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# Diisocyanates (2,4-toluene-, 2,6-toluene-, 4,4'-methylene diphenyl-, isophorone-, 1,5-naphthylene-, 1,6-hexamethylene diisocyanate)

<b>Method number</b>	1
<b>Application</b>	Air analysis
<b>Analytical principle</b>	High performance liquid chromatography
<b>Completed in</b>	February 2006

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## Summary

This method permits the determination of gaseous monomeric diisocyanates, such as 4,4'-methylene diphenyl diisocyanate (MDI), 1,6-hexamethylene diisocyanate (HDI), isophorone diisocyanate (IPDI), 1,5-naphthylene diisocyanate (NADI), and 2,4- and 2,6-toluene diisocyanate (TDI) in a concentration range between 0.1- and 2-fold of the currently valid MAK values and occupational exposure limit (OEL) in the air of workplaces, respectively. For sample collection, ambient air is drawn with a suitable pump through a glass fibre filter which is coated with 1-(2-methoxyphenyl) piperazine (MPP). Thereby, the diisocyanates react with the derivatization agent to form the corresponding urea derivatives, which are determined by HPLC equipped with a UV-detector. Quantitative evaluation is carried out using a calibration function.

## Characteristics of the method for MDI and IPDI

Accuracy:

**Table 1.** Standard deviation (rel) and mean variation  $u$  for  $n = 6$  determinations.

Substance	Spiked mass [ $\mu\text{g}$ ]	Standard deviation (rel) [%]	Mean variation $u$ [%]
MDI	0.196	6.6	17.1
	1.956	1.9	5.1
	3.912	1.8	4.6
IPDI	0.369	6.1	15.1
	3.691	2.2	5.6
	7.381	2.3	5.9

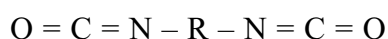
Limit of quantification: MDI:  $0.005 \text{ mg/m}^3$  (40 L air sample volume)  
IPDI:  $0.008 \text{ mg/m}^3$  (40 L air sample volume)

Recovery: MDI:  $\eta = 1 - 1.05$   
IPDI:  $\eta = 0.96 - 1.03$

Sampling recommendation: Sampling time: 2 hours  
Air sample volume: 40 litres

## Characteristics of substances

Diisocyanates are esters of isocyanic acid with the following common chemical structure:



This class of substances is of technical interest since the chemical conversion of di- and polyisocyanates with di- and polyols has led to many uses of polyurethanes, particularly different foams and elastomers in industry. Polyurethanes are preferably applied in automobile, mechanical engineering, and furniture industry, as well as in building and construction industry and refrigeration engineering.

Technical important diisocyanates are 4,4'-methylene diphenyl diisocyanate (MDI), 1,6-hexamethylene diisocyanate (HDI), isophorone diisocyanate (IPDI), 1,5-naphthylene diisocyanate (NADI), and 2,4- as well as 2,6- toluene diisocyanate (TDI).

## Physical data

Substance	CAS	Molar mass [g/mol]	Boiling point [°C]	Density at 20°C [g/mL]
2,4-Toluene diisocyanate (2,4-TDI)	584-84-9	174.2	120 (10 mm Hg)	1.225
2,6-Toluene diisocyanate (2,6-TDI)	91-08-7	174.2	131 (18 mm Hg)	1.214
4,4'-Methylene diphenyl diisocyanate (MDI)	101-68-8	250.3	200 (5 mm Hg)	1.180
1,6-Hexamethylene diisocyanate (HDI)	822-06-0	168.2	255 (760 mm Hg)	1.040
Isophorone diisocyanate (IPDI)	4098-71-9	222.3	158 (15 mm Hg)	1.049
1,5-Naphthylene diisocyanate (NADI)	3173-72-6	210.2	–	–

The in common NCO group of all isocyanates reacts with water via different intermediates (carbamine acid, aminoisocyanates, amines) to oligo- and polyureas. Under certain conditions (e. g., at pH < 5, or solved in aqueous organic media such as H<sub>2</sub>O/DMSO or acetone), hydrolysis of isocyanates up to amines is possible. In competition with this reaction, isocyanates can also react with tissue components itself, e. g. in contact with skin or during inhalation of vapours and aerosols.

At workplaces, inhalation is the most common way of intake, but skin contact can also play a considerable role. Information on the toxicity of diisocyanates is given in the MAK value documentations [1–4].

