. The added known substance is called an internal standard (IS) and losses of the IS will mirror the losses the analyte. The IS also corrects for variations in injections and detector response. The ideal IS when performing MS-detection consists of compounds with the same chemical structure as the analyte, with some hydrogen atoms exchanged for deuterium atoms, giving comparable chromatography but an atomic mass slightly above that of the analyte.

To determine the quantities of the analyte, calibration to a known amount of the analyte is needed. The solution with the known concentrations of analyte is a standard solution. It can consist of one-point calibration or several points with increasing amount of standard solution added forming a calibration curve. If the detector has a very specific response to a functional group the response of the standard can be used as an external standard and compared directly to the analyte response and the concentration of analyte can be calculated. The ratio between IS and standard response can be compared to the ratio between IS and analyte response. From this the concentration of analyte can be calculated.
6.2.1 Isocyanates

In paper I standard solutions synthesised of DBA derivatised isocyanates and of the deuterium labelled DBA derivatised isocyanates as IS was used. The synthesis has been described previously \(^5,370\).

6.2.2 Aromatic amines

Standard solution in paper II contained 0.1 % aqueous acetic acid and various concentrations of the aromatic amines. The IS consisted of deuterium labelled correspondent to 2,4-, 2,6-TDA and MDA.

6.2.3 Aliphatic amines

Standard solutions in paper III consisted of 1:1 water/methanol and an addition of 0.2 % sulphuric acid with added concentrations of aliphatic amines. The IS deuterium-labelled forms of IPA, NBA, CHA, DEA, DIPA and TEA.

The extraction matrix solution was produced by extracting and work-up of several unexposed samplers. The extraction matrix solution was spiked with alkanolamines for comparison with standard solutions.

In paper III the stability of aliphatic amines was studied by accelerated aging in standard solutions and spiked extraction matrix solutions stored for 5 days at 4°C, 24°C and 44°C. A widely used accelerated aging relationship first published by Arrhenius \(^371\) was used to estimate the time and temperature required to accelerate the aging. This relationship is:

\[
AT_R = \frac{SA}{Q_{10}}
\]

Where

- \(AT_R\) = Aging time required (weeks)
- \(SA\) = Simulated age (weeks)
- \(T\) = Aging factor (number of degrees Celsius above ambient/10)
- \(Q_{10}\) = Reaction doubling rate (usually in the range of 1.6-2.0)

Calculated from equation 3 storage for five days at 24°C and 44°C correspond to 13-20 and 33-80 days storage at 4°C. Comparison of the two higher storage temperatures with the lower indicated that the aliphatic amines were not affected by storage in either standard solution or extraction matrix solution.
6.2.4 Alkanolamines

Standard solutions in paper IV consisted of aqueous 0.2 % sulphuric acid with concentrations of alkanolamines in the range of 0.04 - 3.0 µg/mL. The IS consisted N-tripropylamine (NTPA) or NPA and was added in volumes of 0.50 µL.

Standard solutions in paper V consisted of 1:1 water/methanol and an addition of 0.2 % sulphuric acid with added concentrations of alkanolamines. The IS consisted of deuterium-labelled forms of EA, IPA, DEA and TEA.

Extraction matrix solution was produced by extracting and work-up of several unexposed samplers. The extraction matrix solution was spiked with alkanolamines for comparison with standard solutions.

In paper V the stability of the alkanolamines was studied in the same way as the aliphatic amines above (Equation 3) and was found to not be affected by storage in either standard solution or extraction matrix.

6.3 Separation

6.3.1 Liquid chromatography (LC)

In LC the analytes pass with a mobile phase through a column holding a stationary phase. The analytes are retained on the column, depending on their polarity, size, functional groups, etc. If two mobile phases with different polarity are mixed in at a variable ratio a gradient flow can be achieved. With a polar mobile phase and a non-polar stationary a non-polar substance will be retained more than a polar substance. With a decrease of polarity of the mobile phase the retained non-polar substances will elute from the column.

The chromatographic analysis was performed with a micro-LC system. The low flow rate of the micro-LC decreases the amount/volume of mobile phase and allows smaller particles in the column without higher backpressure. This gives higher resolution and selectivity. The composition of the mobile phase was water, acetonitrile, and a volatile organic acid (formic- or acetic acid). On-column focusing injections were performed consisting of a focusing liquid with the opposite polarity of the sample solvent and mobile phase surround the smaller injection plug on both sides\(^ {178, 372, 373}\) (Figure 19). This enabled larger injection volumes without diluting the sample or loss of resolution.
6.3.1.1 Reversed phase (RP)

Nonpolar derivates were analysed with reversed phase (RP) LC on a 50-mm long column filled with octadecylsilica (C18) particles in size 2.5-3.5 µm. The mobile phase consisted of water and acetonitrile with a small addition of formic acid. A gradient was used going from water to organic with a flow rate of 70 µL/min. Water was used as focusing liquid.

