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Determination of organonitrogen compounds in air using liquid chromatography and mass spectrometry —

Part 1:
Isocyanates using dibutylamine derivatives

Détermination des composés organiques azotés dans l'air par chromatographie liquide et spectrométrie de masse —

Partie 1: Isocyanates par les dérivés de la dibutylamine

Reference number
ISO 17734-1:2006(E)

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Foreword

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International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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ISO 17734-1 was prepared by Technical Committee ISO/TC 146, *Air Quality*, Subcommittee SC 2, *Workplace Atmospheres*.

ISO 17734 consists of the following parts, under the general title *Determination of organonitrogen compounds in air using liquid chromatography and mass spectrometry*:

- *Part 1: Isocyanates using dibutylamine derivatives*
- *Part 2: Amines and aminoisocyanates using dibutylamine and ethyl chloroformate derivatives*

Introduction

Isocyanates have been used in industry for about 50 years. They are commercially important chemicals mainly used for the production of polyurethane (PUR). In spite of controls to limit exposures, there are adverse health effects such as asthma, contact dermatitis and hypersensitivity pneumonitis as a consequence of exposure to isocyanates in some industrial sectors.

The analytical method for the determination of isocyanates in workplace air must be sensitive due to the high irritation and sensitization properties of isocyanates. Extremely low occupational exposure limits (OELs) exist in many countries, and concentrations well below the OEL (< 1/100) often must be determined. Isocyanates are very reactive and therefore cannot be analysed directly. Derivatization during sampling is required in order to prevent interfering reactions. Hundreds of different isocyanates are used in industry, and many more are formed during thermal degradation of PUR. Therefore the analytical method must be highly selective.

The determination of isocyanates in the work environment using di-*n*-butylamine (DBA) as a reagent and liquid chromatography-mass spectrometric detection (LC-MS) has been demonstrated to be a robust method. The development of the method was initiated when difficulties using the “older” methods during sampling of isocyanates in complex atmospheres were encountered (e.g. thermal decomposition of PUR) [1], [2], [3]. The reaction rate between DBA and isocyanates was found to be fast, and high concentrations can be used to secure instantaneous reactions and eliminate problems with interfering compounds [4], [5]. Using impinger flasks containing a reagent solution and a filter in series efficiently collects and derivatizes isocyanates in both the gas and the particle phase [6]. LC-MS/MS of the isocyanate-DBA derivatives enables highly selective and precise determinations down to levels below 10^{-6} of the OEL [7].

Solvent-free sampling can also be performed by using a tube coated with a DBA-impregnated glass fibre filter followed by an impregnated filter. An impregnation solution containing DBA together with an acid is used, and the formed ion pair reduces volatility. DBA remains on the filter even after 8 h of sampling [8].

Monomeric isocyanates that are formed during thermal decomposition of polymers [typically PUR and phenol/formaldehyde/urea (PFU)-resins], such as isocyanic acid and methyl isocyanate, can also be determined [6], [7], [8], [9], [10]. Volatile isocyanate DBA derivatives can be determined using gas chromatography (GC)-MS [9]. Using the DBA-method and derivatization with ethyl chloroformate makes simultaneous determinations of amine, aminoisocyanates and isocyanates possible, as described in the companion method ISO 17734-2.

For quantification, reference compounds are necessary but are only available for a few monomeric isocyanates. Most of the isocyanates that are used in industry for the production of PUR can only be obtained in technical grade mixtures. Many isocyanates that are formed during thermal degradation are not available and are not easily synthesized. In this method, a nitrogen sensitive detector has been used for quantifying isocyanates in reference solutions. This technique has been demonstrated to be a useful tool, together with MS characterization, in greatly facilitating the production of reference solutions [10], [11], [12].

For quantifying isocyanates in complex mixtures, MS detection is necessary and provides a unique possibility of identifying unknown compounds. This method has enabled assessment of new areas for which exposure to isocyanates previously was not known and has identified new kinds of isocyanates in the work environment [6], [7], [8], [9], [10], [11], [12].

Determination of organonitrogen compounds in air using liquid chromatography and mass spectrometry —

Part 1:
Isocyanates using dibutylamine derivatives

1 Scope

This part of ISO 17734 gives general guidance for the sampling and analysis of airborne isocyanates in workplace air. When amines and aminoisocyanates are suspected to be emitted (e.g. from thermal degradation of PUR), it is recommended that in addition to isocyanates the amines and aminoisocyanates in air are determined, using DBA and ethyl chloroformate as reagents (ISO 17734-2).

The method is suitable for the determination of a wide range of different isocyanates in both the gas and particle phases. Typical monofunctional isocyanates that can be determined are isocyanic acid (ICA), methyl isocyanate (MIC), ethyl isocyanate (EIC), propyl isocyanate (PIC), butyl isocyanate (BIC), and phenyl isocyanate (PhI). Typical monomeric diisocyanates include 1,6-hexamethylene- (HDI), 2,4- and 2,6-toluene- (TDI), 4,4’-diphenylmethane- (MDI), 1,5-naphthyl- (NDI), isophorone- (IPDI), and 4,4’-dicyclohexylmethane diisocyanate (HMDI). Multifunctional isocyanates that can be determined are typically oligomers in polymeric MDI, biuret-, isocyanurate-, and allophanate-adducts and prepolymeric forms of isocyanates.

The instrumental detection limit for aliphatic isocyanates is about 50 fmol and for aromatic isocyanates, it is 2 fmol. For a 15-l air sample, this corresponds to 0,6 ng·m^{-3} for HDI and 0,02 ng·m^{-3} for TDI.

The useful range, for a 5-l air sample, of the method is approximately 0,001 µg·m^{-3} to 200 mg·m^{-3} for TDI.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 16200-1:2001, *Workplace air quality — Sampling and analysis of volatile organic compounds by solvent desorption/gas chromatography — Part 1: Pumped sampling method*

ISO 5725-2:1994, *Accuracy (trueness and precision) of measurement methods and results — Part 2: Basic method for the determination of repeatability and reproducibility of a standard measurement method* (including Technical Corrigendum 1:2002)

3 Principle

Samples are collected by drawing a known volume of air through a midget impinger flask followed by a filter. The impinger contains 10 ml of 0,01 mol l^{-1} of DBA in toluene and the filter is a glass fibre filter with no binder.

Solvent-free sampling can also be performed by drawing air through a tube coated with a DBA-impregnated glass fibre filter followed by an impregnated filter. An impregnation solution containing DBA together with acetic acid is used, the ion pair so formed reducing the volatility and enabling long-time sampling.

After sampling, deuterium-labelled DBA-isocyanate derivatives (used as internal standard) are added to the sample solutions. The excess reagent and solvent are evaporated, and the samples are dissolved in acetonitrile. The samples are analysed using reversed-phase LC and electrospray (ESP)-MS detection, monitoring positive ions. Quantification is made by monitoring selected ions. See Figure 1.

Quantification and qualitative determinations can be performed using different LC-MS or LC-MS/MS techniques. LC-CLND (chemiluminescent nitrogen detection) or for aromatic isocyanates LC-UV (ultraviolet detection) can be used for the determination of higher concentrations of isocyanates.