The currently valid MAK values and occupational exposure limit values are [5, 6]:

4,4'-Methylene diphenyl diisocyanate (MDI)	0.05 mg/m <sup>3</sup> (MAK)
1,6-Hexamethylene diisocyanate (HDI)	0.035 mg/m <sup>3</sup> (MAK)
Isophorone diisocyanate (IPDI)	0.046 mg/m <sup>3</sup> (MAK)
1,5-Naphthylene diisocyanate (NADI)	0.05 mg/m <sup>3</sup> (TRGS 900)
2,4- and 2,6-Toluene diisocyanate (TDI)	0.035 mg/m <sup>3</sup> (TRGS 900)

In the List of MAK and BAT Values the short-term value of diisocyanates are classified in peak limitation category I with an excursion factor of 1 [5]. The BAT value of 4,4'-methylene diphenyl diisocyanate is 10 µg MDI/g creatine [7].

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# Diisocyanates

## (2,4-toluene-, 2,6-toluene-, 4,4'-methylene diphenyl-, isophorone-, 1,5-naphthylene-, 1,6-hexamethylene diisocyanate)

<b>Method number</b>	1
<b>Application</b>	Air analysis
<b>Analytical principle</b>	High performance liquid chromatography
<b>Completed in</b>	February 2006

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## 1 General principles

This method permits the determination of gaseous monomeric diisocyanates, such as 4,4'-methylene diphenyl diisocyanate (MDI), 1,6-hexamethylene diisocyanate (HDI), isophorone diisocyanate (IPDI), 1,5-naphthylene diisocyanate (NADI), and 2,4- and 2,6-toluene diisocyanate (TDI) in a concentration range between 0.1- and 2-fold of the currently valid MAK values and occupational exposure limit (OEL) in the air of workplaces. For sample collection, ambient air is drawn with a suitable pump through a glass fibre filter which is coated with 1-(2-methoxyphenyl) piperazine (MPP). Thereby, the diisocyanates react with the derivatization agent to form the corresponding urea derivatives, which are determined with HPLC equipped with a UV-detector. Standard solutions are used for calibration. Quantitative evaluation is carried out using a calibration function.

## 2 Equipment, chemicals and solutions

### 2.1 Equipment

Glass fibre filters (diameter 25 mm) coated with 1-(2-methoxyphenyl) piperazine contained in a filter cassette (isocyanate sampling-set, Dräger Safety AG & Co. KGaA, D-23560 Lübeck, Order No. 64 00 131)

Sampling pump with a flow rate regulator in the range from 0.1 to 2.0 L/min, e.g., SKC from Analyt-MTC GmbH & Co KG, D-79379 Müllheim

Tweezers

2, 8, and 25 mL sample vials with PTFE-lined screw caps

50 and 100 µL syringes

- 5 mL disposable syringes
- 10, 50, and 1000 mL volumetric flasks
- 500 mL graduated cylinders
- 0.5, 1, 2, 3, 5, and 10 mL volumetric pipettes
- 5000 µL adjustable piston pipette
- Disposable syringe filters, e.g. Whatman, ReZist® 30/0.2
- Magnetic stirrer
- Ultrasonic bath

- High pressure liquid chromatograph equipped with a UV detector (250 nm)
- Column: length 25 cm, internal diameter 4 mm, stationary phase: Nucleosil 120-5 C18, particle size 5  $\mu\text{m}$

## 2.2 Chemicals

Acetonitrile, ultra gradient HPLC grade, e. g. from J. T. Baker, Order No. 9017

Ultrapure water for HPLC

Ammonium acetate, *p.a.*, e. g. from Merck, Order No. 101116

Acetic acid, anhydrous, *p.a.*, e. g. from Merck, Order No. 100063

Acetic anhydride, Reag. Ph. Eur, e. g. from Merck, Order No. 1.59001.0050

For preparation of derivatives:

4,4'-Methylene diphenyl diisocyanate, 98%, e. g. from Aldrich, Order No. 25,643-9

Isophorone diisocyanate, 98%, e. g. from Aldrich, Order No. 317624

1-(2-Methoxyphenyl) piperazine, 98%, e. g. from Aldrich, Order No. M2,260-1

Toluene, 99.8%, anhydrous, e. g. from Aldrich, Order No. 244511

Methanol, *p.a.*, e. g. from Merck, Order No. 106009

n-Hexane, SeccoSolv, dried, max. 0.005%  $\text{H}_2\text{O}$ , e. g. from Merck, Order No. 104373

## 2.3 Solutions

Solution I:

Eluent for the HPLC:

1.93 g ammonium acetate and 3.3 mL acetic acid are weight in a 1000 mL volumetric flask. The flask is subsequently filled to the mark with acetonitrile/ultrapure water (1 : 1 v/v) and the contents are mixed thoroughly.

