The MAK Collection for Occupational Health and Safety

Formamide, dimethylformamide – Determination of formamide in urine by gas chromatography mass spectrometry

Biomonitoring Method – Translation of the German version from 2018

G. Scherer[1], G. Gilch[1], B. Aust[2], M. Blaszkewicz[2], T. Göen[3,*], A. Hartwig[4,*], MAK Commission[5,*]

1 *Method development, ABF Analytisch-biologisches Forschungslabor GmbH, Goethestraße 20, 80336 München, Germany*

2 *External verification, Leibniz-Institut für Arbeitsforschung an der TU Dortmund, Ardeystraße 67, 44139 Dortmund, Germany*

3 *Head of the working group "Analyses in Biological Materials" of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Friedrich-Alexander-Universität Erlangen-Nürnberg, Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine, Schillerstraße 25 and 29, 91054 Erlangen, Germany*

4 *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

5 *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

***** *email: T. Göen (thomas.goeen@fau.de), A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

Keywords: formamide; dimethylformamide; biomonitoring; urine; GC-MS

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Formamide, dimethylformamide – Determination of formamide in urine by gas chromatography mass spectrometry

Biomonitoring Methods

G. Scherer[1], G. Gilch[1], B. Aust[2], M. Blaszkewicz[2], T. Göen[3,*], A. Hartwig[4,*], MAK Commission[5,*]

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Abstract

The working group "Analyses in Biological Materials" of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area verified the presented biomonitoring method.

The method described herein allows the determination of formamide in urine by gas chromatography mass spectrometry (GC-MS). Due to its sensitivity, this method is suitable for the detection of occupational and environmental exposure to formamide. For the analytical determination 1 mL of urine is lyophilised after being spiked with ^{13}C,^{15}N-formamide as the internal standard. The lyophilisate is extracted with 200 µL methanol. After centrifugation, 1 µL of the extract is injected into a GC-MS system. The method was extensively validated and the reliability data were confirmed by an independent laboratory, which has established and cross-checked the whole procedure.

Keywords

formamide; dimethylformamide; urine; biomonitoring; Analyses in Biological Materials; gas chromatography; mass spectrometry; GC-MS

Author Information

[1] Developer of the method, ABF – Analytisch-biologisches Forschungslabor GmbH, Goethestraße 20, 80336 München, Germany

[2] Examiner of the method, Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Schillerstr. 25 and 29, 91054 Erlangen, Germany

[3] Chair of the working group "Analyses in Biological Materials", Deutsche Forschungsgemeinschaft, Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Schillerstr. 25 and 29, 91054 Erlangen, Germany

[4] Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Department of Food Chemistry and Toxicology, Institute for Applied Biosciences, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Geb. 50.41, 76131 Karlsruhe, Germany

[5] Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany

[*] Email: T. Göen (thomas.goeen@fau.de), A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)

Formamide, dimethylformamide – Determination of formamide in urine by gas chromatography mass spectrometry

Matrix: Urine
Hazardous substances: Formamide
Analytical principle: Gas chromatography mass spectrometry
Completed in: October 2009

Overview of the parameters that can be determined with this method and the corresponding hazardous substances:

Hazardous substance	CAS	Parameter	CAS
Formamide	75-12-7	Formamide	75-12-7
Dimethylformamide	68-12-2	Formamide	75-12-7

Summary

The method described herein allows the determination of unmetabolised formamide in urine by gas chromatography mass spectrometry (GC-MS). Due to its sensitivity, this method is suitable for the detection of occupational and environmental exposure to formamide.

For the analytical determination 1 mL of urine is lyophilised after being spiked with $^{13}C,^{15}N$-formamide as the internal standard. The lyophilisate is extracted with 200 µL methanol. After centrifugation, 1 µL of the extract is injected into a GC-MS system.