Reference materials can be characterized using LC-MS/CLND. For characterization of volatile compounds, GC-thermionic specific detector (TSD) can also be used.

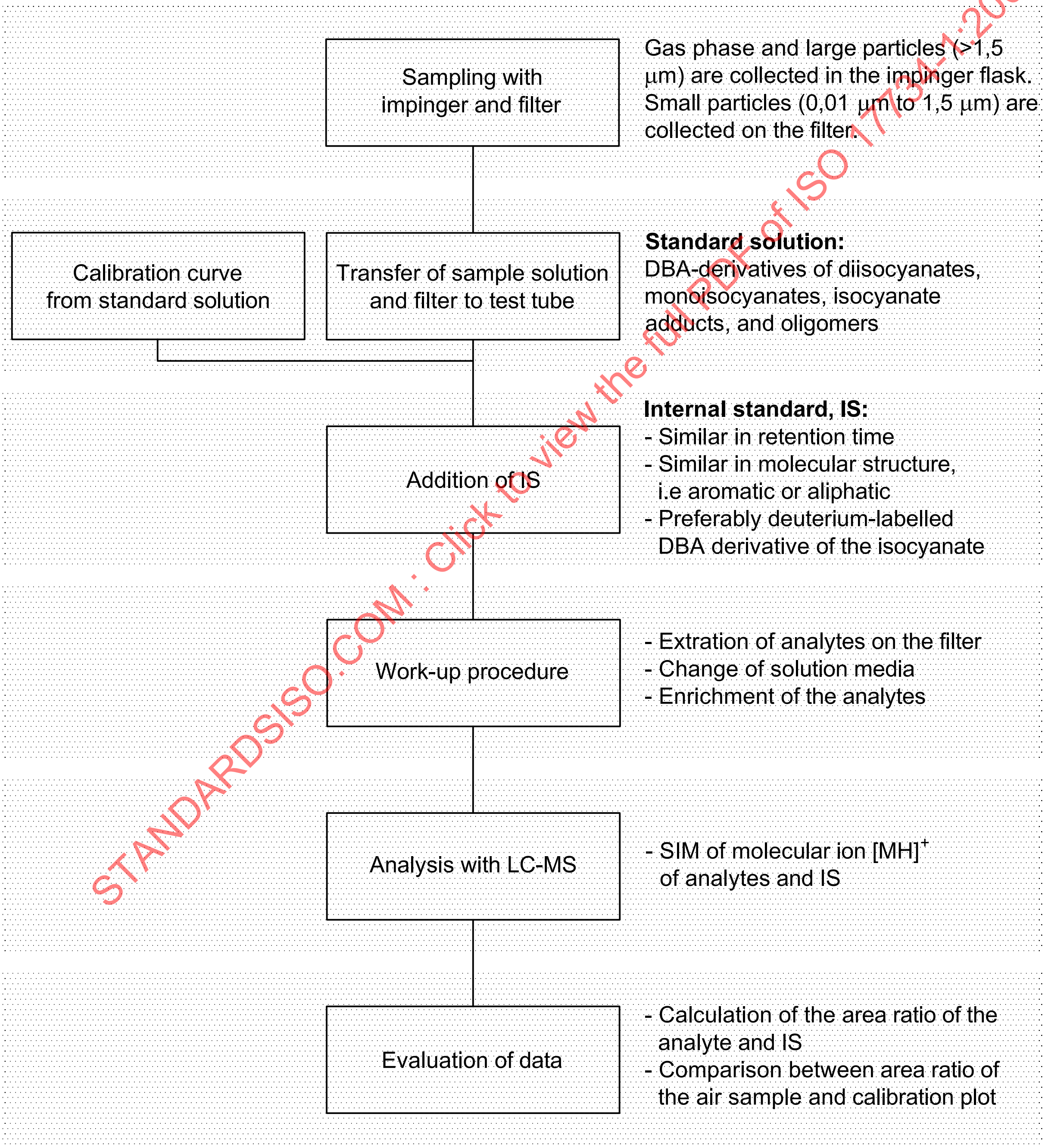


Figure 1 — Principle of the described method

4 Reagents and materials

4.1 DBA reagent.

Analytical grade di-*n*-butylamine is commercially available.

4.2 Solvents.

The reagent solvent, typically toluene, and other solvents, acetonitrile, isooctane and methanol, should be of liquid chromatographic quality.

4.3 Formic acid, concentrated formic acid, analytical grade.

4.4 Acetic acid, concentrated acetic acid, analytical grade.

4.5 Reagent solution.

In a 1-l volumetric flask, dilute 1,69 ml of DBA in toluene, and make up to the mark. The solution is stable and no special care during storage is necessary.

4.6 Reagent solution for solvent-free sampler.

4.6.1 Solution 1: 0,74 mol l^{-1} DBA.

Mix 80 ml methanol and 12,5 ml DBA in a 100 ml volumetric flask. Then while stirring, slowly add 4,16 ml of acetic acid to the flask. Finally, add methanol to the flask, and make up to the mark.

4.6.2 Solution 2: 1,5 mol l^{-1} DBA.

Mix 60 ml methanol and 25 ml DBA in a 100 ml volumetric flask. Then while stirring, slowly add 8,32 ml of acetic acid to the flask. Finally, add methanol to the flask, and make up to the mark.

4.7 HPLC mobile phases.

4.7.1 LC-MS.

The weak mobile phase (mobile phase A) consists of water/acetonitrile (95/5 volume fraction) and 0,05 % formic acid. The strong mobile phase (mobile phase B) consists of water/acetonitrile (5/95 volume fraction) and 0,05 % formic acid. The mobile phases are degassed prior to use.

4.7.2 LC-CLND.

The weak mobile phase (mobile phase C) consists of water/methanol (95/5 volume fraction) and 0,05 % formic acid. The strong mobile phase (mobile phase D) consists of water/methanol (5/95 volume fraction) and 0,05 % formic acid. The mobile phases are degassed prior to use.

5 Preparation of standard solutions

5.1 Reference compounds

Reference compounds are necessary for LC-MS determination of isocyanate derivatives. For the commercially available isocyanates, the DBA derivatives are easily prepared by direct derivatization with DBA. DBA derivatives for the isocyanates not commercially available can be made from the bulk material or from the thermal decomposition of PUR or urea-based resins used at the work place. Alternatively, standard solutions can be purchased.

5.2 Di-*n*-butylamine (DBA) derivatives of isocyanates

5.2.1 Preparation of isocyanate-DBA derivatives of commercially available isocyanates

Many frequently used isocyanates are commercially available from companies supplying laboratory chemicals such as HDI, 2,4-and 2,6-TDI, 4,4’-MDI, 4,4’-HMDI, 1,5-NDI, IPDI, PHI, MIC, EIC, PIC and BIC. The purity of the isocyanates varies, and some contain isomers.

Calibration standards are made by spiking accurately weighed amounts or volumes (ca 0,1 mmol) of isocyanates in 100 ml of isooctane. A 1-ml volume is added to 100 ml of toluene containing 0,01 mol·l^{-1} of DBA (ca 0,01 µmol·ml^{-1} of the DBA derivative).

