Method for the determination of carboxylic acid amides

German Social Accident Insurance
Deutsche Gesetzliche Unfallversicherung
Analytical Subcommittee of the Chemistry Board of Experts*

Carcinogenic substances	Order number:	BGI 505-74-01
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This method has been tested and recommended by the German Social Accident Insurance for the determination of carboxylic acid amides in the air at workplaces. Both personal and stationary sampling can be performed for the assessment of workplaces.

Sampling is carried out with a pump with the particulate fraction being collected on a glass fiber filter and the gaseous fraction adsorbed on charcoal. Analysis is performed by gas chromatography after desorption.

Chemical name	**CAS number**	**Molecular formula**	**Molar mass**
N,N-Dimethylacetamide	127-19-5	C_4H_9NO	87.12
N,N-Dimethylformamide	68-12-2	C_3H_7NO	73.09
N-Methylformamide	123-39-7	C_2H_5NO	59.07
Formamide	75-12-7	CH_3NO	45.04

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Summary

This method can be used with personal or stationary sampling to determine the mean concentration of the carboxylic acid amides *N,N*-dimethylacetamide, *N,N*-dimethylformamide, *N*-methylformamide and formamide at the workplace over the sampling time.

Principle:	A pump draws a defined volume of air through a GGP system equipped with a glass fiber filter and a tube filled with charcoal. Then the collected carboxylic acid amides are desorbed with a mixture of dichloromethane and methanol and analyzed by gas chromatography.
Limits of quantification:	Absolute: 1.1 to 15 ng for each carboxylic acid amide Relative: 0.1 to 1.3 mg/m^3 for each carboxylic acid amide based on an air sample of 120 L, a sample solution of 10 mL and an injection volume of 1 µL (see also Section 5.2).
Selectivity:	Elevated values are possible due to interferents; interference in general can be eliminated by selecting a column with different separation characteristics.
Advantages:	Personal and selective measurements are possible.
Disadvantages:	No indication of peak concentrations.
Apparatus:	Pump with or volumetric flow meter, GGP system with filter and charcoal tubes, gas chromatograph with flame ionization detector (FID).

Detailed description of the method

Contents

1

Equipment, chemicals and solutions

1.1

Equipment

For sampling:

- Pump, suitable for a flow rate of 1 L/min, e.g. PP5, Gilian, supplied by Haan & Wittmer, 71296 Heimsheim, Germany.
- Gas meter or volumetric flow meter, e.g. Gilibrator, Gilian.
- GGP sampling system with intake cone and filter holder for a flow rate of 1 L/min, e.g. from GSM, 41469 Neuss, Germany.
- Modified GGP system: The 3.5 intake cone of the GGP system is replaced by the 1.0 intake cone of the GGP system (the definition of the inhalable dust at a flow rate of 1 L/min is fulfilled due to the smaller diameter of the aperture of the cone). An intermediate part that has holes to accommodate two parallel adsorption tubes is screwed between the lower end of the molded part of the GGP system and the tube adapter. For sampling two opened charcoal tubes are inserted into these holes and the system is tightly sealed (see Fig. 1). As an alternative

Fig. 1 Modified GGP system.

to this in-house design, GSM, Neuss, Germany supplies a sampling system that accommodates three adsorption tubes.

- Glass fiber filter, diameter 37 mm, e.g. type GF/A, Whatman, 37587 Dassel, Germany.
- Adsorption tubes, filled with charcoal (standardized, consisting of two sections of charcoal with a weight of approx. 600 mg (400/200 mg) separated from each other by porous polymer material), e.g. SKC charcoal tubes, supplied by Analyt-MTC, 79379 Müllheim, Germany.

