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N-Nitrosamines – Method for the determination of N-nitrosamines in workplace air using gas chromatography with a thermal energy analyzer (GC-TEA) after elution

Air Monitoring Method

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Abstract

This analytical method is a validated measurement procedure for the determination of 9 N-nitrosamines such as N-nitrosodimethylamine [62-75-9], N-nitrosomethylethylamine [10595-95-6], N-nitrosodiethylamine [55-18-5], N-nitrosodiisopropylamine [601-77-4], N-nitrosodi-n-propylamine [621-64-7], N-nitrosodi-n-butylamine [924-16-3], N-nitrosopiperidine [100-75-4], N-nitrosopyrrolidine [930-55-2], N-nitrosomorpholine [59-89-2] in workplace air averaged over the sampling period after personal or stationary sampling. Sampling is performed by drawing a defined volume of air through a ThermoSorb-N cartridge using a suitable flow-regulated pump. Afterwards the cartridges are eluted with dichloromethane/methanol (3:1, v:v) and the sample solution is analysed by means of gas chromatography with a thermal energy analyser (TEA) detector. The

relative limit of quantification (LOQ) is 0.010 µg/m³ N-nitrosamine per cartridge for an air sample volume of 400 l. The mean recovery for all nine N-nitrosamines was between 96% and 102% and the expanded uncertainty for the analysed N-nitrosamines was between 19% and 27% over the entire measurement range.

This analytical method has been accredited by the accident insurance companies for the detection in workplace air of substances that are carcinogenic, mutagenic or toxic to reproduction.

This method has been tested and recommended for the determination of N-nitrosamines in work areas by the German Social Accident Insurance (DGUV).

Both personal and stationary sampling can be performed for measurements in order to evaluate work areas.

Name	CAS No.	Molar mass
N-nitrosodimethylamine	62-75-9	74.1
N-nitrosomethylethylamine	10595-95-6	88.1
N-nitrosodiethylamine	55-18-5	102.1
N-nitrosodiisopropylamine	601-77-4	130.2
N-nitrosodi-n-propylamine	621-64-7	130.2
N-nitrosodi-n-butylamine	924-16-3	158.3
N-nitrosopiperidine	100-75-4	114.2
N-nitrosopyrrolidine	930-55-2	100.1
N-nitrosomorpholine	59-89-2	116.1

1 Summary

This method enables the determination of the mean concentration of N-nitrosodimethylamine (NDMA), N-nitrosomethylethylamine (NMEA), N-nitrosodiethylamine (NDEA), N-nitrosodiisopropylamine (NDiPA), N-nitrosodi-n-propylamine (NDPA), N-nitrosodi-n-butylamine (NDBA), N-nitrosopiperidine (NPIP), N-nitrosopyrrolidine (NPYR) and N-nitrosomorpholine (NMOR) over the sampling period in work areas using personal or stationary sampling.

Remarks: Lower results can occur with the higher boiling N-nitrosamines.

Measurement Principle: A sampling pump draws a defined volume of air from the breathing zone through a ThermoSorb-N cartridge. The volatile N-nitrosamines occurring in the gaseous state in the workplace air are adsorbed onto the cartridge. The cartridges are then eluted with dichloromethane/methanol (3:1, v:v) and analysed using a TEA detector after separation by means of a gas chromatograph.

Limit of quantification: Absolute: 0.004 µg per N-nitrosamine per cartridge

Relative: 0.010 µg/m³ per N-nitrosamine for an air sample volume of 400 l, a desorption volume of 1 ml and an injection volume of 2 µl

Measurement range: Validated in the range of 0.01 µg/m³ to 0.075 µg/m³ for an air sample volume of 400 l.

Selectivity: Interference from other organic nitrogen compounds is possible. The N-nitrosamines are identified by means of irradiation with UV light, which leads to diminished signals in the chromatogram.

Advantages: Personal and selective measurements are possible.

Disadvantages: Measurement is not possible at a relative humidity of > 60%.