6.3.1.2 Hydrophilic interaction liquid chromatography (HILIC)

Hydrophilic interaction liquid chromatography (HILIC) offers an alternative with a more or less reversal of the elution order compared with RP enabling separation of polar and charge molecules. Two HILIC columns were used. The first column was a 150 x 1.0 mm with 3.5 µm diameter particles of 200Å pore size coated with zwitter ionic particles (ZIC-HILIC). Before the ZIC-HILIC column was a pre-column of 1.0 x 5.0 mm with 3.5-µm diameter particles. The second column was 150 x 2.1 mm with 2.7-µm diameter fused core particles of 90Å pore size coated with a pentahydroxy phase consisting of five hydroxyl groups (OH5). Before the OH5-HILIC column was a guard-column of 0.5 x 2.1 mm with 2.7 µm diameter particles.

The suggested mechanism for HILIC is that the polar particles that make up the hydrophilic stationary phase create an aqueous layer around them causing the analytes to partition between it and the hydrophobic eluent (Figure 20). This gives an elution order more or less reversed compared with RP-LC. The mobile phase consisted of water and acetonitrile with a small addition of formic- or acetic acid (ZIC-HILIC) or formic acid/ammonium.
format buffer (OH5-HILIC). Gradient flow was used going from organic to water. Acetonitrile was used as focusing liquid.

**Figure 20.** Illustration of hydrophilic interaction of an analyte between zwitter ionic stationary phase and the hydrophobic eluent.

The composition of the solution to be injected into the LC column is crucial, and differences in eluotropic strength between the mobile phase and the injection solution affect the chromatography. To achieve good performance for polar compounds on HILIC, the sample solvent should have an organic content greater than 50%, where the scale of relative solvent strengths is: acetone < acetonitrile < isopropanol < ethanol < methanol < water. The use of a high strength sample solvent decreases the partitioning of solutes into the stationary phase, leading to reduced retention, lower chromatographic efficiency, and poor separation, especially for weakly retained compounds and large injection volumes. However, the use of weakly hydrophobic solvents for the extraction or dilution of samples is not always possible.

The higher percentage of acetonitrile in the mobile phase in HILIC compared with RP-LC makes HILIC more suitable for electrospray-mass spectrometry. Higher acetonitrile content can facilitate a more efficient desolvation and ionization.
6.3.2 Isocyanates

Separation with thin layer chromatography (TLC) was the first used separation technique for isocyanate-derivates and has been performed on Nitro, alcohol, and 2-PP derivate. Gas chromatography (GC) separation of isocyanates derivatized with alcohol and DBA has been reported. Size exclusion chromatography has been used with Nitro. Reversed phase liquid chromatography (LC) is the most common way to separate isocyanate derivates and has been used with Nitro, MAMA, 2-PP, 2-MP, Tryptamine, alcohol, DBA, MAP, PAC, NBDPZ, Fe-PZ, MMNTP, and DAN.

The separation of DBA derivatized isocyanates in article I was achieved with RP-LC performing on-column injections onto C18-columns. Samples were injected with on-column concentration consisting of water. The mobile phase composition was A; 95/5/0.05 and B; 5/95/0.05 water/acetoniitrite/formic acid (v/v/v). Gradient elution was performed from 40 % B to 100 % B in 10 min.

6.3.3 Aromatic amines

6.3.3.1 Free amine

Several methods to determine MDA and TDA without derivatization have been presented, both for GC and LC. Amine can be separation with LC either as uncharged or as protonated ions dependent on pH and the used buffer solution in the mobile phase. The commonly used RP column requires unprotonated analyte as protonated small amines normally eluted near the solvent front. Buffered mobile phase has in many cases a negative influence on MS determinations. RP-LC with mobile phase containing buffered solution has been reported but also ion-suppression and ion-pair separation and enrichment column followed by RP-LC.

On-column injections to a ZIC-HILIC-column were used for separation of TDA and MDA in paper II. The elution order of the amines were 4,4’-MDA, 2,6-TDA and 2,4-TDA (Figure 21). The extraction matrix had an influence on the chromatography and shifts in retention time could be observed for different foams. To obtain reliable chromatography the column had to be washed out after each chromatographic run for 3 min with the water phase.
Figure 21. ZIC-HILIC-ESI<sup>+</sup>-MRM chromatograms of solutions of free aromatic amines extracted from PUR foams. The concentration were: 0 mg 4,4'-MDA / kg foam, 0.29 mg 2,6-TDA / kg foam and 0.33 mg 2,4-TDA / kg foam. Mobile phase: linear gradient from 70/30/0.01 to 50/50/0.01 acetonitrile/water/acetic acid (v/v/v) during 10 minutes. Flow rate of 50 µl/min, injections of 5.0 µL.