Reliability of the method

Formamide

Within-day precision:	Standard deviation (rel.)	s_w = 4.6% or 3.4%
	Prognostic range	u = 12.8% or 9.4%
	at a determined concentration of 3.8 mg or 16.9 mg formamide per litre urine and n = 5 determinations	

Day- to-day precision:	Standard deviation (rel.)	s_w = 8.0% or 2.5%
	Prognostic range	u = 20.5% or 6.4%
	at a determined concentration of 3.8 mg or 17.3 mg formamide per litre urine and n = 6 determinations	
Accuracy:	Recovery rate (rel.)	r = 103% or 97.5%
	at a spiked concentration of 4 mg or 16 mg formamide per litre urine and n = 5 determinations	
Quantitation limit:	0.5 mg formamide per litre urine	

General information on formamide

Formamide (molecular formula: CH_3NO, molecular weight: 45.04 g/mol) is a colourless liquid with a faint ammoniacal odour as well as a boiling point of 210 °C and a vapour pressure of 0.06 mm Hg at 25 °C [Römpp 2017].

In Europe formamide is produced in amounts of 10 000–50 000 t per year.

Formamide is used as an industrial solvent for organic synthesis and as an intermediate in the production of dyes and pigments. Moreover, it is used as a softener for paper and gums and as a starting material for synthesis. It is also used for the production of pharmaceuticals, synthetic leather, as well as for printing inks [ECHA 2011]. The Commission has evaluated the toxicity of formamide and summed up the toxicological data in a documentation. However, as only few toxicological data is available, no MAK Value could be set for formamide [Hartwig 2013]. Formamide is marked with an "H" because of its potential teratogenic effects in case of skin absorption [DFG 2017]. For details on the assessment of formamide, please refer to the toxicological occupational documentation of the Commission [Hartwig 2013].

There is a lack of information concerning formamide resorption, metabolisation and excretion in humans [Fail et al. 1998; NTP 1992a, 1992b]. According to animal studies, both, inhalative uptake and dermal resorption of formamide can be expected at the workplace.

After oral administration of 2–4 g formamide to rabbits, approximately 39% of the dose was found unchanged in the urine [Snyder 1990], which suggests that formamide in urine is a suitable marker of exposure. So far, no studies on formamide in urine as a biomarker of exposure to formamide are available. However, it is reported that formamide is a metabolite of *N,N*-dimethylformamide (DMF), whose concentration in urine increases with exposure to DMF [Lareo and Perbellini 1995a].

Animal studies have shown that formamide causes irritation to the skin and the eyes. However, data about effects to humans are not available. As yet, systemic effects as well as irritating effects to the respiratory tract and to the eyes in humans could not be assessed [Hartwig 2013].

Occupational exposure limits for formamide in other countries are 10 ppm (= 15 mg/m^3; e.g. USA [ACGIH 2017, NIOSH 2016], Australia, Belgium) or 20 ppm (= 30 mg/m^3) (e.g. Denmark, Finland, Netherlands, Switzerland). The German "Technical Instructions on Air Quality Control" [TA Luft 2002] imposed a limit value of 20 mg/m^3.

In a collective of 47 non-exposed persons an average formamide concentration in urine of 2.4 mg/L (range: 0.76–5.8 mg/L) was determined using this method. For the 21 smokers, the measured mean formamide concentration was 1.9 mg/L (range: 0.76–4.6 mg/L). For the 26 non-smokers, the concentration was 2.9 mg/L (range: 0.94–5.8 mg/L). Thus, no effect of smoking was observed. Other authors described in some cases even higher urinary excretion levels of formamide in non-occupationally exposed persons [Lareo et al 1995b], which, however, can most likely be attributed to artefact formation (see Section 10).

Contents

1 General principles

The method described below allows the determination of unmetabolised formamide excreted in urine using gas chromatography mass spectrometry (GC-MS). Due to its sensitivity, this method is suitable for the detection of occupational and environmental exposure to formamide.

For the analytical determination 1 mL of urine is lyophilised after being spiked with $^{13}C,^{15}N$-formamide as the internal standard. The lyophilisate is extracted with 200 µL methanol. After centrifugation, 1 µL of the extract is injected into a GC-MS system.