Solution for resolving the residue:

0.5 mL acetic anhydride is pipetted into a 100 mL volumetric flask and the flask is filled to the mark with acetonitrile.

## 2.4 Preparation of the derivatives

For preparation of the derivatives only fresh purchased diisocyanates in sealed original flasks should be used [8].

For preparation of 1-(2-methoxyphenyl) piperazine derivatives (MP-derivatives), 0.1 g diisocyanate are placed in a solution, consisting of 0.6 g 1-(2-methoxyphenyl) piperazine in 10 mL of anhydrous toluene. After 1 hour the crystalline derivative is filtered and washed several times with toluene in order to separate the excess reagent. For further purification, the MP-derivative is recrystallized from toluene. For that procedure, the crystalline MP-derivative is added to toluene and heated up to 60 °C. By adding methanol slowly to this solution the MP-derivative is resolved. After cooling, the

re-precipitated derivative is filtered and subsequently washed with anhydrous toluene. Finally, the MP-derivative is dried in air. The prepared urea derivatives are hardly soluble in toluene but well soluble in acetonitrile and methanol. As MDI (4,4'-methylene diphenyl diisocyanate) is hardly soluble in toluene, the MP-derivative of MDI can be prepared according to the following method:

0.5 g MDI are solved in 25 mL dichloromethane and added to a solution of 1.0 g 1-(2-methoxyphenyl) piperazine in 50 mL dichloromethane. Stirring constantly the formed white suspension is transferred drop by drop to 500 mL *n*-hexane in a beaker containing a magnetic stirrer. The formed precipitate is filtered and resolved again in a few millilitre of dichloromethane. By adding *n*-hexane to the solution the derivative precipitates again. The residue is filtered, washed with *n*-hexane and afterwards the derivative is dried in air.

## 2.5 Calibration standards

Stock solution (contain a mixture of all prepared diisocyanate derivatives):

2 mg of each diisocyanate derivative are weighed accurately in a glass weighing boat and subsequently transferred to a 50 mL volumetric flask. The flask is filled to the mark with acetonitrile and the contents are mixed thoroughly. The concentration of each diisocyanate derivative in the stock solution is 40 µg/mL. The corresponding diisocyanate concentration is calculated according to equation (1) (see also Table 2).

$$C_{Diisocyanate} = \frac{C_{Diisocyanate-MP} * M_{Diisocyanate}}{M_{Diisocyanate-MP}} \quad (1)$$

Where:

$C_{Diisocyanate}$  is the concentration of a diisocyanate in µg/mL

$C_{Diisocyanate - MP}$  is the concentration of a diisocyanate-MP-derivative in µg/mL

$M_{Diisocyanate}$  is the molecular mass of a diisocyanate in g/mol

$M_{Diisocyanate - MP}$  is the molecular mass of a diisocyanate-MP-derivative in g/mol

**Table 2.** Molecular masses of diisocyanates and diisocyanate-MP-derivatives.

Substance	Diisocyanate [g/mol]	Diisocyanate-MP [g/mol]
4,4'-Methylene diphenyl diisocyanate (MDI)	250.3	634.8
1,6-Hexamethylene diisocyanate (HDI)	168.2	552.7
Isophorone diisocyanate (IPDI)	222.3	606.8
1,5-Naphthylene diisocyanate (NADI)	210.2	594.7
2,4-Toluene diisocyanate (2,4-TDI)	174.2	558.6
2,6-Toluene diisocyanate (2,6-TDI)	174.2	558.6

The stock solution is stable for at least one year when stored in a refrigerator.

Calibration standard solutions:

Calibration standard solutions are prepared from the stock solution by dilution with acetonitrile according to the following pipetting scheme (Table 3 and 4).

**Table 3.** Pipetting scheme for the preparation of the calibration standard solutions of 4,4'-methylene diphenyl diisocyanate (MDI).