6.3.3.2 Acid Anhydride

Separation of both TDA- and MDA-isomers as PFPA-derivates on GC<sup>387-390</sup> and on LC<sup>217, 220</sup> has been reported. In paper II of the previously developed RP-LC methods was used for comparison to the HILIC method<sup>217</sup>.

6.3.3.3 Chloroformate

TDA carbamate ester derivates have been separated on GC<sup>223</sup>. LC has been used to separate both TDA and MDA carbamate ester derivates<sup>49, 224</sup>. As a comparison to the HILIC method a previously developed RP-LC method was used in paper II<sup>49</sup>.

6.3.4 Aliphatic amines

GC has been used to separate aliphatic amines derivatized with DNFB<sup>391, 392</sup>, TFBza-suc<sup>356</sup>, TBCF<sup>231</sup>, IBCF<sup>251, 252, 326, 393</sup>, PFBAY<sup>325, 355, 394, 395</sup>, benzoyl chloride<sup>351</sup>, BSC<sup>233, 392</sup> and NPTFA<sup>325</sup>. Separation on LC has been attained for aliphatic amines derivatized with NITC<sup>256, 270, 321, 322</sup>, DNB<sup>262, 264</sup>, Dansyl<sup>259, 271, 352, 353</sup>, FBQCA<sup>247</sup>, Fluorescamine<sup>354, 396</sup>, NDA<sup>258</sup>, MDPF<sup>397</sup>, NBD-Cl<sup>259, 323, 324</sup>, TMPAB-Osu<sup>245</sup>, PITC<sup>260</sup>, SAMF<sup>13</sup>, OPA<sup>259</sup>, OPA/NAC<sup>29, 398</sup>, FMOC<sup>251, 350</sup>, PPIA<sup>244</sup>, BCEOC<sup>255</sup>, DBCEC-Cl<sup>253</sup>, and DBCPC-Cl<sup>254</sup>. Capillary electrophoresis (CE) has been used to separate FITC derivatized aliphatic amines<sup>257, 273, 399</sup>.
Free aliphatic amines have been separated with GC, LC as quaternary ammonium salt, pressure-assisted CE, a hybrid technique between CE and capillary high-performance liquid chromatography (pCEC) and with various forms of ion chromatography, cation and ion-exchange/ion interaction. Due to the polarity of free amines very few application of LC separation can be found.

On-column injections with an OH5-HILIC-column and a four-minute linear eluent gradient were used for separation of the aliphatic amines in paper III. The elution order of the aliphatic amines was DIPA, TEA, CHA, d11-CHA, NBA, DEA, DMEA, IPA, AA, and EA (Figure 22).

![Figure 22. OH5-HILIC-ESI\(^+\)-MRM chromatograms of free aliphatic amines in extraction matrix from the dry-sampler (2.0 µg/mL DEA, DIPA, DMEA, TEA, 4.0 µg/mL of NBA and CHA, 8.0 µg/mL of AA, 10 µg/mL of IPA and 20 µg/mL of NBA, DEA, DMEA, IPA, AA, and EA (Figure 22).](image)
6.3.5 Alkanolamines

Derivatized alkanolamines have been separated with GC, $^{274, 337}$, CE $^{273}$ and HPLC $^{270-272}$. Separation of underivatized alkanolamines has been performed with CE $^{366}$, GC $^{146, 364, 369, 403}$, RP-HPLC $^{339}$, ion pair RP-HPLC $^{288, 401}$, and ion exchange liquid chromatography (IC) both Cation $^{363, 402}$ and Anion $^{404, 405}$.

In paper IV a ZIC-HILIC-column with on-column focusing was used. A 25-minute linear eluent gradient achieved separation with an elution order of the alkanolamines of DIPEAA, DEEAA, DIPAA, DMEAA, MDEAA, IPAA, TEAA, NPAA, DEAA and EAA.

In paper V on-column injections onto an OH5-HILIC-column with a 6-minute linear eluent gradient achieved separation with an elution order of the alkanolamines of DEEAA, DIPAA, DMEAA, MDEAA, TEAA, IPAA, NPAA, DEAA, and EAA (Figure 23).
6.3.5.1 Evaluation of alkanolamines on the ZIC-HILIC-column

A minimum of 5 minutes was necessary to equilibrate the HILIC column between chromatographic runs and obtain reproducible retention times.