Synthesis of derivatives:

- Dilute 6 mmol of isocyanate in 2 ml of isooctane, and dissolve 60 mmol of DBA in 20 ml of isooctane.
- Add the isocyanate solution to the DBA solution dropwise under continuous stirring.
- Evaporate the reaction mixture to dryness in a rotating evaporator, and dry the residue under vacuum to remove excess DBA.

It is also possible to prepare the isocyanate-DBA derivatives by collecting thermal degradation products of corresponding carbamate esters in an impinger flask containing DBA solution (as in 5.2.3.3).

5.2.2 Preparation of ICA and MIC-DBA

When urea is thermally degraded, isocyanic acid (ICA) is formed.

Heat an amount of urea (20 mg) to about 300 °C in a glass tube. Collect the degradation products in an impinger flask containing DBA in toluene (0,5 mol·l^{-1}). Wash the toluene solution containing the ICA-DBA derivatives with water, whereupon the organic phase is evaporated in a vacuum centrifuge and the residue is dissolved in methanol. Characterize the solution as described in 5.2.4.

The same procedure can be applied for preparation of MIC-DBA derivatives, by collecting thermal degradation products of 1,3-dimethyl urea.

5.2.3 Preparation of deuterium-labelled isocyanate-DBA derivatives

5.2.3.1 Internal standards

For accurate LC-MS quantifications, it is important to use proper internal standards, not only to compensate for variations during the work-up procedure, but also to compensate for fluctuation in the MS instrument response. Ideally, each analyte should have its own deuterium-labelled analogue. For isocyanate-DBA determinations, it is possible to use DBA derivatives of deuterium-labelled isocyanates or d_9- and d_{18}-DBA derivatives of the isocyanates as internal standards.

The quality of the quantification is influenced by the number of deuterium substitutions in the internal standard (less deuterium in the molecule resulting in higher precision). Having the deuterium on the isocyanate, and not on the DBA, has advantages when performing structural identification using MS and MS/MS. It is then possible to distinguish between labelled and non-labelled fragments that originate from the isocyanate itself. Therefore, the ideal internal standards are the DBA derivatives of the deuterium-labelled isocyanates. However, they are labour intensive to prepare, and they are only available for a few isocyanates.

The deuterium-labelled d_9- and d_{18}-DBA derivatives are easy to prepare, and any technical isocyanate or thermal degradation product can be derivatized and used as internal standard.

5.2.3.2 DBA derivatives of deuterium-labelled isocyanates

Dissolve a 10 mmol aliquot of the deuterium-labelled corresponding amine in 20 ml of toluene. Thereafter, add 150 µl pyridine and 40 ml of 5 mol·l^{-1} NaOH. Then add 1,5 ml of ethyl chloroformate dropwise under continuous stirring. After 10 min, the toluene phase is separated, and the solvent is evaporated.

Place the residue containing the formed amine carbamate ester (10 µl) in a glass tube. Heat the tube to about 300 °C. By connecting the tube to an impinger flask, containing 0,5 mol·l^{-1} DBA in toluene, the formed deuterium-labelled isocyanate is collected as a DBA derivative. Evaporate the solvent, and dissolve the residue in methanol to an appropriate concentration. Characterize the solution as described in 5.2.4.

5.2.3.3 d$_9$-DBA and d$_{18}$-DBA derivatives of the isocyanates.

Prepare the deuterium-labelled d$_9$- and d$_{18}$-DBA derivatives by dissolving accurately weighed amounts of the isocyanates in 10 ml of 0,1 mol·l^{-1} d$_9$-DBA or d$_{18}$-DBA in toluene.

Prepare the deuterium-labelled derivatives of ICA and MIC by placing an amount (20 mg) of urea (for ICA) and 1,3-dimethyl urea (for MIC) in a glass tube. Heat the tube to about 300 °C and collect the formed ICA and MIC in impinger flasks containing 0,1 mol·l^{-1} d$_9$-DBA or d$_{18}$-DBA in toluene. Evaporate the solutions containing the isocyanate d$_9$-DBA or d$_{18}$-DBA derivatives to dryness, and dissolve the residues in methanol. Characaterize the solution as described in 5.2.4.

5.2.4 Characterization

The solutions are diluted in methanol to appropriate concentrations and characterized on the LC-MS and quantified on the LC-CLND. This technique is nitrogen specific and any nitrogen-containing compound can be used as external standard, e.g. caffeine. The technique is used in several applications [13], [14], [15]. Quantification of volatile isocyanate-DBA derivatives can also be made by using GC-TSD.

5.3 DBA derivatives of bulk isocyanates

5.3.1 Preparation

Technical isocyanates used in industry are typically available in mixtures such as oligomers in polymeric MDI, biuret-, isocyanurate-, alophanate-adducts and prepolymeric forms of isocyanates. These isocyanates are typically multifunctional.

If product data sheets are available and correct, standard solutions for the technical grade isocyanates can be prepared in the same way as described in 5.2.1 by adding a known amount of bulk isocyanate to a toluene solution of DBA. If data regarding the composition and concentrations of different isocyanates are of poor quality or missing, the bulk material must to be characterized.

The procedure for technical grade isocyanate is as follows.

— Add an aliquot of 10 mg of the isocyanate product to a 10 ml vial containing 0,5 mol DBA·l^{-1}.

— Sonicate the solution and evaporate it to dryness and then dissolve it in methanol.

— Further dilute the solution with methanol to appropriate concentrations.

— Characterize the solution as described in 5.3.2.

5.3.2 Characterization

If the isocyanates that are present in the bulk are known or reference compounds are available, calibration standards can be prepared as in 5.2.1.

If the isocyanates that are present in the bulk are unknown, qualitative data are obtained with full scan chromatograms for DBA derivatized bulk material. Obtained structural data together with the LC-CLND data make it possible to calculate the concentrations of the different components in the solution. The characterized bulk sample solution is used as a calibration standard for LC-MS.

When prepolymeric forms or complex isocyanates are to be determined, it may be difficult to quantify each individual isocyanate using LC-MS. However, one or more components can be used as index compounds. The total isocyanate group (NCO) concentration of the bulk is obtained by titration with DBA [16] and standard solutions can be prepared (dilution). The concentration of isocyanates in the air sample is estimated by comparison of peak areas. This may be performed with the assumption that the composition of the bulk material reflects the composition of the airborne isocyanates. The obtained result gives the concentration of total isocyanate content in the air. However, detection limits are increased by the factor of the ratio of total isocyanate concentration and the assumed concentration of the index isocyanate. Still, in most cases, levels below 1/10 of the threshold limit value (TLV) are possible to determine.

5.4 DBA derivatives of isocyanates in thermal decomposition products of polyurethane (PUR) or urea-based resins

5.4.1 Preparation

During the thermal decomposition of e.g. PUR or urea-based resins, isocyanates are formed that are not commercially available. PUR or urea-based material can be thermally decomposed at appropriate temperatures. Emitted degradation products are collected in impinger flasks (filters in series) containing 0,5 mol DBA$\cdot$l^{-1}. The solutions are evaporated to dryness and the residues are dissolved in methanol.