2 Equipment, chemicals and solutions

2.1 Equipment

- Gas chromatograph coupled to mass spectrometer with cooled injection system (e.g. gas chromatograph GC 6890 N (Agilent, Waldbronn) coupled with MS 5975 (Agilent, Waldbronn) and cooled injection system CIS 4 (Gerstel, Mühlheim)
- Gas chromatographic column: length: 30 m; inner diameter: 0.25 mm; film thickness: 1 µm (e.g. ZB-WAX, Phenomenex, Aschaffenburg)
- Vacuum concentrator (e.g. RC 1022, Thermo Electron, Dreieich)
- Refrigerated centrifuge (e.g. EBA 12 R, Hettich, Tuttlingen)
- Vortex mixer (e.g. Heidolph, Schwabach)
- Microlitre pipettes, variable from 1–10 µL, 10–100 µL and from 100–1000 µL with suitable pipette tips (e.g. Eppendorf, Hamburg)
- 0.65-mL PP tubes (e.g. Sorenson, VWR, Darmstadt)
- 1.5-mL Safe-Lock Tubes (e.g. Eppendorf, Hamburg)
- Autosampler microvials (e.g. Ziemer, Langerwehe)
- Containers for the collection of urine samples (e.g. Sarstedt, Nürnbrecht)
- 10-mL volumetric flask (e.g. Brand)

2.2 Chemicals

Unless stated otherwise, the quality of all used chemicals must be at least p.a.

- Formamide, ≥ 99.5% (e.g. Fluka, No. 93572)
- $^{13}C,^{15}N$-formamide (e.g. Chemotrade, No. SS00061)
- Water for analysis EMSURE® (e.g. Merck, No. 1.16754)
- Methanol for HPLC Promochem® (e.g. LGC, No. SO-3041)
- Human urine with low formamide content

2.3 Solutions

Stock solution

- Formamide stock solution (1 g/L)
  8.85 µL of formamide are pipetted into a 10-mL volumetric flask, made up to the mark with water and mixed thoroughly.

Working solutions

- Formamide working solution I (100 mg/L):
  1 mL of the formamide stock solution is pipetted into a 10-mL volumetric flask, made up to the mark with water and mixed thoroughly.
- Formamide working solution II (10 mg/L):
  1 mL of formamide working solution I is pipetted into a 10-mL volumetric flask, made up to the mark with water and mixed thoroughly.

The stock solution is stable for about 8 weeks when stored at 2–8 °C. The working solutions must be freshly prepared.

2.4 Internal standard

- $^{13}C,^{15}N$-formamide stock solution (1 g/L):
  8.85 µL $^{13}C,^{15}N$-formamide are pipetted into a 10-mL volumetric flask, made up to the mark with water and mixed thoroughly.
- $^{13}C,^{15}N$-formamide working solution (10 mg/L):
  100 µL of the $^{13}C,^{15}N$-formamide stock solution are pipetted into a 10-mL volumetric flask, made up to the mark with water and mixed thoroughly.

The stock solutions of the internal standard are stable for about 8 weeks when stored at 2–8 °C. At this temperature the solution is stable without significant losses for eight weeks. The working solutions must be freshly prepared.

2.5 Calibration standards

For calibration, human urine with a very low formamide background level is chosen, which is subsequently spiked with increasing quantities of formamide. The calibration covers a concentration range of 0.5–64 mg/L urine. The calibration is prepared according to the pipetting scheme of Table 1. A blank sample is also prepared for the analysis of the formamide background level in pooled urine.

The calibration standards are prepared (Section 3.2) and analysed (Section 5) analogously to the samples.

Table 1 Pipetting scheme for the calibration standards.

Calibration level	Volume of urine [µL]	Volume of formamide working solution II [µL]	Volume of formamide working solution I [µL]	Volume of formamide stock solution [µL]	Formamide concentration [mg/L]
0	200	–	–	–	0
1	200	10			0.5
2	200	20			1
3	200		4		2
4	200		8		4
5	200		16		8
6	200			3.2	16
7	200			6.4	32
8	200			12.8	64

3 Specimen collection and sample preparation

3.1 Specimen collection

The urine samples are collected in urine containers. The samples should be stored cooled or frozen at –25 °C for subsequent analysis. Otherwise, during short term storage of the samples at room temperature, the analyte is also stable.

The short-term stability of the analyte in the matrix was analysed using a high-spiked urine sample which was stored for 24 h at room temperature. A decrease in formamide concentration could not be detected during this period.