The composition of the focusing liquid was investigated with different ratios of organic phase (acetonitrile and acetone) and water ranging from 100 % organic phase to 100 % water. The focusing liquid required organic solvent in high concentrations to achieve chromatographic stability (Figure 24).
Figure 24. Varied composition of the focusing liquid: (A) 100 % acetone, (B) 100 % acetonitrile, (C) 3:1 (v/v) acetonitrile/water and (D) 1:1 (v/v) acetonitrile/water. (Injection volume: 1.0 µL, propanol amine conc: 0.2 µg/mL).

The range of injection volumes was tested with and without the use of on-column focusing. The use of on-column focusing made possible injections of 3 µL still maintaining good chromatographic characteristics, without on-column focusing a maximum of 1 µL injection could be performed (Figure 25).

Figure 25. Variation on injection volume of sample solution containing propanol amine (0.45 µg/mL): (A) with focusing liquid (20 µL loop injection, 1.5 µL) and (B) without focusing liquid (injection directly on the column, 1.5 µL).

The composition of the sample solution was examined with different ratios of water/acetonitrile ranging from 100 % water to 100 % acetonitrile, with and without the additions of sulphuric- or phosphoric acid of 0.01 %. Neither the sample solution composition nor the concentration of alkanolamines significantly affected the retention times. The height-to-area ratio increased with increased proportion of acetonitrile, whereas increased proportion of water decreased it, and the addition of acid had no significant effect.

The sample solution acidity-level impact on the chromatography was investigated and found to be optimal around pH 4 (Figure 26). For pH values below 4 peak splitting occurred for alkanolamines with the shortest retention times. At pH 7 alkanolamines with longer retention times could not be separated, and at pH 9.5, peak splitting occurred.
Figure 26. Alkanolamines in sample solutions with varied pH: pH 2 potassium dihydrogen phosphate buffer (0.1 M), pH 4.5 acetic buffer (0.2 M), pH 7 ammonium acetate buffer (0.2 M) and pH 9.5 ammonium buffer (Injection volume: 0.5 µL, Conc: 1.0 µg/mL).

The stability of the chromatography over time with consecutive runs was investigated after regeneration of the column. After regeneration of the column, 1-2 injections were needed before the peak shape stabilised and up to 100 injections before the retention times stabilised. After approximately 550 injections, the retention times became more erratic for all the alkanolamines, and the peak shapes for the four alkanolamines with the shortest retention times were altered (Figure 27). The peak shape for alkanolamines with longer retention time was not affected.
Figure 27. Consecutive chromatographic runs (2-702) for (A) m/z: 134 → 116 DIPA, (B) m/z 76 → 58 IPA, and (C) NPA (Injection volume: 0.5 µL, Conc: 0.45 µg/mL).

6.4 Detection

6.4.1 Mass spectrometer (MS)

6.4.1.1 Triple quadropole (Q3)

The mass spectrometer technique used was a triple quadropole. It is based on quadropoles that separate the molecular ions by their mass-to-charge ratio (m/z). A quadropole consists of four metal rods that function as electrodes with alternated voltage on the different rods but with an overall constant voltage. Depending on voltage only ions with a specific m/z can keep a sta-
ble trajectory. Ions that don’t match the voltage collide with the rods. Gradual increase of the voltage scans the spectrum. Selective ion recording (SIR) means selecting a limited number of voltage settings allows only specific m/z to pass through, increasing analysis time which lowers detection limit. A set of three quadrupoles connected in series becomes a triple quadrupole. Scans and SIR can be performed with the first and the third quadrupole. Multiple reaction monitoring (MRM) use the first quadrupole in SIR, the second quadrupole performs collision induced dissociation (CID) which fragments the selected ions from the first, and the third quadrupole measures selected fragments with SIR, improving selectivity compared with single quadrupole SIR. Production ion scan is similar to MRM, but the third quadruple is scanning the fragmentation products. Precursor ion scan reverses the order so the first quadrupole scans, and the third performs SIR, detecting all ions that have a fragment of a specific m/z. Electron multipliers are used for ion detection.

When a MS is connected with a LC-system an interface is needed to ionize the analytes and evaporate the mobile phase. For this Electro Spray Ionisation (ESI) was used. The mobile phase with analyte is sprayed with heated nitrogen gas through a capillary that has a positive or negative potential. The exact mechanism for ESI is not fully understood, but it evaporates the mobile phase so that only charged ions enter the inlet to the MS. With limited fragmentation ESI is considered a soft ionization method.