5.4.2 Characterization

Qualitative data are obtained with LC-MS. Obtained structural data together with the LC-CLND data make it possible to calculate the concentrations of different components in the solution. The characterized diluted sample solution is used as a calibration standard for LC-MS.

5.5 Stability

Solutions of isocyanate-DBA derivatives (MDI, 2,4- and 2,6-TDI, HDI, IPDI, PhI, BIC, PIC, EIC, MIC and ICA) have been found stable in toluene, acetonitrile and methanol for six months when stored at 8 °C. NDI-DBA has limited stability and must be freshly prepared and quantified before using as a calibration standard.

6 Apparatus

6.1 Sampler.

Sample the air with an impinger flask followed by a filter.

6.1.1 Filter.

Use a 13-mm glass fibre filter (binder free) with a pore size of 0,3 µm.

6.1.2 Filter holder.

Use a 13-mm polypropylene filter holder with luer-lock connections.

6.1.3 Midget impingers.

A midget impinger consists of a tapered inlet tube. Match the two parts so that the distance between the inlet and the receiver bottom is 1 mm to 2 mm. A luer-lock fitting is attached to the outlet of the impinger.

6.1.4 Solvent-free sampler.

Cut out two kinds of glass fibre filters from a filter sheet of type MG 160 with a pore size of 0,3 µm:

- one rectangular filter, 2,5 cm × 6 cm; and
- one round filter with a diameter of 13 mm.

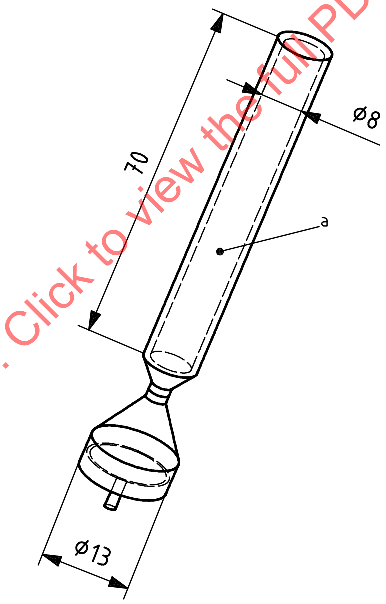
Impregnate the filters with by adding

- 1 ml of solution 2 (1,5 mol·l^{-1} DBA) to the rectangular filter, and
- 0,1 ml of solution 1 (0,74 mol·l^{-1} DBA) to the round filter.

Allow the solvent to evaporate from the filters at room temperature for 1 h.

Place the rectangular filter inside a polypropylene tube ($L = 7$ cm, ID = 0,8 cm), so that it covers the inner walls of the tube, and the round filter in a 13-mm polypropylene filter holder. Connect the filter holder in series after the tube (Figure 2). Plug both ends of the sampler with polypropylene plugs and store the sampler in refrigerator prior to air sampling.

Dimensions in millimetres



[a] Quantity = 0,21 l min^{-1}.

NOTE Glass-fibre filter was impregnated with DBA and acetic acid 0,3 µm pore size.

Figure 2 — Solvent-free sampler

6.1.5 Sampling pump.

The sampling pump needs to have a calibrated flow of 1 l·min^{-1} for impinger-filter sampling and 0,2 l·min^{-1} for solvent free sampling.

6.1.6 Tubing.

Use rubber tubing of suitable length and of appropriate diameter to ensure a leak-proof fit to both the pump and the sampler outlet.

6.1.7 Vapour trap.

Use a vapour trap (with an internal diameter of 17 mm and a length of 140 mm) filled with charcoal (with a medium particle size < 3 mm) between the impinger-filter and the sampling pump.

6.2 Flow meter.

Use a portable flow meter capable of measuring the appropriate flow rate with an acceptable accuracy.

6.3 Liquid chromatographic system.

In this method, a micro-LC system is used, in order to improve the sensitivity, to minimize the maintenance on the MS and to minimize the consumption of the mobile phase. The micro-LC system is described in the following paragraphs. If desired, this system can be replaced by a conventional LC-system.

6.3.1 Autosampler.

6.3.1.1 LC-MS.

On-column focusing is performed by partially filled loops (typically 10 µl total volume) of 2 µl loop injections between 4+4 µl of 50/20/30 water/methanol/acetonitrile. Any commercially available autosampler capable of making partially filled loop injections and making sample injections of acceptable accuracy and precision can be used.

6.3.1.2 LC-CLND.

On-column focusing is performed by partially filled loops (typically 10 µl total volume) of 2 µl loop injections between 4+4 µl of 50/50 methanol/water. Any commercially available autosampler capable of making partially filled loop injections and making sample injections of acceptable accuracy and precision can be used.

6.3.2 Pumping system (LC-MS and LC-CLND).

An HPLC-pump capable of gradient elution with a flow rate of 100 µl min^{-1} is required.

6.3.3 Analytical column (LC-MS and LC-CLND).

An HPLC-column capable of separating the different isocyanate derivatives is required.

EXAMPLE An example of a suitable column is a PepMap® C_{18}[1] (50 × 1,0 mm with 3 µm particles).

6.3.4 Tubing.

Use short (< 40 cm) tubing with a small internal diameter (typically ID < 0,1 mm).

6.3.5 Detectors.

6.3.5.1 LC-MS.

Any modern MS equipped with a robust and stable electrospray interface will have the necessary performance. MS detection is performed with atmospheric pressure ionization, monitoring positive ions. For quantification, selected ions are monitored. Full spectra are obtained using continuum scans (typically 50 amu to 1 500 amu) for identification of unknown isocyanates. If desired, a UV-detector can be used in series, prior to the MS. The UV-detector needs to be equipped with a micro flow cell (typically 300 nl) to minimize peak band broadening.

6.3.5.2 LC-CLND.

Use a detector which is specific for bound nitrogen.

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1) PepMap® is an example of a suitable product available commercially. This information is given for the convenience of users of this part of ISO 17734 and does not constitute an endorsement by ISO of this product.

7 Air sampling

7.1 Pre-sampling laboratory preparation

7.1.1 Cleaning of sampling equipment

Impingers should be taken apart and soaked in alkaline cleaning solution for a minimum of 2 h. The upper part must be rinsed with an alkaline cleaning solution, pure water and finally deionized water. If the nozzle is clogged, place it in an ultrasonic bath, and then continue with the cleaning procedure. The lower part should be cleaned in a laboratory dishwasher. Both parts should be dried in an oven.

The filter cassettes and the gaskets should be immersed in ethanol in a glass beaker, sonicated for at least 15 min, rinsed with deionized water and dried in an oven.

7.1.2 Preparation of reagent solution and extraction solution tubes

Prepare test tubes containing 10 ml of 0,01 mol·l^{-1} DBA as the reagent solution for the impingers. If the gas phase and the particulate phase are to be collected separately, prepare test tubes containing 10 ml of 0,01 mol l^{-1} DBA as extraction solution tubes for the filters.

7.2 Pre-sampling field preparations

Assemble the sampling system with the filter cassette containing the glass fibre filter coupled to the outlet of the impinger. Transfer the reagent solution to the impinger.

Calibrate the pumps with the impinger-filter sampling system in line, using a portable flow meter. Fill the impinger with the appropriate amount of reagent solution during calibration. The sampling rate should be 1 l·min^{-1}.