Dilution	Volume of the stock solution [mL]	Final volume of the calibration standard solutions [mL]	Concentration of the calibration standard MDI [µg/mL]	Corresponds a MDI concentration in air at 40 L sample volume [mg/m <sup>3</sup> ]
1:200	0.05	10	0.079	0.002
1:100	0.1	10	0.158	0.005
1:50	0.2	10	0.316	0.010
1:20	0.5	10	0.790	0.025
1:10	1	10	1.580	0.049
1:5	2	10	3.160	0.099

**Table 4.** Concentrations of diisocyanates in the calibration standard solutions.

Substance	Dilution [µg/mL]						
	1:200	1:100	1:50	1:20	1:10	1:5	1:2
MDI	0.079	0.158	0.316	0.79	1.58	3.16	7.9
HDI	0.061	0.122	0.244	0.61	1.22	2.44	6.1
IPDI	0.074	0.147	0.294	0.74	1.47	2.94	7.4
NADI	0.071	0.142	0.284	0.71	1.42	2.84	7.1
TDI	0.063	0.125	0.250	0.625	1.25	2.50	6.25

### 3 Sampling and sample preparation

#### 3.1 Sampling

The sampling equipment consists of the isocyanate sampling-set, a connection tube, and a suitable pump. Both personal and stationary sampling can be conducted for the assessment of working areas.

For determination of the shift average value, the air sample is drawn through the isocyanate sampling-set using a flow rate of 0.33 L/min for at least 2 h. For monitoring the short-term value, the air sample is drawn through the isocyanate sampling-set using a flow rate of 2 L/min over a time period of 15 min. The parameters which are important



for the determination of the diisocyanate concentrations in air (sample volume, temperature, atmospheric pressure, and relative humidity) are documented in a sampling record.

### 3.2 Sample preparation

After transportation the samples are stored in a refrigerator at a maximum temperature of +4 °C. They are stable for at least 2 weeks under these conditions. For sample preparation, the loaded collection filter and the supporting plate are placed in a 25 mL sample vial and covered with 5 mL acetonitrile. After treatment in an ultrasonic bath for 10 min, 4 mL of the sample solution are removed with a disposable syringe and filtered into a 8 mL sample vial using a 0.2 µm disposable syringe filter. The solvent is evaporated in an air stream of N<sub>2</sub> and the residue is resolved in 1 mL of solvent II (0.5 mL acetic anhydride in 100 mL acetonitrile). Afterwards the solution is transferred to a 2 mL sample vial and sealed tightly with a PTFE-lined screw cap.

## 4 Operating conditions for HPLC

Apparatus:	HPLC equipped with a UV-Detector (Finnigan Spectra System P 4000)
Column:	Material: e.g. Nucleosil 120-5 C <sub>18</sub> Length: 250 mm Internal diameter: 4 mm Particle size: 5 µm
Column temperature:	Room temperature (20 °C)
Mobile phase:	Solution I
Mode:	Isocratic
Flow rate:	1.2 mL/min
Pressure:	180 bar
Detector:	UV-detector (Finnigan Spectra System UV 6000 LP)
Detector wavelength (γ):	250 nm
Injection volume:	20 µL

In Figure 1, an example of a chromatogram is shown as obtained under the described conditions.

## 5 Analytical determination

20 µL of the prepared sample solution are injected into the sample loop of the HPLC and analysed under the conditions as described in Section 4. If the calculated concentration is outside the calibration range, the sample solution must be suitably diluted with acetonitrile and analysed again.

## 6 Calibration

Quantitative evaluation is carried out using a calibration function [8, 9].

For this purpose the calibration standard solutions according to Section 2.5 are analysed as described in Section 4. The calibration graphs are obtained by plotting the detected peak areas against the corresponding concentrations of the diisocyanates. The calibration graph of each diisocyanate is linear in the investigated range from 0.06 to 7 µg/mL. In Figures 2 and 3, the calibration graphs for 4,4'-methylene diphenyl diisocyanate (MDI) and isophorone diisocyanate (IDPI) are shown exemplarily.

In order to check the calibration function, control samples should be analysed prior to each measurement. Calibration must be prepared again, if the analytical conditions changed or quality control shows this to be necessary.

## 7 Calculation of the analytical result

The diisocyanate concentrations in the workplace air are calculated using the concentrations of the substances in the measurement solution calculated by the data processing unit. The data processing unit uses the calibration functions established during calibration for this purpose.