To establish the fragmentation pattern from a precursor ion scan a technique called the hydrogen deuterium exchange technique can be used. The hydrogen deuterium exchange technique is based on exchangeable backbone hydrogen in the molecule, which will exchange with deuterium atoms when placed in a heavy water (D₂O) solution. The exchangeable backbone hydrogen constitutes of such functional groups as primary and secondary amines, alcohols, carboxylic acids, and thiols. It does not exchange the hydrogen of an alkyl group. The exchange is very slow on aromatic rings.⁴⁰⁶, ⁴⁰⁷

6.4.1.2 Proton transfer reaction mass spectrometry (PTR-MS)

A direct reading mass spectrometer instrument was used based on proton transfer reaction of H₃O⁺ for chemical ionization (CI) coupled with quadrupole MS, Proton Transfer Reaction Mass Spectrometry (PTR-MS)⁴⁰⁸-⁴¹⁰. This allows the measurement of volatile chemical ionization (VOC) at a ppb level in real-time. The PTR-MS has an open heated head-space inlet that makes it less sensitive to memory effects but more vulnerable to particles. The inlet pressure is regulated and lowered with membrane and turbo pumps. A negative pressure gradient coupled with an electric field transports the charged water from the ion source to the drift chamber where the ions react with the sample gas if the sample molecules have greater proton affini-
ty than water and then via several lenses to the quadropole to be detected by multichannel plate detector.

6.4.2 Chemiluminescent nitrogen detector (CLND)

A chemiluminescent nitrogen detector (CLND) coupled with LC was used for determination of reference solutions. The CLND reacts with organic compounds containing nitrogen giving an equimolar response. Any organic-nitrogen compounds can thus be used as an external standard. The flow from the LC is nebulized with argon and oxygen in an oven set to 1050°C. The pyrolysis products containing nitrogen are oxidized to nitrogen oxide, split, dried and reacted with ozone to form nitrogen dioxide in excited state. When the excited nitrogen dioxide relaxes to ground state it emits a photon that is detected by photomultiplier tube. To avoid nitrogen in the mobile phase, that otherwise would overload the detector, methanol and water is used. Caffeine was used as an external standard. Caffeine is inexpensive, easy to weigh in, stable for extended times in solutions, and has low hygroscopicity and a high melting point.

6.4.3 Isocyanates

The first detection methods for isocyanate derivates were spectral analyses. Detection with UV became the most widespread method for detection of isocyanates until the end of the twentieth century and several reagents were developed with primarily UV-detection in consideration, enabled by containing aromatic rings. UV-detection has been performed with Nitro, 2-PP, MAMA, 2-MP, Alcohol, MAP, PAC, NBDPZ, MMNTP and DAN. If the reagent lacks aromatic ring, such as DBA, only aromatic isocyanates can be detected with UV.

To improve selectivity UV-detection can be combined with FL- or EC-detection. Reagents containing an anthracene group are especially suitable for a combination of UV-FL detection techniques such as MAMA, MAP, and PAC, but a combination of UV and FL has also been used for 2-PP and NBDPZ. Reagents analysed with UV-EC are 2-MP, ethanol, MAP, and DAN. Tryptamine was developed for a combination of EC-FL detection.

In the first decade of the twenty-first century MS detection became the more common detection method and has supplanted UV-detection. MS is more expensive than UV, but offers better selectivity and higher sensitivity. Some of the earlier developed reagents are not suitable for MS detection but several have been adapted for MS such as DBA, NBDPZ, and 2-MP. Fc-PZ was developed for MS in combination with EC.
In paper I ESI\textsuperscript{-}-MSMS in MRM mode was used to monitor the protonated DBA-isocyanate derivates and the DBA fragment. The deuterium-labelled d\textsubscript{9}-DBA-isocyanates used as IS was monitored in the same way.

PTR-MS was used for measuring gas phase isocyanates in the exposure chamber in paper I. On-line measurement of isocyanates with the PTR-MS enabled tuning of the isocyanate generation apparatus.

The CLND was used in paper I to quantify the DBA-isocyanate derivates used as standard and the deuterium labelled d\textsubscript{9}-DBA-isocyanates used as IS to determine the concentration prior to the preparation of standard solutions.

6.4.4 Aromatic amines

6.4.4.1 Free amine

TDA and MDA without derivatization have been determined with ultraviolet detection\textsuperscript{95, 283, 320, 412} and electrochemical detection\textsuperscript{95, 320, 368}.

Electro spray coupled with triple quadrupole was used for detection in paper II. The structure of the production ions was established by comparison with deuterium labelled standards and by hydrogen-deuterium exchange of both amines and their internal standards. TDA primarily fragmented with either the loss an ammonia or a methyl-group with corresponding fragments for deuterium labelled and for the deuterium exchanged TDA (Figure 28). For MDA loss of aniline was the most abundant followed by the loss of ammonia with corresponding fragments for deuterium labelled and for the deuterium exchanged MDA.

\textbf{Figure 28.} Product ion scan of 2,4-TDA in water(A) and in heavy water (B) with corresponding structures for the fragments.