7.3 Collection of air samples

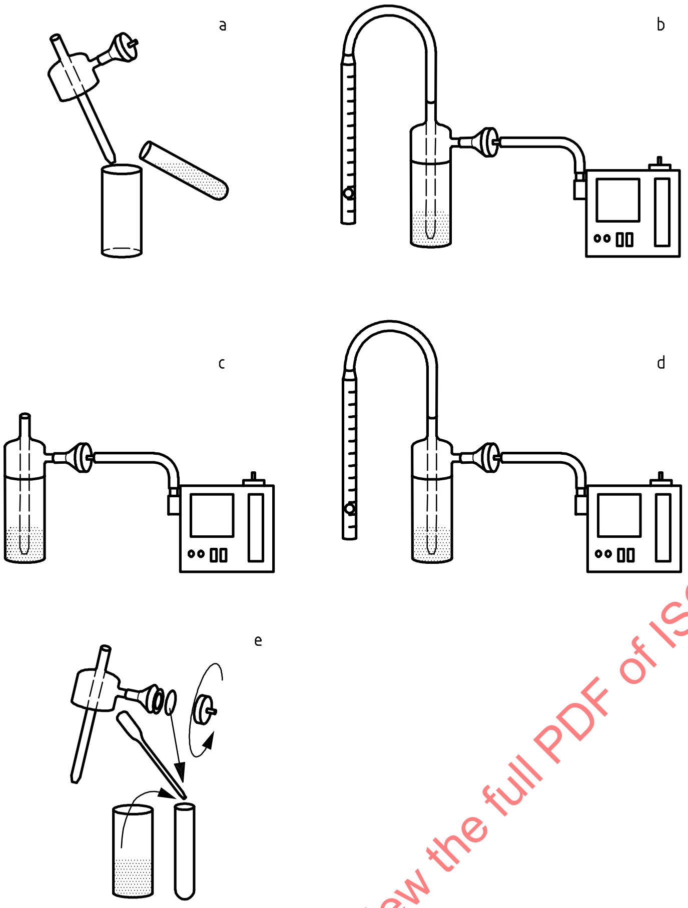
7.3.1 Sampling

In order to relate measurement results to occupational exposure limit values, take samples in the worker's breathing zone. In order to illustrate risks of being exposed, take stationary samples at every place at the worksite where isocyanates can be emitted into the air. It is also important to include operations that are not frequently performed, for example repair and maintenance. Differences in materials and batch-to-batch variations are factors that also should be taken into account when sampling. Collect a sufficient number of samples in order to make a representative exposure assessment.

7.3.2 Impinger-filter sampling

Position the sampling system, either attached to the worker with the inlet in the breathing zone for personal samples, or stationary for area samples. Connect the pump to the sampling system, and place a charcoal vapour trap in line between the pump and the sampling system in order to protect the pump from the solvent vapour. Make sure that the equipment does not disturb the work operation, and that the impinger can be held in a vertical position during the whole sampling period.

When ready to begin sampling, switch on the pump. Record the time of sampling. At the end of the sampling period, measure the flow and turn off the pump. Transfer the impinger solution to a test tube, and immerse the glass fibre filter into either the sampling solution or an extraction solution tube using tweezers. If the filter is transferred to an extraction solution, it is possible to determine the amount of isocyanates in the particulate phase that passes through the impinger (i.e. particles approx. 0,01 µm to –1,5 µm), separately from the gas phase and large particles (>1,5 µm) sampled in the impinger. For an illustration of the sampling procedure, see Figure 2. Calculate the volume drawn through the sampler from the sampling time and the average sampling flow. The total sampling time is limited (about 30 min), unless the reagent solution is refilled during sampling.



[a] The impinger solution is transferred to the impinger flask.

[b] The airflow is measured and the sampling pump is calibrated to 1 l/min.

[c] Air sampling.

[d] The airflow is measured.

[e] The impinger solution is transferred to a test tube. The filter is either transferred to the impinger solution tube or to an extraction solution tube.

Figure 3 — Illustration of the sampling procedure

7.3.3 Solvent-free sampling

Take off the plugs in both ends just prior to the air sampling. Connect an air sampling pump to the filter-holder outlet with a charcoal vapour trap between the sampler and the pump. Perform air sampling with an air flow of 0,2 l min^{-1} before and after sampling. After sampling, disconnect the sampler from the pump, and plug both ends with polypropylene plugs. Keep the samplers cold during transport back to the laboratory.

7.4 Blanks

From every series of samples, there should be an appropriate number of field blanks collected. Field blanks are samples that have been handled exactly like the other samples out in the field, except that no air has been drawn through.

7.5 Raw material

From each work-site, it is desirable to collect samples of the raw material suspected of emitting isocyanates during the work operation. If the material is a bulk isocyanate product, it could be useful for qualitative identification of isocyanate species in the air samples. These products are also applicable for preparation of reference solutions for quantification of unknown isocyanates (see 5.2 and 5.3).

Collecting and subsequent laboratory testing of materials that are known or are suspected of emitting isocyanates is useful for assessing the exposure. The testing may consist of extraction, heating or other processing of the material, as similar to the original work operation as possible.

7.6 Shipment of samples

The test tubes containing the DBA-toluene samples should be shipped in individual plastic cases and preferably kept in an upright position. The sampling solution tubes should be placed well apart from any raw material collected.

8 Laboratory sample preparation

8.1 Sample sequence

In each sample sequence (typically 50 samples), a number of samples consist of field blanks, two chemical blanks, two internal standard blanks and an appropriate number of calibration standards. Internal standard blanks are reagent solutions from the same batch as the reagent solution used for air sampling spiked with internal standard in the work-up procedure. Chemical blanks are pure toluene with no addition of internal standard in the work-up procedure.

8.2 Work-up procedure

8.2.1 General

For preparation of calibration standards, aliquots of 10 ml toluene solutions, containing 0,01 mol l^{-1} DBA, are spiked with the isocyanate-DBA derivatives to concentrations appropriate for the calibration curve.

Upon receiving air samples from the field, add internal standards (deuterium-labelled isocyanate derivatives) to the air samples, to the standard solutions, to the field blanks and to the internal standard blanks. Place the samples in an ultrasonic bath for 15 min. If the solutions contain filters, place the samples in a centrifuge for 10 min (3 000 r/min). Remove the sample solutions from the filters with a pipette into new test tubes. Evaporate the solvent from the samples and the standards. Dissolve the residues in 0,5 ml acetonitrile and place them in an ultrasonic bath for 15 min.

8.2.2 Solvent-free sampling

Connect the samplers to a work-up station, where vacuum suction can be applied. Fill the samplers with 3 ml of 1 mmol l^{-1} H_2SO_4 (aq), wait approx. 2 min and then let the extraction solution be sucked down through the sampler. When the samplers are dry, repeat this procedure once with 3 ml of methanol and twice with 3 ml of toluene. Collect all the four-step extraction solutions in the same test tube.