Apparatus:

Pump
Flow meter
ThermoSorb-N adsorption cartridges
Gas chromatograph with TEA detector
UV lamp

2 Equipment and chemicals

2.1 Equipment

For sampling and sample preparation:

- ThermoSorb-N adsorption cartridges, from Ellutia, Great Britain, supplied by e.g. Ellutia GmbH & Co. KG, 34132 Kassel, Germany
- Sampling pump, suitable for a flow rate of 100 l/h, e.g. Personal Air Sampler Gil Air 5, from Gilian, supplied by DEHA Haan & Wittmer, 71296 Heimsheim, Germany
- Flow meter, e.g. Gilibrator, from Gilian

For analysis:

- Gas chromatograph with split/splitless injector, e.g. from Agilent, 76337 Waldbronn, Germany
- Polar capillary column, e.g. 'Stabilwax' (Crossbond Carbowax polyethylene glycol, length 30 m, ID 250 µm, film thickness 0.25 µm), e.g. from Restek, 61348 Bad Homburg, Germany
- Microlitre syringes: 2, 5, 10, 25, 50 and 100 µl, e.g. from Hamilton, 7402 Bonaduz, Switzerland
- Volumetric pipette, 25 ml
- Volumetric flasks, 1, 2 and 200 ml
- Autosampler vials made of amber glass with screw caps with PTFE/silicone/PTFE septa
- Autosampler vials made of clear glass
- Micro inserts made of ceramic glass for autosampler vials
- Disposable filter, pore size 0.45 µm, e.g. from Sartorius, 37079 Göttingen, Germany
- Disposable syringes, 2 ml volume with disposable hypodermic needles (0.9 × 40 mm)
- Solid phase extraction (SPE) with 12 slots, corresponding column funnel with Luer connector and vacuum manifold, e.g. from Macherey-Nagel, 52355 Düren, Germany
- UV lamp for the irradiation with UV light at 366 nm, e.g. UV-Kabinett 4, from CAMAG AG & Co. GmbH, 12169 Berlin, Germany

2.2 Chemicals

- Nitrosamine Mix 9 (with NDMA, NMEA, NDEA, NDiPA, NDBA, NDPA, NPIP, NPYR, NMOR), 10 µg/ml of each in methanol, e.g. from Neochema GmbH, 55294 Bodenheim, Germany, Article No. 16005
- Nitrosamine Mix 9 (with NDMA, NMEA, NDEA, NDiPA, NDBA, NDPA, NPIP, NPYR, NMOR), 100 µg/ml of each in methanol, e.g. from Neochema GmbH, 55294 Bodenheim, Germany, Article No. 16007

- N-Nitroso-n-butyl-n-propylamine (NBPA), 10 µg/ml in dichloromethane, e.g. from AccuStandard Europe, 4704 Niederbipp, Switzerland, Article No. S-3106-0.1 X
- Dichloromethane, p.a., ≥ 99.8%, e.g. from Merck, 64293 Darmstadt, Germany, Article No. 1.06050
- Methanol, p.a., ≥ 99.9%, e.g. from Merck, Article No. 1.06009
- Toluene, p.a., ≥ 99.9%, e.g. from Merck, Article No. 1.08325
- Hydrogen bromide (32% solution in acetic acid), e.g. from Merck, Article No. 818856
- Gases for the operation of the gas chromatograph and the detector: Helium 5.0, Oxygen 5.0

2.3 Solutions

N-Nitroso-n-butyl-n-propylamine (ISTD): N-nitroso-n-butyl-n-propylamine in dichloromethane at a concentration of 10 µg/ml is used as an internal standard (ISTD).

Elution solution: Solution of dichloromethane and methanol (3:1, v:v):
First, 150 ml of dichloromethane and then 50 ml of methanol are measured into a 200 ml volumetric flask and subsequently mixed. The solution is stored in an amber glass bottle.

Stock solution: The Nitrosamine Mix 9 (10 µg/ml) referred to in Section 2.2 is used as a stock solution.

Calibration stock solution 1: Solution of approx. 5.71 mg of 2-bromoethanol per ml of desorption solution.
33 µl of 2-bromoethanol (density 1.763 g/cm^3) are pipetted into a 10 ml volumetric flask, into which several millilitres of desorption solution have been previously placed, it is weighed exactly to the nearest 0.1 mg, filled to the mark with desorption solution and shaken.