6.4.4.2 Acid Anhydridez

Determination of MDA and TDA as PFPA-derivates has been performed with MS coupled with GC\textsuperscript{387-389, 413} and LC\textsuperscript{217, 220}. Electron Capture with GC has also been reported\textsuperscript{219}. Characteristics of Amino-PFPA-derivatives on ESI-MS have been described previously\textsuperscript{217}, used in paper II.
6.4.4.3 Chloroformate

TDA and MDA as carbamate ester derivates have been determined with MS, ultraviolet and nitrogen selective detector coupled with LC. Amine-ETCF-derivatives characterized with ESI-MS have previously been described, used in paper II.

6.4.5 Aliphatic amines

Since most reagents for aliphatic amines have been developed for detection with FL and/or UV detector almost all derivates have been detected with FL/UV, dansyl, dabsyl, ninhydrin, NBD-Cl, NITC, OPA, OPA-NAC, FMOC, fluorescamine, fluorescein, MDPF, SIBA, PPIA, DNB, PITC, BCEC-Cl, BCEOC, FBQCA, and TMPAB-Osu. Other detection methods for derivatized aliphatic amines are electron capture detection (ECD) with PFBAY, thermospecific detector (TSD) with PFBAY and IBCF, FID with SIBA, TFBza-suc, PFBAY, and NPTFA, amperometric detection with NDA, and amperometric oxidative detection with PITC. MS coupled with chromatographic methods have been performed with GC-MS for PFBAY, benzoyl chloride, BSC, TCECF, IBCF, DNFB, and SIBA; and with LC-MS for NITC, DBCEC-Cl, DBCPC-Cl, and Dansyl.

Free aliphatic amines have been determined with FID, nitrogen-specific detector, and with thermal desorption system (TDS). Detection methods coupled with chromatographic systems for determination of free aliphatic amines are GC-MS, LC-MS, pCEC-MS, ion chromatography with Electrochemical Detector Model ED, and indirect conductivity.

In paper III the aliphatic amines were detected with MS in MRM mode of the most abundant fragment. The fragmentation of the primary aliphatic amines resulted in the loss of the amino group (Figure 29). Both secondary and tertiary amines fragmented with the loss of an alkene-group, and the amine reduced to a primary/secondary amine (Figure 29). The cyclic CHA and d11-CHA fragmented with loss of amino group and the loss of ethylamine though retro-Diels–Alder (Double α-cleavage) (Figure 29).
Figure 29. Product ion scan of deuterium labelled NBA (A), DEA (B) and CHA (C) with corresponding structures for the fragments.

PTR-MS was used for measuring gas phase aliphatic amines in the exposure chamber in paper III. On-line measurement of aliphatic amines with the PTR-MS enabled tuning of the aliphatic amines generation apparatus.

Mass spectra were obtained and the fragmentation pattern was studied for gas-phase AA, IPA, IBA, DEA, DMEA, TEA, and CHA. For all studied aliphatic amines the protonated molecular ions were the most abundant ion.

The response time for the PTR-MS (the time before a stable response is obtained when introducing the PTR-MS inlet to a standard atmosphere) was studied as well as the influence of the response time and possible losses when using different length of glass transfer lines. 50- and 100-cm glass transfer lines at the same linear flow rate were used for the sampler. No losses of the aliphatic amines were seen when introducing glass transfer lines prior to the inlet. However, the response time of the PTR-MS increases for some aliphatic amines with increasing length of glass transfer line. All tested aliphatic amines, except CHA, reached stable concentrations for all the lengths of glass tube in less than 2 minutes. CHA required 3 minutes to achieve stable concentrations without glass connection and an increase of 2 minutes per meter glass tube.

6.4.6 Alkanolamines

Detection of derivatized alkanolamines has been performed with Flame Ionization detection (FID) \(^{276, 337}\), FL \(^{272, 418}\), TSD/nitrogen phosphorous selective detection \(^{274}\), Chemiluminescence \(^{419}\), conductivity detector \(^{362, 420}\), Spectrofluorimeter \(^{250}\), laser-induced fluorescence (LIF) \(^{273}\), MS \(^{279, 280}\), MSMS \(^{271}\), and UV \(^{267, 269}\).
Detection of underivatized alkanolamines has been performed with FID, FL, UV, TSD/nitrogen phosphorous selective detection, Amperometric, and MS, both with SIR and MRM.

The combination of chromatography with mass spectrometry has been done both with GC and IC (LC/MS).