For sample preparation and analysis:

- Mechanical shaker
- Adjustable piston pipette, e.g. Multipette pro, Eppendorf, 22366 Hamburg, Germany
- Microliter syringes with volumes from 10 to 250 µL
- Volumetric flasks, 10 and 250 mL
- Sample vessels, 20 mL
- Gas chromatograph with flame ionization detector (FID)

1.2

Chemicals and solutions

N,N-Dimethylacetamide, purity 99%, e.g. Aldrich, 82024 Taufkirchen, Germany
N,N-Dimethylformamide, purity 99.8%, e.g. from Aldrich
N-Methylformamide, purity 99%, e.g. from Aldrich
Formamide, purity 99.5%, e.g. from Aldrich
β-Citronellol, purity > 95% (internal standard), e.g. from Merck, 64271 Darmstadt, Germany
Dichloromethane, p.a., e.g. from Merck
Methanol, p.a., e.g. from Merck

Gases for operation of the gas chromatograph:
- Helium 5.0, purity 99.999%
- Hydrogen 5.0, purity 99.999%
- Synthetic air, free of hydrocarbons
- Nitrogen 5.0, purity 99.999%

Desorption solution: Solution of 16.3 µg of *β*-citronellol per mL of the dichloromethane/methanol mixture.
5 µL of *β*-citronellol are pipetted into a 250 mL volumetric flask which is almost completely filled with a mixture of dichloromethane and methanol (9 + 1, v + v). The volumetric flask is then filled to the mark with the dichloromethane/methanol mixture and shaken.

Calibration stock solution: Solutions of approx. 9.5 mg of N,N-dimethylacetamide, 9.4 mg of N,N-dimethylformamide, 9.6 mg of N-methylformamide and 11.6 mg of formamide per mL of desorption solution.
Approx. 94.5 mg of N,N-dimethylacetamide, 94.2 mg of N,N-dimethylformamide, 96.5 mg of N-methylformamide and 115.7 mg of formamide are weighed to the nearest 0.1 mg in a 10 mL volumetric flask. The volumetric flask is then filled to the mark with desorption solution and shaken.

Calibration solutions: Solutions of approx. 5 to 144 mg of carboxylic acid amide per liter of desorption solution (see Table 1).
The six volumes of the calibration stock solution shown in Table 1 are each pipetted into separate 10 mL volumetric flasks, the flasks are then filled to the mark with desorption solution and shaken.
Based on an air sample volume of 120 L, a concentration range from approx. 0.4 to 12 mg/m^3 of each carboxylic acid amide (see Table 2) is covered by these calibration solutions.

Table 1 Concentrations of the carboxylic acid amides in the calibration solutions in mg/L.

Calibration solution No.	Volume of the stock solution added [µL]	N,N-Dimethyl-acetamide [mg/L]	N,N-Dimethyl-formamide [mg/L]	N-Methyl-formamide [mg/L]	Formamide [mg/L]
1	5	4.68	4.70	4.78	5.76
2	25	23.4	23.5	23.9	28.8
3	50	46.8	47.0	47.8	57.6
4	75	70.2	70.5	71.7	86.3
5	100	93.6	94.0	95.5	115
6	125	117	118	119	144

Table 2 Concentrations of the carboxylic acid amides in the calibration solutions in mg/m^3.

Calibration solution No.	N,N-Dimethyl-acetamide [mg/m^3]	N,N-Dimethyl-formamide [mg/m^3]	N-Methyl-formamide [mg/m^3]	Formamide [mg/m^3]
1	0.4	0.4	0.4	0.5
2	1.9	2.0	2.0	2.4
3	3.9	3.9	4.0	4.8
4	5.9	5.9	6.0	7.2
5	7.8	7.8	8.0	9.6
6	9.7	9.8	10.0	12.0

2
Sampling procedure

A filter and two charcoal tubes are inserted into the modified GGP system (see Section 1.1), which is connected to the pump. The flow rate is adjusted to 1 L/min. The definition of the inhalable dust is fulfilled by this flow rate [1]. The pump and the sampling system are worn by a person during sampling or they are used for stationary sampling. The method was tested up to a sample volume of 120 L (corresponding to a sampling time of 2 hours). 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 discount the measurement (see BGI 505-0 “General Part”, Section 3). The filter holder and the adsorption tubes are removed from the sampling system and sealed.

3
Analytical determination

3.1
Sample preparation and analysis

The filter and the contents of both charcoal tubes are transferred together to a 20 mL sample vessel. After addition of 10 mL of desorption solution, the vessel is subsequently sealed and shaken for 10 minutes on a mechanical shaker. Then an aliquot of the supernatant solution (sample solution) is transferred to an autosampler vial.