Calibration solutions: Ten solutions of the N-nitrosamines with concentrations of approx. 0.003 to 0.03 µg/ml.
Using a microlitre syringe, different amounts of the stock solution as well as 30 µl of the internal standard are dosed into ten 2-ml volumetric flasks, into which 1 ml of elution solution has been previously placed. The volumetric flasks are then filled to the mark with elution solution. The calibration solution series serves to determine the characteristics of the method and also represents the working range of the method.
Based on an air sample volume of 400 l, a concentration range from approx. 0.0075 to 0.075 µg/m^3 is covered by these calibration solutions. The exact concentrations can be found in Table 1.

Tab. 1 Concentrations of the N-nitrosamines in the calibration solutions

Calibration solution	Addition of stock solution [µl]	Addition of ISTD [µl]	Concentration of N-nitrosamines [µg/ml]	Concentration of N-nitrosamines [µg/m^3][a)]
1	0.6	30	0.003	0.0075
2	1.2	30	0.006	0.015
3	1.8	30	0.009	0.023
4	2.4	30	0.012	0.030

Tab. 1 *(continued)*

Calibration solution	Addition of stock solution	Addition of ISTD	Concentration of N-nitrosamines	Concentration of N-nitrosamines
	[µl]	[µl]	[µg/ml]	[µg/m³][a)]
5	3.0	30	0.015	0.038
6	3.6	30	0.018	0.045
7	4.2	30	0.021	0.053
8	4.8	30	0.024	0.600
9	5.4	30	0.027	0.068
10	6.0	30	0.030	0.075

[a)] based on an air sample volume of 400 l

3 Sampling

The validation of the method was carried out at a temperature range of approx. 20 to 25 °C.

3.1 Influence of the air humidity

Before sampling, the relative humidity at the workplace must be measured. The subsequent procedure during sampling depends on this parameter (see Table 2).

- Determination of N-nitrosamines is not possible for a relative humidity higher than 60%.
- At relative humidities less than 40% sampling can be carried out with a ThermoSorb-N cartridge and over a sampling period of four hours.
- At relative humidities between 40% and 60% two sample series should be carried out in parallel:
  1. Sampling with one Thermosorb-N cartridge over a sampling period of four hours.
  2. Sampling with two sample carriers connected in series and a reduced sampling period of three hours. In this case it is important to note that the limits of quantification of the N-nitrosamines are increased.

Tab. 2 Procedure for the measurement of N-nitrosamines

Relative humidity	Number of sample carriers (ThermoSorb-N)	Sampling period
[%]		[h]
> 60	Evaluation not possible	Evaluation not possible
≤ 40	1	4
40 –60	1 2 (measurement in parallel)	4 3 (measurement in parallel)

If the relative humidity is greater than 40%, it is necessary to carry out measurements in parallel using both the procedures described above to ensure that a valid conclusion can be drawn about the concentrations of all the N-nitrosamines in the tested measurement range.

3.2 Sampling method

The two screw caps are opened and the ThermoSorb-N cartridge is connected to the pump. When a double sample carrier is used, one cartridge is connected to the air inlet and another to the air outlet. The pump and cartridge are worn by a person during working hours or stationary sampling is carried out. The air sample volume is 400 l when a

single sample carrier is used and 300 l when a double sample carrier is used. The flow rate should not exceed 100 l/h. After sampling, the flow rate must be tested for constancy. If the deviation from the adjusted flow rate is greater than ± 5%, it is advisable to discard the sample (see DGUV Information 213-500 "General Part", Section 3 (DGUV 2015)).

After sampling, the cartridge is sealed with the screw caps provided. If two cartridges were used, then their order should be labelled. The important parameters for the determination of the concentration in air (sample volume, temperature, air pressure, relative humidity) are documented in a sampling record.

4 Analytical determination

4.1 Sample preparation and analysis

15 µl of the internal standard are introduced into the 'Air In' aperture of the loaded ThermoSorb-N cartridge. The cartridge is placed onto the extraction device with the 'Air In' aperture pointing downwards for the purpose of elution. The column funnel is used to elute the cartridges with 2 ml of elution solution. It is crucial that the ISTD is applied to the cartridges before the elution solution. In this way it was established that the ISTD is completely eluted. The eluate (approx. 1 ml) is collected, drawn into a disposable syringe and filtered into an autosampler vial through a disposable filter.