The concentrations of the diisocyanates in the workplace air in mg/m<sup>3</sup> are determined from the concentrations (calculated by the data processing unit) after subtraction of any blank values and taking into account dilution steps and the sampled air volume. Equation (2) applies for the concentrations of diisocyanates in the workplace air:

$$\rho = \frac{X \times 1,25}{V_z \times \eta} \quad (2)$$

At 20 °C and 1013 hPa:

$$\rho_0 = \rho \times \frac{273 + t_a}{293} \times \frac{1013}{p_a} \quad (3)$$

The corresponding concentration by volume  $\sigma$  – independent of the variables atmospheric pressure and temperature – is given by equation 4 and 5:

$$\sigma = \rho_0 \times \frac{V_m}{M} \quad (4)$$

$$\sigma = \rho \times \frac{273 + t_a}{p_a} \times \frac{1013}{293} \times \frac{V_m}{M} \quad (5)$$

For  $t_a = 20^\circ\text{C}$  and  $p_a = 1013\text{ hPa}$ , the following conversion factors apply:

$$\sigma(MDI) = \rho \times 0.096 \frac{\text{mL}}{\text{mg}} \quad (6)$$

$$\sigma(HDI) = \rho \times 0.143 \frac{\text{mL}}{\text{mg}} \quad (7)$$

$$\sigma(IPDI) = \rho \times 0.108 \frac{\text{mL}}{\text{mg}} \quad (8)$$

$$\sigma(NADI) = \rho \times 0.115 \frac{\text{mL}}{\text{mg}} \quad (9)$$

$$\sigma(TDI) = \rho \times 0.138 \frac{\text{mL}}{\text{mg}} \quad (10)$$

where:

- $X$  is the concentration of the substance determined from the calibration function in  $\mu\text{g/mL}$
- 1.25 is the conversion factor for the mass of 4 mL (evaporated sample solution) 5 mL (amount of the extraction solvent)
- $V_z$  is the sampled air volume in L
- $\eta$  is the recovery
- $\rho$  is the concentration by weight of the substance in the ambient air at  $t_a$  and  $p_a$  in  $\text{mg/m}^3$
- $\rho_0$  is the concentration by weight of the substance in the ambient air at  $20^\circ\text{C}$  and  $1013\text{ hPa}$  in  $\text{mg/m}^3$
- $t_a$  is the temperature in the ambient air in  $^\circ\text{C}$
- $p_a$  is the atmospheric pressure in the ambient air in hPa
- $\sigma$  is the concentration of diisocyanates in the ambient air in  $\text{mL/m}^3$
- $V_m$  is the molecular volume of diisocyanates in  $\text{L/mol}$
- $M$  is the molecular weight of diisocyanates in  $\text{g/mol}$

## 8 Reliability of the method

The characteristics of the method were determined according to EN 482 [10].

### 8.1 Accuracy

#### 8.1.1 Precision

As it was not possible to generate stable test gas atmospheres, the filters in the cassettes (coated with 1-(2-methoxyphenyl) piperazine) were spiked with solutions of diisocyanates (in anhydrous toluene) with defined compositions. Afterwards, 40 L air with 50 % relative humidity was drawn through the system with a flow rate set at 0.33 L/min. Each 6 samples were loaded according to this procedure. Analyses of the samples were carried out as described in Sections 3, 4, and 5. The results of 4,4'-methylene diphenyl diisocyanate (MDI) and isophorone diisocyanate (IPDI), analysed in the concentration range between the 0.1- and 2-fold of the MAK values, are listed in Table 5.

**Table 5.** Standard deviation (rel) and mean variation  $u$ ,  $n = 6$  determinations.

Substance	Spiked mass [ $\mu\text{g}$ ]	Standard deviation (rel) [%]	Mean variation $u$ [%]
MDI	0.196	6.64	17.1
	1.956	1.98	5.1
	3.912	1.78	4.6
IPDI	0.369	6.14	15.1
	3.691	2.18	5.6
	7.381	2.29	5.9

#### 8.1.2 Reliability

For determining the recoveries, each 6 isocyanate sampling-sets were spiked with defined toluene solutions of MDI and IPDI in three concentrations (0.1-, 1- and 2-fold of the MAK value). Afterwards, 40 L air with 50 % relative humidity was drawn through the sampling-sets at room temperature. Analyses of the samples were carried out as described in Sections 3, 4, and 5. The data are listed in Table 6.