Prepare calibration standards in test tubes containing the same extraction solutions as the extracted air samples. Add internal standards to the air samples, to the standard solutions, to the field blanks and to the internal standard blanks. Shake the extraction solutions for 10 min, centrifuge for 10 min, and transfer the toluene phases to new test tubes. Remove the solvent and the excess reagent from the samples by evaporation. Dissolve the residues in 0,5 ml acetonitrile and place them in an ultrasonic bath for 15 min.

9 Instrumental settings

9.1 HPLC program (LC-MS)

For simultaneous determination of the DBA derivatives of mono-isocyanates and diisocyanates, the following mobile phase composition can be used:

- Flow rate: 100 µl min^{-1};
- 0 – 15 min: Linear gradient from 50 % mobile phase B to 90 % mobile phase B;
- 15 – 20 min: Re-equilibrate at 50 % mobile phase B.

If a single or a few derivatives are to be determined, isocratic elution or gradient elution with appropriate mobile phase composition can be performed.

If high molecular weight DBA derivatives (e.g. prepolymers, isocyanate adducts) are to be determined together with DBA monomers, it is necessary to continue with the gradient up to 100 % B and maintain at 100 % B for isocratic elution.

9.2 HPLC program (LC-chemiluminescent nitrogen detector) (LC-CLND)

- Flow rate: 100 µl min^{-1};
- 0 – 15 min: Linear gradient from 40 % mobile phase D to 100 % mobile phase D;
- 15 – 30 min: 100 % mobile phase D;
- 30 – 35 min: Re-equilibrate at 40 % mobile phase D.

Depending on the properties of the analytes in the sample, stronger, weaker or isocratic elution can be used.

9.3 Mass spectrometer

Settings of the MS depend greatly on which type of instrument that is used. Optimization is normally performed by the introduction of flow at 100 µl/min of mobile phase containing low and high mass aromatic and aliphatic isocyanate derivatives. Optimal settings vary for the analytes and the ions to be monitored. Practical settings are not the optimum for all of the compounds to be studied.

For quantification, selected ions are monitored, e.g. the molecular ion $[MH]^+$, but other typical ions can be used: $[(DBA)H]^+$ ($m/z = 130$), $[(DBA)CO]^+$ ($m/z = 156$), $[MH-129]^+$ and $[MNa]^+$ (see B.4).

For LC-MS/MS quantifications, multiple reaction monitoring is performed by monitoring the daughter ion $[(DBA)H]^+$, $[(DBA)CO]^+$ or $[MH-129]^+$ from the protonated molecular ion $[MH]^+$.

For identification of unknown isocyanates, full spectra are obtained using continuous scans (typically 50 amu to 1 500 amu).

10 Data handling

10.1 Identification

For identification, the retention times of sample peaks in the selected ion chromatograms are compared to the standards and the internal standards.

10.2 Calibration curves

The peak areas of the isocyanate-DBA-derivative and the internal standard are measured, and the ratio is calculated. The ratio versus the concentration is plotted. The coefficient of correlation should be better than 0,98.

10.3 Quantification

Quantification is accomplished by comparing the area ratio of the sample peak and internal standard to the calibration plot.

11 Interferences

The reactions between aromatic and aliphatic isocyanates with DBA in the presence of some possibly interfering compounds water, morpholine, phenol, ethanol, TDA, MDA, HDA and IPDA have been investigated [4], [5]. No losses of the studied isocyanates were observed.

12 Determination of performance characteristics

12.1 Introduction

The measurement of the concentration of isocyanates in workplace air has associated with it an uncertainty that may be expressed as overall uncertainty (EN 482 [17]) or expanded uncertainty (See Reference [18]). Thus, an uncertainty assessment has to be performed according to one or other of these definitions of uncertainty. In both cases, this consists of the determination of uncertainty contributions evaluated by means of laboratory and simulated field tests or from existing information. The values obtained of the measurement uncertainty may then be compared with pre-set criteria, for example those in EN 482 [17], or defined in national or international legislation.

12.2 Relevant uncertainty contributions and criteria

Uncertainty contribution	Quantity	Subclause	Criterion
Sample volume	V_{sam}	12.3.2	
Sample flow – calibration	q_{cal}		Relative uncertainty < 2 %
Sample flow – variation	Δq		< 5 %
Sampling time	t		Relative uncertainty < 0,1 %
Temperature during sampling	T		Relative uncertainty < 4 %
Pressure during sampling	p		Relative uncertainty < 2 %
Analyte mass	m_{sam}	12.3.3	
Analyte stability during storage	k_{AS}		No significant difference between results of analysis of samples before and after storage
Reaction/extraction efficiency	E_{RE}		> 90 % at the limit value with a relative uncertainty of < 3 %
Mass of isocyanate in calibration standards	m_{CS}		Relative uncertainty < 2 %
Calibration lack-of-fit	LOF		Relative residuals over the calibration range < 3 %; at the limit value < 2 %
Response drift between calibrations	D_{R}		< 3 %
Analytical precision	r		< 1 %
Selectivity	s		Resolution factor > 1
Blank level	m_{BL}	12.3.4	< 50 ng with a relative uncertainty of < 5 %
Between-laboratory variations	bl	12.3.5	Relative uncertainty < 7,5 %

12.3 Assessment of performance characteristics, following the detailed approach in Reference [18]

12.3.1 Collection efficiency — relative to particle size distribution

For a complete description of the performance requirements and tests to be performed, see Reference [18].

12.3.2 Air sampling

12.3.2.1 Sampling volume

The sampled volume of air is calculated on the basis of measuring the sample flow rate before and after sampling as specified in ISO 16200:

$$V_{\mathrm{sam}} = \frac{\left(q_{\mathrm{start}} + q_{\mathrm{end}}\right)}{2} \cdot t \qquad (1)$$

in which

q_{start} is the sample flow rate at the beginning of the sampling period (usually in millilitres per minute);

q_{end} is the sample flow rate at the end of the sampling period;

t is the sampling time (in minutes).

The uncertainty in the volume of air sampled is built up of contributions from

- the measurements of the flow rates before and after sampling,
- the measurement of the sampling time, and
- variations in the flow rate during the sampling period.

and may be expressed as

$$\frac{u^2(V_{\text{sam}})}{V_{\text{sam}}^2} = \frac{u^2(q_{\text{start}}) + u^2(q_{\text{end}})}{(q_{\text{start}} + q_{\text{end}})^2} + \frac{u_t^2}{t^2} + \frac{u_{\text{var},q}^2}{\left[\frac{(q_{\text{start}} + q_{\text{end}})}{2}\right]^2} \qquad (2)$$

where which the last term represents the uncertainty contribution due to flow rate variations during sampling.

12.3.2.2 Sampling time

The sampling time, t, can be measured to within ± 0,5 min. For a sampling time of 8 h, the relative uncertainty due to the measurement of t is about 0,1 % and is negligible.