3.2 Sample preparation

After thawing and mixing thoroughly, about 1 mL of the urine is pipetted into safe-lock tubes and centrifuged at 15,000 × *g* for 10 min at room temperature. 20 µL of the ^{13}C,^{15}N-formamide working solution are transferred to 0.65-mL PP tubes and subsequently 200 µL of the centrifuged urine sample are added. After mixing briefly, the sample is frozen at –25 °C (for about 1 h). The frozen sample is evaporated to dryness in the vacuum concentrator (<1 mbar) for 2–3 hours, depending on the quality of the vacuum and the number of samples. The lyophilisate is then resuspended in 200 µL methanol and vortexed. After the precipitate has been separated by centrifugation (10,000 × *g*, 10 min at room temperature), an aliquot of the clear supernatant is transferred to a GC-microvial.

4 Operational parameters

4.1 Gas chromatography

Capillary column:	Stationary phase:	ZB-WAX
	Length:	30 m
	Inner diameter:	0.25 mm
	Film thickness:	1 µm or equivalent
Temperatures:	Column:	Initial temperature 40 °C (2 min), then increase at a rate of 5 °C/min to 180 °C
	Injector, cold injection:	Initial temperature 120 °C, hold for 6 s, then increase at a rate of 5 °C/s to 180 °C, hold for 1.5 min, then decrease at a rate of 5 °C/s to 120 °C, hold for 28 min
	Transfer line:	190 °C
Carrier gas:	Helium 5.0	
	Flow rate:	1.2 mL/min
Injection volume:	1 µL; split 50:1	

4.2 Mass spectrometry

The detection is performed in selected ion monitoring mode using electron impact ionisation.

Ionisation mode:	Electron impact ionisation (EI)
Ionisation energy:	70 eV
Dwell time:	50 ms
Source temperature:	150 °C
Solvent delay:	6 min
Detection mode:	Single Ion Monitoring (SIM)

All the other parameters have to be optimised according to the manufacturer's instructions.

5 Analytical determination

For the analytical determination of the urine samples, prepared according to Section 3.2, the GC-microvials are placed into the instrument. At a split ratio of 1:50 1 µL of each sample is injected into the GC-system. The identification of the analyte is based on the retention time and on characteristic ion traces. The resulting retention times of the individual analytes as well as the characteristic ion traces for the

analytes, by usage of the stated operational parameters (see Section 4), are illustrated in Table 2.

Table 2 Characteristic ion traces and retention times of the analyte and the internal standard.

Analyte	Quantifier Ions (m/z)	Retention time (min)
Formamide	45.04	29.12
$^{13}C,^{15}N$-Formamide	47.03	29.13

A chromatogram of a urine sample with a formamide concentration of 3.63 mg/L is given in Figure 1 in the Appendix.

6 Calibration

The calibration standards in urine are processed in the same way as the urine samples (see Section 3.2) to be analysed and measured according to Sections 4 and 5. A calibration curve is calculated by plotting the ratio of the peak area of the analyte and the peak-area of the internal standard against the spiked concentration. The background level of formamide in pooled urine must be considered for each calibration point. A calibration curve for formamide in urine is given in Figure 2 in the Appendix.

7 Calculation of the analytical results

The formamide background level of the human urine used for calibration is added to the spiked concentration. With this relevant concentration, the calibration point is entered into the graph (abscissa). The respective ordinate depicts the response ratio (analyte to internal standard). Using linear regression with 1/x weighting, the calibration function is calculated by the ChemStation software and the coefficient of determination is given. Figure 2 shows an example of an calibration curve, that almost runs through the zero point. The results in mg/L are directly calculated by the ChemStation software. However, it has to be borne in mind that the background level of spiked samples must be subtracted from the result to obtain the spiked concentration.

8 Standardisation and quality control

Quality control of the analytical results is carried out as stipulated in the guidelines of the Bundesärztekammer (German Medical Association) and in a general chapter of the MAK-Collection for Occupational Health and Safety Part IV: Biomonitoring Methods [Bader et al. 2010; Bundesärztekammer 2008].

To check precision, urine spiked with a known and constant analyte level is analysed as a control within each analytical run. As material for quality control is not commercially available, it must be prepared in the laboratory. Urine from a healthy person with a very low formamide background level is spiked with a defined quantity of formamide. Urine can also be collected from several persons (pooled urine). Aliquots of this material can be stored frozen at −25 °C for at least one year.