**Table 6.** Recoveries  $\eta$  at  $n = 6$  determinations.

Substance	Spiked mass	Mean value	Relative measurement uncertainty	Recovery
	[ $\mu\text{g}$ ]	[ $\mu\text{g}$ ]	[%]	[ $\eta$ ]
MDI	0.196	0.197	13.8	1.00
	1.956	2.050	9.0	1.05
	3.912	3.970	5.1	1.01
IPDI	0.369	0.353	16.2	0.96
	3.691	3.799	7.4	1.03
	7.381	7.554	7.0	1.02

## 8.2 Recovery

For determining the recoveries, each 6 isocyanate sampling-sets were spiked with defined toluene solutions of MDI and IPDI in three concentrations (0.1-, 1-, and 2-fold of the MAK value). Afterwards, 40 L air with 50% relative humidity was drawn through the sampling-sets at room temperature. Analyses of the samples were carried out as described in Sections 3, 4, and 5. The recoveries were calculated from the results of the measurement for precision. For MDI and IPDI, the following recoveries were obtained:

MDI:  $\eta = 1.00\text{--}1.05$

IPDI:  $\eta = 0.96\text{--}1.03$

## 8.3 Limits of quantification

The limits of quantification were calculated according to DIN 32645 [11]. For MDI and IPDI the limits of quantification were calculated for a 40-litre air sample under the analytical conditions given in Section 4:

MDI:  $0.005 \text{ mg/m}^3$

IPDI:  $0.008 \text{ mg/m}^3$

The quantification limits are related to the blank values from the glass fibre filters coated with 1-(2-methoxyphenyl) piperazine, which can vary from batch to batch.

## 8.4 Shelf-life

Loaded sample carriers can be stored in a refrigerator for at least 14 days without losses.

## 8.5 Interferences

Substances that react with 1-(2-methoxyphenyl) piperazine in a similar way as isocyanates, and also show a comparable chromatographic behavior, can influence the determination.

As diisocyanates can already react with air humidity, only fresh purchased diisocyanates (in original flasks) should be used for preparing the derivatives.

## 8.6 Capacity of the sample carrier

The adsorption capacity of the filters coated with 1-(2-methoxyphenyl) piperazine is assessed in a way that 0.5 mg of MDI can be adsorbed.

## 9 Discussion of the method

The presented analytical method is suitable for the determination of monomeric diisocyanates in the workplace air. Sample collection can be performed as stationary or personal sampling. Besides of the diisocyanates MDI and IPDI described herein, also the concentration of other monomeric diisocyanates can be determined by using this analytical method. Through the use of a fluorescence detector, lower limits of quantification can be realized. However, the presented analytical method is not feasible for the determination of aerosolic polymeric isocyanates.

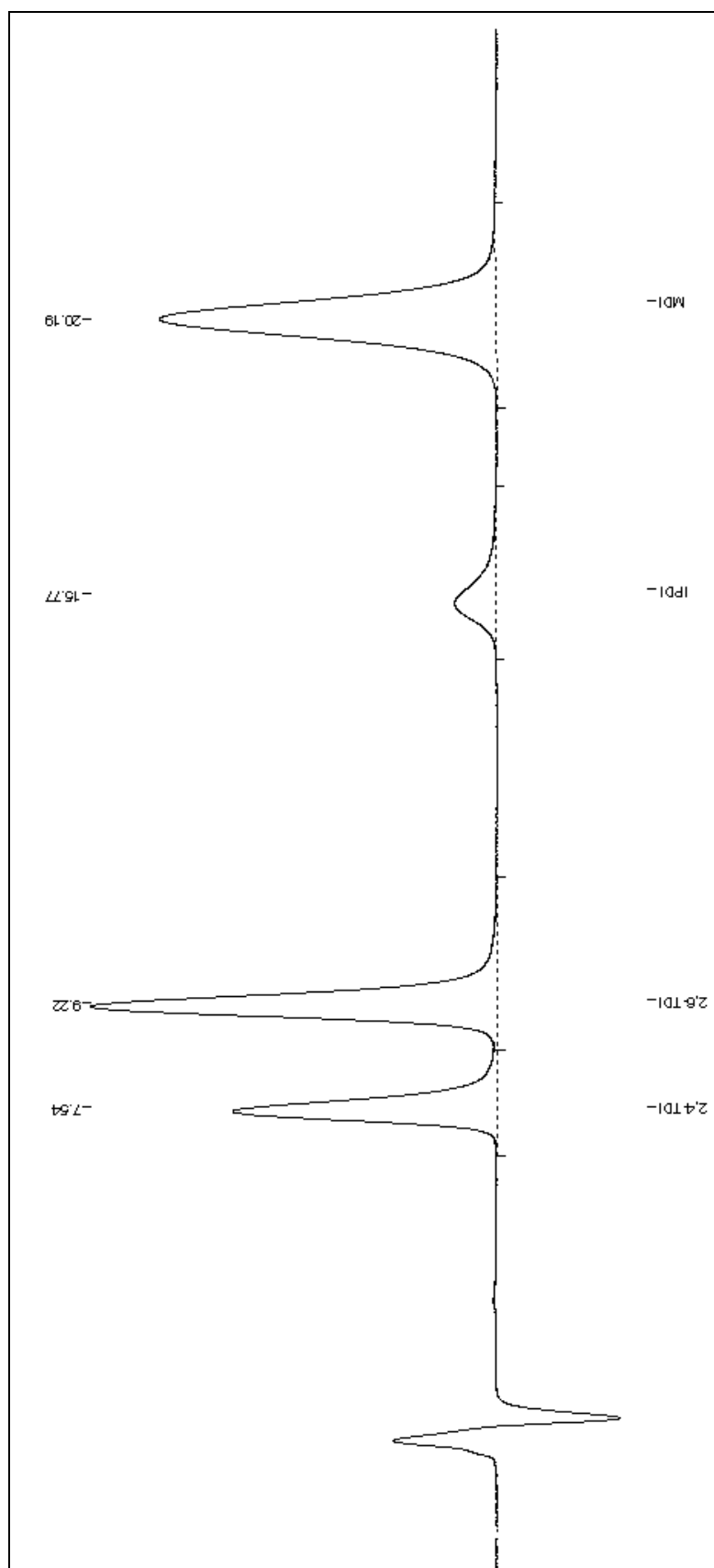
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**Fig. 1.** Example of a HPLC chromatogram for separation of the diisocyanates (see Section 4 for the chromatographic conditions).