2 µl of the sample solution are injected into the gas chromatograph and analysed as described below. The quantitative evaluation is carried out according to the internal standard method using the peak areas of the relevant substance with respect to that of N-nitroso-n-butyl-n-propylamine as the ISTD.

To ensure identification of the N-nitrosamines, irradiation of a subsample with UV light is carried out over a period of two to three hours. Due to their lack of UV stability, the N-nitrosamines partially break down during the process. The signal of one N-nitrosamine in the irradiated sample is therefore diminished by approx. half in a repeated analysis cycle.

4.2 Operating conditions for chromatography

The characteristics of the method stated in Section 6 were obtained under the following operating conditions:

Apparatus:	Gas chromatograph with split/splitless injector and TEA detector	
Separation column:	Quartz capillary "Stabilwax" Crossbond Carbowax polyethylene glycol, length 30 m, ID 250 µm, film thickness 0.25 µm	
Carrier gas:	Helium, 1 ml/min	
Oven programme:	Initial temperature 38 °C, isothermal for 0.75 min Heating rate I: 40 °C/min until 80 °C, 1.8 min Heating rate II: 25 °C/min until 200 °C, 12.6 min	
Injection volume:	2 µl, splitless up to 0.75 min, temperature: 155 °C	
Detector:	Interface:	200 °C
	Pyrolyzer:	500 °C
	Vacuum:	0.64 Torr
	Coldtrap:	–20 °C
	Oxygen flow:	3.2 ml/min

5 Evaluation

5.1 Calibration

The calibration standards described in Section 2.3 are analysed as described in Section 4.2. The linear calibration functions are obtained with the help of linear regression by plotting the ratios of the peak areas of the N-nitrosamines to the peak areas of the ISTD versus the mass ratios of the N-nitrosamines and the ISTD.

5.2 Calculation of the analytical result

The peak areas of the N-nitrosamines and of N-nitroso-n-butyl-n-propylamine are obtained from the recorded chromatograms, the quotient is calculated and the corresponding value for the mass concentration in the sample solution in µg/ml is determined from the calibration function taking the mass concentration of the internal standard into consideration.

$$c_{Nitrosamin\_Measurement\ Solution} = c_{ISTD\_Measurement\ Solution} \times \frac{AQ - a}{b} \quad (1)$$

where:

$c_{Nitrosamine\_Measurement\ Solution}$	is the mass concentration of N-nitrosamine in the measurement solution in µg/ml
$c_{ISTD\_Measurement\ Solution}$	is the mass concentration of the internal standard in the measurement solution in µg/ml (0.15 µg/ml)
AQ	is the area ratio, see below
a	is the intercept
b	is the gradient

$$AQ = \frac{A_{Nitrosamine}}{A_{ISTD}} \quad (2)$$

where:

$A_{Nitrosamine}$	is the area of N-nitrosamine
A_{ISTD}	is the area of internal standard

The mass concentration of the relevant individual substances in the air sample in µg/m³ is calculated using the following equation.

$$c_{air\ sample} = \frac{c_{Measurement\ Solution} \times V_E}{V_{air} \times \eta} \quad (3)$$

where:

$c_{air\ sample}$	is the mass concentration of the N-nitrosamine in the air sample in µg/m³
$c_{Measurement\ Solution}$	is the mass concentration of the N-nitrosamine in the measurement solution in µg/ml
V_E	is the elution volume in ml (1 ml)
V_{air}	is the air sample volume in m³
η	is the recovery (1.0)

5.3 Calculation of the analytical result for parallel sampling

If sampling is carried out in parallel with a single and two sample carriers connected in series (see Section 3) then all three sample carriers are prepared and analysed as described in Section 4.

In this case it must be taken into consideration that the limit of quantification for the two sample carriers connected in series is higher than that of the single sample carrier (4 h) due to the reduced sampling period (3 h).