In paper IV and V the alkanolamines was detected with MS in MRM mode of the most abundant fragment. The structure of the production ions was studied with hydrogen-deuterium exchange. The most common fragmentation pattern was the loss of one or more water molecules as has been shown before. The exception was DIPEAA where the loss of a propylene group was the most prominent fragment. Alpha cleavage was the dominant reaction of amines with the loss of the largest alkyl group resulting in a double bond between nitrogen and carbon, a comparison between alkanolamines with and without deuterium indicated that a similar double bond is generated with the loss of water instead of alkyl group in alkanolamines (Figure 30). For secondary and tertiary alkanolamines the loss of alkyl group and/or alkanol-groups results in the lower molecular weight fragments.

**Figure 30.** Product ion scan of IPAA (A) and DEAA (B) solved in water and of IPAA (C) and DEAA (D) solved in heavy water with corresponding structures for the fragments.

PTR-MS was used for measuring gas phase alkanolamines in the exposure chamber in paper V. On-line measurement of alkanolamine with the PTR-
MS enabled tuning of the alkanolamine generation apparatus. Mass spectra were obtained and the fragmentation pattern was studied for EAA, IPAA, DMEAA and DEEAA. For EA and IPA the most abundant fragmentation was the loss of water [MH-18]+. The most abundant fragment for DMEAA and DEEAA were the protonated molecular ion.

The response time for the PTR-MS was studied in a similar way as for aliphatic amines. No losses of the alkanolamines were seen with transfer lines prior to the inlet. The response time for DEEAA and DMEAA were less than 4 minutes for all lengths of glass tube (Table 7). EAA had 7 minutes, and IPAA had 6 minutes of response time without glass connection and for both EAA and IPAA the response time increase by 7 minutes per meter glass tube.

Table 7. PTR-MS response time (the time required before a stable response is obtained when introducing the PTR-MS inlet to a standard atmosphere) with and without glass transfer lines prior to the inlet. Linear relationship was for DEEA: \( y = 0.02x+2 \) \( R^2 = 0.99 \), DMEA: \( y = 0.01x+1.8 \), \( R^2 = 0.75 \), IPA: \( y = 0.07x+5.8 \), \( R^2 = 0.99 \) and EA: \( y = 0.07x+7.2 \), \( R^2 = 0.99 \).

<table>
<thead>
<tr>
<th>PTR-MS inlet</th>
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<td>DEEAA</td>
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7 General discussion

"The robustness of analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage" 424

To investigate the robustness of an air-sampler, stable sampling conditions are necessary. A constant generation of the analytes within desired concentrations and sampling in a controlled atmosphere must be accomplished. For this the availability of climate chamber technology is necessary.

Several factors need to be clarified to ensure the robustness of a sampler. It is essential to know the capacity of a certain sampler, the maximum amount of the analyte in air that the sampler is capable to reliably collect. The capacity must exceed levels of air-borne compounds expected to occur in working life to be able to perform efficient collection. The capacity should be well above the OEL levels to make certain that air levels are secure and not exceeding toxic levels. Further, both gas phase and particle-borne compounds must be taken into account.

The ability to monitor compounds of interest for an entire working day is essential. There is also a need to collect samples during shorter periods of time, e.g., 5 minutes. Short sampling times result in less collected amount. Hence the sampler needs to be able to sample with > 2 orders of magnitude different sampling times. In addition the sampler must collect short-time high-exposure peaks without breakthrough.

In working life humans may typically be exposed at temperatures between 5 C° to at least 50 C°. There is therefore a need to know how different temperatures affect sampler performance.

A certain flow rate is often described to standardize sampling conditions. Still the recommended flow rate must often be exceeded in cases where the sampling equipment is not appropriate for a certain flow rate. In such case there is a need to know if the performance is still within an acceptable range. If the sampler is based on a certain kind of flow (laminar or turbulent) flow rates beyond the recommended might completely disable the sampling capabilities. If the flow rate is too low, misleading results may be obtained. At low flow rates the “real” flow rate is the sum of the pump flow rate and the passive sampling flow rate. Often the passive flow rate is uncertain. If the
flow rate is too high a breakthrough may occur. This has also been observed in this thesis.

Even if the sampling time and the sampling flow rate are well known there is a need to find out the phenomena that are involved during sampling. The knowledge of how the analyte is distributed during sampling at different conditions adds information regarding the robustness.

The properties of the sampler may be affected by other compounds present in air. E.g., water is always present in air at different concentrations. Possible losses of sampling reagent or side reactions that consume the sampling reagent must be investigated. In addition, compounds that have been collected in the sampler may be lost by side reactions during and after sampling.

The storage times of the sampler, both prior to exposure and after sampling prior to analysis are important factors especially from a practical aspect. Field preparation of a sampler or work-up in the field is possible but not practical. The sampler’s sensitivity to light, air, heat, cold, and physical interactions over time also govern the storage conditions and capability.