12.3.2.3 Variations in flow rate during sampling

The flow rate during sampling is unknown. The uncertainty due to variations in the flow rate during sampling can be estimated by assuming a uniform distribution as

$$u_{\text{var},q}^2 = \frac{(q_{\text{start}} - q_{\text{end}})^2}{12} \qquad (3)$$

12.3.2.4 Conversion of sample volume to STP

For the conversion of concentrations to STP, knowledge is required of the actual mean temperature and pressure during sampling. Uncertainties in values of T and p used for conversion may be obtained from:

- actual measurements, taking into account the uncertainty in the calibration of temperature and pressure sensors used as

$$u^2 = u_{\text{cal}}^2 + \frac{s_{\text{meas}}^2}{n} \qquad (4)$$

where

u_{cal} is the uncertainty due to calibration of the sensor;

s_{meas} is the standard deviation of the temperature/pressure measurements;

n is the number of temperature/pressure measurements; and

- knowledge of extremes of temperature and pressure during sampling, assuming these to be uniformly distributed.

For example, if the temperature extremes are known to be T_{min} and T_{max}, the uncertainty in T may be calculated from

$$u_T^2 = u_{\text{cal}}^2 + \frac{\left(T_{\text{max}} - T_{\text{min}}\right)^2}{12} \tag{5}$$

Generally, the first term will be negligible compared to the second.

12.3.2.5 Combined uncertainty of sample volume

The above uncertainty contributions are combined to give the uncertainty in the sample volume converted to SPT as

$$\frac{u^2\left(V_{\text{sam, SPT}}\right)}{V_{\text{sam, SPT}}^2} = \frac{u^2\left(V_{\text{sam}}\right)}{V_{\text{sam}}^2} + \frac{u^2(T)}{\bar{T}^2} + \frac{u^2(p)}{\bar{p}^2} \tag{6}$$

where

$\bar{T}$ is the mean temperature during sampling; and

$\bar{p}$ is the mean pressure during sampling.

12.3.3 Analysis

12.3.3.1 Sampled mass

The mass of isocyanate in the air samples may be expressed as

$$m_{\text{sam}} = \frac{m_{\text{anal}}}{E_{\text{coll}} \cdot \Delta S \cdot k_{\text{AS}} \cdot E_{\text{RE}}} \tag{7}$$

where

E_{coll} is the collection efficiency;

ΔS is the sampler variability;

k_{AS} is the analyte stability in the sample;

E_{RE} is the reaction/extraction efficiency;

m_{anal} is the uncorrected analytical mass of isocyanate in the analytical sample.

12.3.3.2 Analyte stability

The analyte stability shall be experimentally established for storage under conditions (time, temperature, environment) typical to the individual laboratory. Tests shall be performed at an isocyanate level corresponding to a concentration equivalent to the Limit value.

At time $t = 0$ and time t, samples each shall be analysed under repeatability conditions ($n \geqslant 6$). For both times, the samples shall be randomly picked from a batch of representative samples in order to minimize possible systematic concentration differences. As a test of (in)stability a t-test will be performed (95 % confidence, two-sided). The uncertainty of the stability determination consists of contributions from

— desorption (random part of desorption efficiency),

- calibration (random part of calibration),
- analytical precision, and
- inhomogeneity of the sample batch.

As such, the contribution of the determination of k_{AS} will already be incorporated in other contributions and needs not to be taken into account.

12.3.3.3 Reaction/extraction efficiency

The reaction/extraction efficiency of isocyanate and its uncertainty are typically obtained from replicate measurements on certified reference materials (CRM) of the isocyanate or of its reaction product(s). The uncertainty due to incomplete reaction/extraction for the isocyanate level corresponding to the limit value is calculated from contributions of

- the uncertainty in the concentration of the CRM,
- the standard deviation of the mean recovery, and
- the bias between the mass of isocyanate in the CRM and the mean mass of isocyanate determined as

$$\frac{u_{E_{\mathrm{RE}}}^2}{E_{\mathrm{RE}}^2} = \frac{u_{m_{\mathrm{CRM}}}^2}{m_{\mathrm{CRM}}^2} + \frac{s^2(\bar{m}_{\mathrm{DE}})}{\bar{m}_{\mathrm{DE}}^2} + \frac{(\bar{m}_{\mathrm{DE}} - m_{\mathrm{CRM}})^2}{m_{\mathrm{CRM}}^2} \tag{8}$$

where

m_{CRM} is the mass of isocyanate CRM;

$u_{m_{\mathrm{CRM}}}$ is the uncertainty in the mass of isocyanate CRM;

$\bar{m}_{\mathrm{DE}}$ is the mean mass of isocyanate determined;

$s(\bar{m}_{\mathrm{DE}})$ is the standard deviation of the mean of the replicate measurement results.

The latter term, representing the uncertainty due to a significant bias between certified and determined mass, may be ignored if

- the bias is statistically insignificant at the 95 % level,
- a correction is applied for the bias.

If a CRM is not available, the material with the highest metrological quality available should be used.

12.3.3.4 Uncorrected analytical mass of compound

The uncertainty in the uncorrected analytical mass of a compound is determined by

- the uncertainty in the concentrations of the calibration standards used,
- the lack-of-fit of the calibration function,
- drift of detector response between calibrations,
- the precision of the analysis, and
- the selectivity of the chromatographic system.

12.3.3.5 Calibration standards

The uncertainty of the concentration of isocyanate in the calibration standards used depends on the type of calibration standard used.

For calibration standards consisting of solutions in toluene or acetonitrile, the uncertainty is built up of contributions from

- the purity of isocyanate; this is generally known from manufacturer's specifications as a minimum purity, p, e.g.,
  - $p = 99$ %, the relative uncertainty due to impurity is given by (100–p) %, or
  - $p \geqslant 99$ %, the relative uncertainty can be estimated assuming a uniform distribution as

$$u_{\mathrm{pur}}^2 = \frac{(100 - p)^2}{12} \tag{9}$$

- the uncertainties in the weighings of compounds and solutions, i.e. the uncertainty of the balance used.

The latter contribution is generally expressed for differential weighings as

$$u_{\mathrm{weigh}}^2 = 2u_{\mathrm{bal}}^2 \tag{10}$$

where u_{bal} is the uncertainty of the balance used.

If this method is used for the determination of other compounds besides isocyanate, the concentration of isocyanate in the chemicals used and its uncertainty shall be established and used in the above uncertainty assessment.

12.3.3.6 Lack-of-fit of calibration function

The uncertainty due to lack-of-fit of the calibration function can be calculated for the relevant concentration (corresponding to a mass of isocyanate sampled at the limit value) from residuals of a calibration function obtained by a least-squares linear regression weighted in the concentration of isocyanate in the calibration standard as

$$u_{\mathrm{LOF}}^2 = \frac{\left(m_{\mathrm{regr}} - m_{\mathrm{std}}\right)^2}{m_{\mathrm{std}}^2} = \rho^2 \tag{11}$$

where

m_{regr} is the mass of isocyanate calculated from the regression equation at the level of the calibration standard corresponding closest to the mass of isocyanate representing a sample at the limit value;

m_{std} is the mass of isocyanate present in the corresponding calibration standard;

ρ is the relative residual for the particular concentration level.

NOTE The lack of fit of the calibration function will contribute to the uncertainty due to incomplete extraction or reaction if the latter's efficiency is significantly different from 1. In that case – irrespective of whether or not a correction for incomplete reaction/extraction is applied – the uncertainty due to lack of fit of the calibration function needs not to be taken into account in the uncertainty assessment.