If the N-nitrosamine concentrations on the collection layer as well as the control layer of the double sample carrier are greater than the limit of quantification, the results for the N-nitrosamines are added and the result for the single sample carrier is not taken into account for these N-nitrosamines, as it must be assumed that a breakthrough has occurred. If the content of N-nitrosamine detected on the control layer exceeds 25% of the value that was detected on the collection layer, then the result is of limited validity, as further losses of this N-nitrosamine cannot be ruled out.

If N-nitrosamines with a concentration above the limit of quantification are found on the collection layer of the double sample carrier and if these N-nitrosamines are qualitatively detected on the control layer, but below the limit of quantification, then only the measurement value of the collection layer is used. In order to take account of the slight breakthrough onto the control layer, the limit of quantification of these N-nitrosamines is also added to this measurement value. The single sample carrier is not considered for these N-nitrosamines.

If N-nitrosamines at levels higher than the limit of quantification are detected on the collection layer of the double sample carrier, but these N-nitrosamines are not qualitatively detected on the control layer, then the evaluation for these N-nitrosamines is carried out using the single sample carrier with the limits of quantification as described in Section 6.2. However, should the value for these N-nitrosamines on the collection layer of the double sample carrier be higher than the value for the single sample carrier, then the higher value must be stated, as a breakthrough cannot be ruled out due to the longer sampling period of the single sample carrier.

6 Reliability of the method

The characteristics of the method were calculated as stipulated in DIN EN 482 (DIN 2021 a). The validation was carried out with dilutions of two N-nitrosamine stock solutions with different concentrations (Nitrosamine Mix 9, see Section 2.2). For this purpose, the sample carriers were directly spiked with defined volumes of the corresponding N-nitrosamine solution. Then air at the desired humidity was drawn through the sample carriers in the dynamic test gas apparatus for 4 h at 100 l/h. Six ThermoSorb-N cartridges were loaded per concentration. The experiments were carried out at room temperature. The preparation of the sample carriers was carried out as described in Section 4.

6.1 Precision and recovery

The precision and recovery were determined by loading six ThermoSorb-N cartridges in each case with different concentrations of the N-nitrosamines. These experiments were carried out at a relative humidity of approx. 38%. The analysed concentrations of N-nitrosamines can be found in Table 3. The ThermoSorb-N cartridges were spiked with different concentrations of the stock solution and then air was drawn through the cartridges as described above. The air sample volume was 400 l for all experiments.

Tab. 3 Characteristics of the validation

Substance	Concentration	Spiked volume of stock solution	Recovery	Relative standard deviation
	[µg/m³]	[µl]	[%]	[%]
N-nitrosodimethylamine	0.010	0.4	108.8	6.5
	0.030	0.6	106.6	3.7
	0.075	3.0	99.8	1.3
	0.750	3.0[a)]	92.0	6.4
N-nitrosomethylethylamine	0.010	0.4	97.0	4.0
	0.030	0.6	96.4	2.5
	0.075	3.0	101.9	1.1
	0.750	3.0[a)]	95.9	3.7
N-nitrosodiethylamine	0.010	0.4	95.0	4.4
	0.030	0.6	103.1	6.6
	0.075	3.0	101.5	1.9
	0.750	3.0[a)]	96.5	3.6
N-nitrosodiisopropylamine	0.010	0.4	99.5	1.9
	0.030	0.6	96.4	4.6
	0.075	3.0	97.8	2.7
	0.750	3.0[a)]	98.4	3.5
N-nitrosodi-n-propylamine	0.010	0.4	97.3	4.3
	0.030	0.6	96.6	8.2
	0.075	3.0	100.9	2.3
	0.750	3.0[a)]	100.2	3.1
N-nitrosodi-n-butylamine	0.010	0.4	103.6	3.6
	0.030	0.6	93.2	12.2
	0.075	3.0	100.6	2.0
	0.750	3.0[a)]	111.0	2.2
N-nitrosopiperidine	0.010	0.4	98.1	4.1
	0.030	0.6	95.5	7.6
	0.075	3.0	98.2	1.4
	0.750	3.0[a)]	94.5	4.4
N-nitrosopyrrolidine	0.010	0.4	99.3	3.8
	0.030	0.6	97.0	8.7
	0.075	3.0	98.5	1.8
	0.750	3.0[a)]	93.7	2.1
N-nitrosomorpholine	0.010	0.4	99.2	3.7
	0.030	0.6	94.8	6.5
	0.075	3.0	97.8	1.8
	0.750	3.0[a)]	91.1	2.3

[a)] concentrated N-nitrosamine stock solution (100 µg/ml, see Section 3.2) was used

As the mean recoveries are between 96% and 102% for all seven N-nitrosamines, no correction was made when calculating the result.