Knowledge of the robustness of the sampler will in large part determine the precision and reliability of the analysis. The robustness of the work-up, how completely the recovery is following sampling and analysis, and the precision of separation and determination constitute the ultimate factors in deciding if the results of the analysis are to be trusted.
8 Conclusions

For collection of gas-phase isocyanates and isocyanate aerosols generated during thermal degradation of polyurethane, the dry air-sampler was demonstrated to be a superior alternative to impinger flask-filter sampling, allowing easy and precise sampling without the need of field extraction. The dry-air sampler enables sampling for more than a day and possibly longer. The dry–air sampler was found to be unaffected by variation in temperature, humidity, flow rate and pre- and post-sampling of ambient air, with no breakthroughs. The dry sampler can be stored several weeks.

The new air sampler is able to collect gas-phases of both aliphatic- and alkanolamines. The combination of the acid-impregnated denuder followed by a filter improves the sampling efficiency, and sampling can be made under dry conditions. The amines become protonated and hence are stabilised. The air sampler has the potential to separate gas-phase from particle-borne amines. A low back pressure during sampling enables a variety of flow rates. This makes the air sampler practical for field work. Essentially non-toxic compounds are used which makes it easy to ship and handle. The work-up includes a simple extraction of amines to an aqueous solution, drastically reducing the work-up time compared to methods based on derivatization.

The air sampler is able to perform collections during both short- and long-time sampling. It is robust against presence of moisture and the air-sampler can be stored several months, both pre and post exposure. The air sampler was found to be unaffected by half day of pre- or post-sampling to ambient air. The capacity is sufficiently high to collect amines at the occupational exposure limits levels or above. Depending on diffusion the gas phase is predominantly collected in the first part of the denuder. The other parts of the denuder continue to trap the amines and are also a reservoir of impregnation media. Higher flow rates disturb the laminar flow throughout the denuder and more of the gas phase ends up on the filter. Climate chamber studies are essential to study the robustness of the air sampler.

Hydrophilic interaction liquid chromatography (HILIC) was demonstrated to efficiently separate various amines on routine basis with a properly maintained system. Compared to reversed-phase liquid chromatography (RP-LC) the peaks were found to be somewhat broader, but different compounds with very similar chemical structure can be separated by slightly changing the
chromatographic conditions. In RP-LC such separations can be difficult to obtain. Aqueous injection of amines on HILIC was enabled by partially filled loop injections where the central sample plug was surrounded by organic phase. The composition of the sample solution did not alter RP, with only minor effects on peak shape but with greatly affected peak area. Extreme pH-change did affect both retention times and peak shape. RP for the different compounds was found to be about the same during several weeks of chromatographic runs. The pentahydroxy phase-HILIC column (OH5-HILIC) required less the half the time to achieve separation compared to the zwitterionic-HILIC-column (ZIC-HILIC), whereas ZIC-HILIC was better at isomer separation. The overall impression was that the OH5-HILIC was more robust.

ZIC-HILIC enabled determination of aromatic amines in solutions of extracts from polyurethane foam without derivatization. The extraction matrix solutions varied between different foams and affected the chromatography and the limit of detection. Immediate analysis after extraction was necessary due to oxidation of the free amines in extraction matrix solutions. In contrast, solutions of pentafluoropropionic anhydride (PFPA) or ethyl chloroformate (ETCF) derivatives were stable after work-up. The chromatography and the detection limits are also improved for the PFPA and ETCF derivatives. An agreement was observed when comparing results obtained by ZIC-HILIC with tandem mass spectrometry (MSMS) determinations of free amines and RP-LC-MSMS determinations of ETCF amines. RP-LC-MSMS determinations of PFPA derivatized amines were generally higher and reflect a fraction of free aromatic amines and compounds that liberates aromatic amines.

With two different linear elution gradients on the OH5-HILIC separation of both aliphatic- and alkanolamines was achieved. Precise determinations were made possible for the compounds having corresponding amines that were deuterium labelled for use as internal standards. For the amines that lacked such deuterium-labelled standards the precision were less precise. A drawback of the OH5-HILIC is the buffer in the mobile phase and the high flow rates required that affect the performance of the ion source resulting in the need to routinely rinse the inlet to the MSMS.

The hydrogen-deuterium exchange technique provided valuable data for the electrospray-MSMS characterization work. The main fragmentation pattern for the aromatic amines was found to be either methyl or ammonia. For alkanolamines the main fragmentation pattern was found to be the loss of one or more water molecules. Other products of the fragmentation were the loss of one or more alcohol groups. For aliphatic amines the main fragmentation pattern was observed to be the loss of ammonia for primary amines and the loss of one alkyl group for secondary and tertiary amines.
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