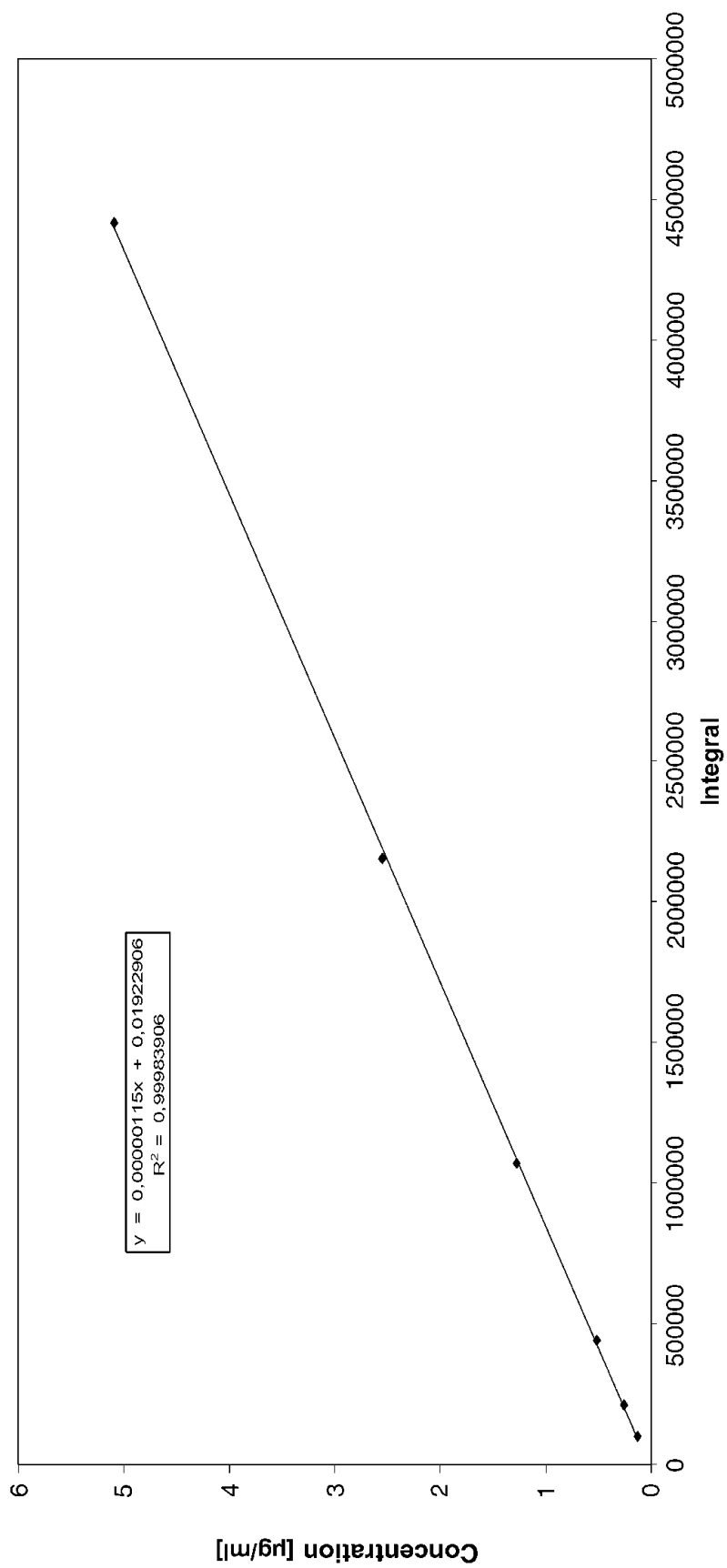


Fig. 2. Calibration graph for 4,4'-methylene diphenyl diisocyanate.