In order to ensure that the desorption solution, the filter and the charcoal used contain no interfering impurities, a filter and the contents of two charcoal tubes that have not been used for sampling are eluted with 10 mL of the desorption solution at regular intervals as described above (blank solution).

1 µL each of the sample solution and the blank solution are injected into the gas chromatograph and a gas chromatogram is recorded as described in Section 3.2. The quantitative evaluation is performed according to the internal standard method taking the peak areas of each carboxylic acid amide and that of β-citronellol as the internal standard into account.

3.2
Operating conditions for gas chromatography

The characteristics of the method stated in Section 5 are determined under the following experimental conditions:

Apparatus:	Hewlett Packard 5890 gas chromatograph with two flame ionization detectors and split/splitless injector
Separation columns:	Double capillary technique; the two capillaries are connected via a capillary connector (e.g. Press connect, from Chrompack) with a 40 to 50 cm retention gap (internal diameter 0.32 mm) that is inserted into the injector. Fused silica capillaries: Column I: DB-WAX cross-linked, internal diameter 0.25 mm, film thickness 0.5 µm, length 30 m Column II: RTx-35, cross-linked, internal diameter 0.25 mm, film thickness 0.5 µm, length 30 m
Temperatures:	Injector: 250 °C Detector: 250 °C

:	Column with the following temperature program:	
	Initial temperature:	45 °C, isothermal for 3 min
	Heating rate I:	3 °C/min to 65 °C, 1 min isothermal
	Heating rate II:	6 °C/min to 120 °C, 3 min isothermal
	Heating rate III:	10 °C/min until the final temperature
	Final temperature:	220 °C, 10 min isothermal
Injection:	Splitless (splitter: 1 min closed) split ratio 1 : 10	
Injection volume:	1 µL	
Carrier gas:	Helium 5.0:	pre-pressure 125 kPa
Detector gases:	Hydrogen 5.0:	approx. 30 mL/min
	Synthetic air:	approx. 330 mL/min
Make-up gas:	Nitrogen 5.0:	approx. 30 mL/min

4
Evaluation

4.1
Calibration

1 µL each of the six calibration solutions described in Section 1.2 as examples is injected into the gas chromatograph.

The calibration function is calculated by regression from the plots of the peak area ratios of the carboxylic acid amides and β-citronellol as the internal standard versus the weight ratios of the carboxylic acid amides and β-citronellol contained in the corresponding calibration solutions.

4.2
Calculation of the analytical result

The peak areas of the carboxylic acid amides and that of β-citronellol are obtained from the chromatograms recorded for each capillary, the quotient is calculated and the corresponding value for the mass in the sample in µg is determined from the calibration function. If the difference between the values obtained from the two capillaries is less than 10%, the mean value is used. If the difference is greater, the lowest measured value is taken (see also Section 5.3).

The concentration by weight of each carboxylic acid amide in the air sample in mg/m^3 is calculated according to equation (1).

$$c = \frac{m}{V \times \eta} \tag{1}$$

where:

c is the concentration by weight of the corresponding carboxylic acid amide in the air sample in mg/m^3
m is the corresponding mass of the carboxylic acid amide in the sample solution in µg
V is the air sample volume in L
η is the recovery (see Section 5.1)

If the content of the individual carboxylic acid amides is outside the calibration range, then the sample solution must be appropriately diluted with desorption solution and the quantification of these carboxylic acid amides must be repeated with the diluted sample solution.

5

Reliability of the method

5.1

Precision and recovery

The precision in the lowest measurement range according to DIN EN 482 [2] and the recoveries were determined for three different concentrations (see Table 3). The following validation solution was prepared for this purpose:

Validation solution:	Solution of approx. 11 to 76 mg of carboxylic acid amide per mL of methanol. The masses of carboxylic acid amides stated in Table 3 were each weighed to the nearest 0.1 mg in separate 10 mL volumetric flasks. Then the volumetric flasks were filled to the mark with methanol and shaken.