The nominal value and the tolerance ranges of this quality control material are determined in a pre-analytical period (one analysis each of the control materials on ten different days) [Bader et al. 2010].

9 Evaluation of the method

The reliability of the method was proven by comprehensive validation and by implementation and validation of the procedure in a second independent laboratory.

9.1 Precision

For determining the within-day precision, urine samples were spiked with the analyte at concentrations in the lower and the upper calibration range, respectively, prepared and analysed. Based on the 5-fold determination of these urine samples the within-day precision was calculated (see Table 3).

Table 3 Precision in series for the determination of formamide in urine (n = 5).

Determined concentration [mg/L]	Standard deviation (rel.) [%]	Prognostic range [%]
3.8	4.6	12.8
16.9	3.4	9.4

For the determination of the precision from day-to-day the spiked urine samples were analysed. Based on the 6-fold determination of these urine samples the day to day precision was calculated (see Table 4).

Table 4 Precision from day to day for the determination of formamide in urine (n = 6).

Determined concentration [mg/L]	Standard deviation (rel.) [%]	Prognostic range [%]
3.8	8.0	20.5
17.3	2.5	6.4

9.2 Accuracy

Recovery tests were carried out in order to determine the accuracy of the method. For this purpose, urine was spiked with the analytes in levels of 4 mg/L or 16 mg/L, respectively, prepared and analysed by the examiner of the method. Based on the 5-fold determination of these urine samples the accuracy was calculated (Table 5).

Table 5 Accuracy for the determination of formamide in urine (n = 5).

Spiked concentration [mg/L]	Accuracy [%]	Relative standard deviation [%]
4	103	5.2
16	97.5	3.7

To determine the absolute recovery rate, human urine was spiked on the lower (4 mg/L) and upper (16 mg/L) end of the concentration range and analysed six times each as described in Section 3.2.

The same urine was processed and a methanolic formamide standard was added (4 mg/L (n = 3) or 16 mg/L (n = 6)) after the methanolic reconstitution of the lyophilisate and finally analysed. The peak area ratios (analyte/internal standard) thus determined served as a reference value (100%). A comparison of the analyte/internal standard ratio, respectively, yielded the following absolute recovery rates (Table 6):

Table 6 Absolute recovery for the determination of formamide in urine (n = 3 or 6).

Spiked concentration	4 mg/L	16 mg/L
Analyte/IS ratio with spiking before work-up, mean value n = 6	4.16	13.94
Analyte/IS ratio with spiking after work-up, mean value n = 3, reference value	4.23	13.17
Recovery	98.2%	106%

9.3 Quantitation limit

When performing the calibration, the lowest spiking concentration of 0.5 mg/L could still clearly be distinguished from the background level of the urine used for calibration (1.3 mg/L), with the deviation from the nominal value being <20%. The lowest detected concentration of formamide in 47 urine samples, which were analysed using the presented method, amounted to 0.76 mg/L.

These findings suggest a quantitation limit of 0.5 mg/L for the determination of formamide in urine.

9.4 Sources of error

When urine is directly injected into the GC-MS system, formamide formation might occur in the injector. Thus, the accurate determination of the formamide concentration in the samples might be impaired.

In order to avoid artificial formamide formation, urine with very little contents of both, salt and proteins, resulting from lyophilisation and methanol extraction, was used for injection to the GC-MS system. Moreover, a cooled injection system (injection temperature 120–180 °C) was used.

The EI mass spectra show that the fragment ion m/z = 45 is formed only to a minor degree (approx. 15%) from ^{13}C,^{15}N-formamide (molecular ion m/z = 47). Consequently, the addition of internal standard was limited to 1 mg/L urine to minimise interference of the fragment m/z = 45 on the analyte. Alternatively, the use of the deuterated compound d_3-formamide (molecular ion m/z = 48) could be considered.

The complete removal of water from the urine sample is the decisive step in the sample work-up. Studies have shown that traces of water considerably decrease detection sensitivity. Apart from technical aspects (good vacuum, etc.) the duration of lyophilisation also depends on the non-volatile matter content in urine. High concentrated urine requires a longer lyophilisation time than low concentrated urine.