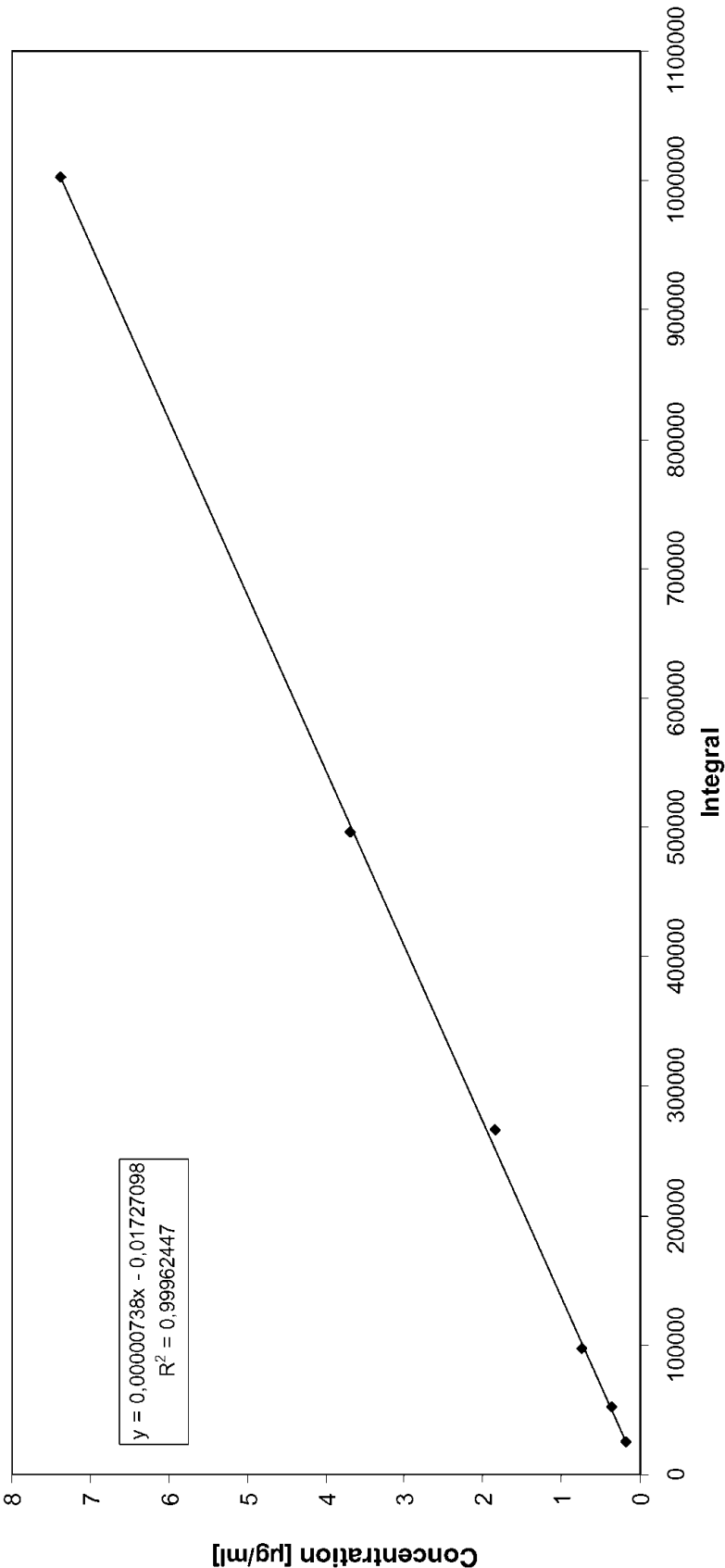


Fig. 3. Calibration graph for isophorone diisocyanate (IPDI).