A microliter syringe was used to spike the filter of the previously assembled modified GGP system with 5 µL, 55 µL and 110 µL of the corresponding validation solution. Then laboratory air was drawn through the sampling system for two hours at an ambient temperature of 23 °C at a flow rate of 1 L/min. The preparation and analytical determination are carried out as described in Section 3. Based on an air sample of 120 L, the spiked masses correspond to the validation concentrations given in Table 3.

The recoveries and relative standard deviations of the carboxylic acid amides shown in Table 4 were obtained for the individual concentrations when the procedure described above (120 L air sample volume, flow rate 1 L/min) was carried out six times in each case.

Table 3 Concentrations of carboxylic acid amides in the validation solution and for validation.

Carboxylic acid amide	Mass [mg]	Concentration [mg/mL]	Validation concentration c_1 [mg/m^3]	 c_2 [mg/m^3]	 c_3 [mg/m^3]
N,N-Dimethylacetamide	770.1	76.2	3.2	35.0	69.9
N,N-Dimethylformamide	665.6	66.4	2.8	30.4	60.9
N-Methylformamide	272.5	27.0	1.1	12.4	24.7
Formamide	415.3	41.3	1.7	18.9	37.9

Table 4 Characteristics of the method.

Carboxylic acid amide	Recovery				Relative standard deviation (RSD) [%]			
	η (c_1)	η (c_2)	η (c_3)	Mean η	s (c_1)	s (c_2)	s (c_3)	mean RSD
N,N-Dimethylacetamide	1.01	1.02	1.05	**1.03**	1.8	1.0	0.4	**1.1**
N,N-Dimethylformamide	1.02	1.02	1.05	**1.03**	1.1	1.1	0.6	**0.9**
N-Methylformamide	0.92	0.96	0.99	**0.96**	2.0	2.1	1.8	**2.0**
Formamide	0.93	0.89	0.92	**0.92**	2.9	3.1	2.5	**2.8**

The mean recoveries of the carboxylic acid amides were between 92 and 103% and the mean relative standard deviations between 0.9 and 2.8%.

5.2
Limits of quantification

The limits of quantification were determined on the basis of the rapid estimation method described in DIN 32645 [3]. The standard deviations required for calculation were obtained by six-fold injection of a solution of the carboxylic acid amides with concentrations ranging from approx. 0.45 to 5.8 mg/L (corresponding to 0.04 to 0.48 mg/m^3 for an air sample of 120 L).

The absolute limits of quantification for the individual carboxylic acid amides were between 1.1 and 15.3 ng. This corresponds to relative limits of quantification between 0.1 to 1.3 mg/m^3 based on an air sample of 120 L, a sample solution of 10 mL and an injection volume of 1 µL (see Table 5).

5.3
Selectivity

The selectivity of the procedure depends above all on the type of separation column used. The separation columns given here have proved successful in practice. The

Table 5 Limits of quantification of the carboxylic acid amides.

Carboxylic acid amide	Limits of quantification	
	Absolute [ng]	**Relative [mg/m^3]**
N,N-Dimethylacetamide	1.1	0.09
N,N-Dimethylformamide	1.5	0.13
N-Methylformamide	2.2	0.19
Formamide	15	1.3

presence of interferents is recognized by comparison of the results from the two capillary columns on account of their different separation characteristics. In the case of a difference of > 10% it is advisable to take only the lower result into account (on the assumption that the higher result was caused by overlapping with an interferent).

6
Remarks

The adsorbed carboxylic acid amides can be stored at room temperature without losses for at least 14 days.

Individual carboxylic acid amides show poorer peak shapes in the chromatogram obtained using the less polar RTx-35 column (a marked leading edge in some cases) than on the DB-WAX column, which can lead to problems in the integration of the peaks (in particular at higher concentrations).

References

1 DIN EN 481 (1993) Workplace atmospheres – Size fraction definitions for measurement of airborne particles. Beuth Verlag, Berlin.

2 DIN EN 482 (2006) Workplace atmospheres – General requirements for the performance of procedures for the measurement of chemical agents. Beuth Verlag, Berlin.

3 DIN 32645 (2008) Chemical analysis – Decision limit, detection limit and determination limit under repeatability conditions – Terms, methods, evaluation. Beuth Verlag, Berlin

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