12.3.3.7 Drift in detector response

The uncertainty due to response drift, D_R, can be estimated from data on the relative differences in responses between subsequent calibrations as

$$u_{D_\mathrm{R}}^2 = \frac{\left(r_n - r_{n\text{-}1}\right)^2}{12\left(\frac{r_n + r_{n\text{-}1}}{2}\right)^2} \tag{12}$$

where

n is the number of replicate analyses; and

r_n is the detector response for a calibration standard corresponding closest to the mass of isocyanate representing a sample at the limit value.

12.3.3.8 Precision of the analysis

The uncertainty due to the (im)precision of the analysis is determined by analysis under repeatability conditions of calibration standards of the same composition; a minimum of 6 replicate analyses shall be performed. The uncertainty is then calculated as

$$u_{\overline{r}}^2 = \frac{s_\mathrm{anal}^2}{\overline{r}^2} \tag{13}$$

where

s_anal is the standard deviation of the replicate responses;

$\overline{r}$ is the mean response.

In the uncertainty assessment, this contribution is already incorporated in contributions from the determination of desorption efficiency and needs not be taken into account.

12.3.3.9 Analytical selectivity

The separation system used (liquid chromatographic column, gradient program) shall be optimized in order to minimize uncertainty due to (unnoticed) co-elution of potential interferents.

The resolution, R, of the liquid chromatographic system used – given by Equation (14) – shall be better than 1. In that case, the maximum uncertainty due to co-elution is 2,5 %. The typical uncertainty contribution will then be ± 0,7 %.

$$R = \frac{\Delta t_\mathrm{r}}{0{,}85\left(w_\mathrm{B} + w_\mathrm{I}\right)} \tag{14}$$

where

Δt_r is the difference in retention time of isocyanate and interferent (in seconds);

w_B is the peak width at half height of the peak (in seconds), with subscript B referring to isocyanate;

w_I is the peak width at half height of the peak (in seconds), with subscript I referring to interferent.

12.3.3.10 Combined uncertainty in the analytical mass of isocyanate

The above contributions are combined to give the uncertainty of the analytical mass of isocyanate excluding the uncertainty due to imprecision as

$$\frac{u^2(m_{\text{anal}})}{m_{\text{anal}}^2} = \frac{u_{\text{std}}^2}{m_{\text{std}}^2} + u_{\text{LOF}}^2 + u_{\text{drift}}^2 + u_{\text{sel}}^2 \tag{15}$$

12.3.3.11 Combined uncertainty in the sampled mass of isocyanate

The contributions given in 12.3.3.4 through 12.3.3.8 and in 12.3.3.10 are combined to give the uncertainty of the mass isocyanate in the air sample as

$$\frac{u^2(m_{\text{sam}})}{m_{\text{sam}}^2} = \frac{u^2(m_{\text{anal}})}{m_{\text{anal}}^2} + \frac{u_{E\text{RE}}^2}{E_{\text{RE}}^2} \tag{16}$$

12.3.4 Mass of compound in sample blank

The mass of isocyanate in a sample blank is determined by analysis under repeatability conditions of a series of sample blanks; a minimum of 6 replicate analyses shall be performed. The uncertainty is then calculated using the slope of the calibration function extrapolated to the blank response level as

$$u^2(m_{\text{BL}}) = \frac{s_{\text{BL}}^2}{b_{\text{BL}}} \tag{17}$$

where

s_{BL} is the standard deviation of the replicate analytical results;

n is the number of replicate analyses;

b_{BL} is the slope of the calibration function at the blank response level.

If the blank response is below 3 times the noise level of the detector at the retention time of isocyanate, then the blank level and its uncertainty shall be calculated from the detector noise level using the slope of the calibration function extrapolated to zero response assuming a uniform distribution as

$$m_{\text{BL}} = \frac{3r_0}{2b_0} \tag{18}$$

$$u^2(m_{\text{BL}}) = \frac{9r_0^2}{12} \tag{19}$$

where

r_0 is the noise level;

b_0 is the slope of calibration function at zero response.

12.3.5 Between-laboratory uncertainty contributions

The procedures described above are not restrictive but allow for possible variations in approaches between laboratories. The resulting additional uncertainty contributions can be quantified by performing interlaboratory comparisons involving

- the complete measurement procedure inclusive of sampling, and
- the analytical part of the measurement procedure.

Interlaboratory comparisons shall be organized in accordance with ISO 5725-2 using samples of sufficient homogeneity to assure that the contribution to the between-laboratory uncertainty due to inhomogeneity is negligible. In practice, an uncertainty due to inhomogeneity of < 2 % will usually be sufficient.

12.3.6 Combined uncertainty

The combined uncertainty of the isocyanate concentration in the air sampled is obtained by combination of contributions given in Equations (6), (14), (18) and (19) adding the between-laboratory uncertainty (if considered appropriate) as

$$u_\mathrm{c}^2\left(C_\mathrm{m}\right) = u^2\left(m_\mathrm{sam}\right) + u^2\left(m_\mathrm{BL}\right) + u^2\left(V_\mathrm{sam,\ SPT}\right) + u_\mathrm{bl}^2 \qquad (20)$$

where u_bl is the between-laboratory uncertainty contribution.

12.3.7 Expanded uncertainty

The expanded uncertainty in C at the 95 % confidence level is obtained by multiplying $u_\mathrm{c}(C_\mathrm{m})$ with a coverage factor of 2.

12.3.8 Uncertainty from performance criteria

When combining the uncertainties specified for the performance characteristics (12.2) a worst-case situation will result. The resulting combined relative uncertainty, calculated as described in 12.3.6 will be about 10 %. The expanded uncertainty will be 20 %.

Annex A
(informative)

Performance characteristics

A.1 Uncertainty estimates

The data in Table A.1 on uncertainty contributions were obtained from the literature and validation of ISO 17734-1.

Table A.1 — Uncertainty contributions

Uncertainty contribution	Uncertainty %	Comments
Sample volume	4	For a 15-min air sample at a flow rate of 1 l min^{-1}
Sample flow – calibration	2	Calibration instrument specification
Sample flow – variation	3	Estimation
Sampling time	0,2	
Temperature during sampling	1	Estimation
Pressure during sampling	1	Estimation
Analyte mass (weighing)	6	Isocyanate content in calibration standards determined by weighing or LC-CLND
Analyte mass (CLND)	12	
Analyte stability during storage	negligible	References [5], [9] and [19]
Reaction/extraction efficiency	6	Calculated using titration data as reference material
Mass of isocyanate in calibration standards (weighing)	1	Isocyanate content in calibration standards determined by weighing or LC-CLND [20]
Mass of isocyanate in calibration standards (CLND)	10	
Calibration lack-of-fit	1	
Response drift between calibrations	negligible	Instrumental drift is corrected by using internal standards [6], [7]
Analytical precision	2	
Selectivity	negligible	LC-MS provides highly selective determinations
Blank level	negligible	
Between-laboratory variations	10	Estimation, no data is available

A.2 Combined uncertainty

If the isocyanate content in the calibration standards are based on accurately weighed amounts of isocyanates that are derivatized with DBA, the combined uncertainty is estimated as 12 %. If the isocyanate content in the calibration standards is based on LC-CLND quantification, the combined uncertainty is estimated as 16 %.