However, at relative humidities of between 40% and 60% the recovery of the N-nitrosamines is concentration-dependent. Breakthroughs occur at higher concentrations. Therefore, in this humidity range sampling must be carried out as described in Section 4.

Due to breakthroughs of the N-nitrosamines, quantitative evaluation is not possible in the case of a relative humidity greater than 60%.

An air sample volume of 400 l (sampling for 4 h at a flow rate of 100 l/h) must not be exceeded, as otherwise a breakthrough cannot be ruled out.

6.2 Limit of quantification

The limits of quantification were calculated in accordance with DIN 32645 (DIN 2008). The numeric values were determined based on an equidistant 10-point calibration over one order of magnitude in the lower working range. The limits of quantification for N-nitrosopiperidine and N-nitrosomorpholine were determined using the blank value method.

The calculated absolute limits of quantification per cartridge are between 0.0001 and 0.004 µg/l for all the N-nitrosamines. This is equivalent to a relative limit of quantification of 0.0003 to 0.010 µg/m^3 at an air sample volume of 400 l and a desorption volume of 1 ml. The limits of quantification were consistently determined at 0.010 µg/m^3 for all the N-nitrosamines.

6.3 Storage stability

The storage stability without losses of the N-nitrosamines in an adsorbed state is at most 7 days at room temperature. Eluted samples can be stored in the refrigerator for at least 4 weeks.

6.4 Selectivity

The N-nitrosamines can be conclusively identified due to their sensitivity to UV light. After irradiation with UV light, the N-nitrosamine peaks are diminished due to decomposition of the N-nitrosamines, which allows them to be identified with certainty.

6.5 Uncertainty

The expanded uncertainty was determined taking all relevant influencing factors into consideration as stipulated in DIN EN 482 (DIN 2021 a) and DIN EN ISO 22065 (DIN 2021 b). The uncertainty of the entire method and thus also of the analytical result consists principally of the uncertainty contributions of sampling (e.g. air sample volume) and the analytical preparation (complete desorption, scatter of the calibration function, fluctuations in the recovery and the reproducibility). The expanded uncertainty for the investigated substances is between 19% and 27%. The results are shown in Table 4.

Tab. 4 Expanded uncertainty

Substance	Concentration [µg/m^3]	Expanded uncertainty [%]
N-nitrosodimethylamine	0.010	25
	0.030	24
	0.075	23
	0.750	25
N-nitrosomethylethylamine	0.010	18
	0.030	18
	0.075	17
	0.750	18
N-nitrosodiethylamine	0.010	20
	0.030	20
	0.075	19
	0.750	20
N-nitrosodiisopropylamine	0.010	17
	0.030	18
	0.075	18
	0.750	18

Tab. 4 *(continued)*

Substance	Concentration [µg/m³]	Expanded uncertainty [%]
N-nitrosodi-n-propylamine	0.010	19
	0.030	20
	0.075	19
	0.750	19
N-nitrosodi-n-butylamine	0.010	25
	0.030	27
	0.075	24
	0.750	27
N-nitrosopiperidine	0.010	19
	0.030	21
	0.075	19
	0.750	20
N-nitrosopyrrolidine	0.010	19
	0.030	21
	0.075	19
	0.750	20
N-nitrosomorpholine	0.010	20
	0.030	21
	0.075	20
	0.750	22

7 Remarks

Instead of the sample preparation method described in Section 4.1, it is also possible to apply the internal standard to the sample carrier in the form of the stock solution together with the elution solution. Therefore, the internal standard must have a concentration of 15 µl/ml elution solution. 2 ml of this stock solution are placed on the loaded sample carrier. The resulting eluate is prepared and analysed as described in Section 4.1.

Experiments have shown that both sample preparation methods lead to comparable results.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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