The setting of the injector conditions was extensively examined using synthetic urine spiked with ammonium formiate. Studies have shown that artefact formation [Hill 2002] can largely be avoided, if the sample is not injected at 180 °C, but at 120 °C with a gradual increase in temperature to 180 °C. Under these conditions, using ammonium formate (1 g/L) formation of artefacts in the order of 1 mg/L was found in synthetic urine. Even lower start temperatures cause lower recoveries.

10 Discussion of the method

The presented method allows a quick, precise and, above all, a quantification of formamide in human urine with very low artefact formation. The sensitivity of the method allows the determination of formamide not only in occupational medicine, but also in environmental medicine. The method validation data can be considered as good and were sucessfully reproduced by the examiner of the method.

The removal of methanol-insoluble urine constituents from the extract is essential, not only because of a device- and column-saving effect but mainly because of the prevention of a potential artificial formamide formation in the injector. The findings of Lareo et al. [Lareo et al. 1995b] clearly indicate a potential artefact formation if urine without prior work-up is injected. On the one hand, these authors found relatively high formamide concentrations in non-occupationally exposed persons (mean value: 8.6 mg/L). On the other hand, the measured formamide concentration has tripled if the injector temperature was increased from 200 °C to 250 °C.

However, in a collective of 47 non-exposed persons we determined an average formamide concentration in urine of 2.4 mg/L (range: 0.76–5.8 mg/L) using this method. For the 21 smokers, the measured mean formamide concentration was 1.9 mg/L (range: 0.76–4.6 mg/L). For the 26 non-smokers, the concentration was 2.9 mg/L

(range: 0.94–5.8 mg/L). Thus, no effect of smoking was observed. Our studies moreover show that when implementing the two measures to avoid artefact formation (methanolic extraction of the lyophilisate and initial injector temperature of 120 °C), a formamide formation of considerably less than 1 mg/L can be achieved.

As the presented method enables the determination of formamide in urine of the occupationally non exposed general population, the procedure can also be used for the quantification of formamide in urine of occupationally exposed workers.

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Developers of the method: G. Scherer, G. Gilch

Examiners of the method: B. Aust, M. Blaszkewicz

Chair of the working group „Analyses in Biological Materials“, Deutsche Forschungsgemeinschaft: Th. Göen

Chair of the “Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area”, Deutsche Forschungsgemeinschaft: A. Hartwig

Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft: MAK Commission

12 Appendix

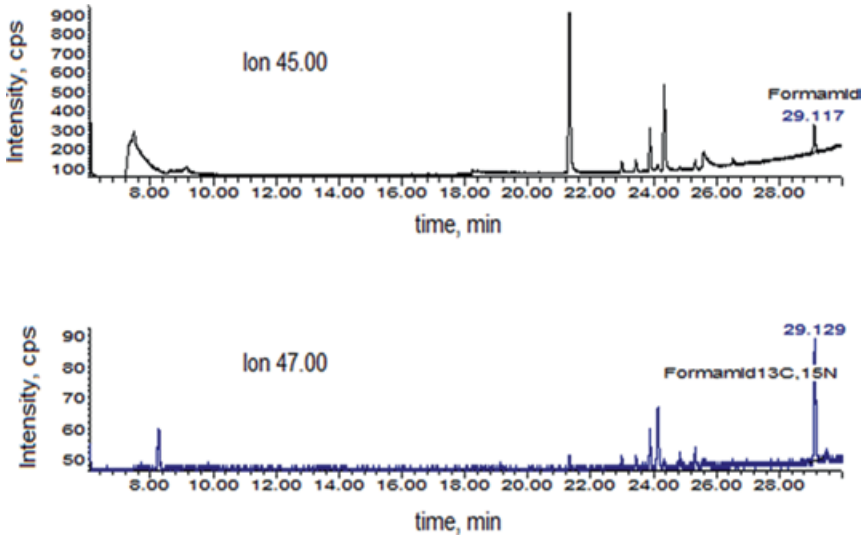

Figure 1 Typical chromatogram of human urine after lyophilisation and extraction using methanol. Formamide concentration: 3.63 mg/L. Top: mass trace of the analyte (formamide). Bottom: mass trace of the internal standard ($^{13}C,^{15}N$-formamide).

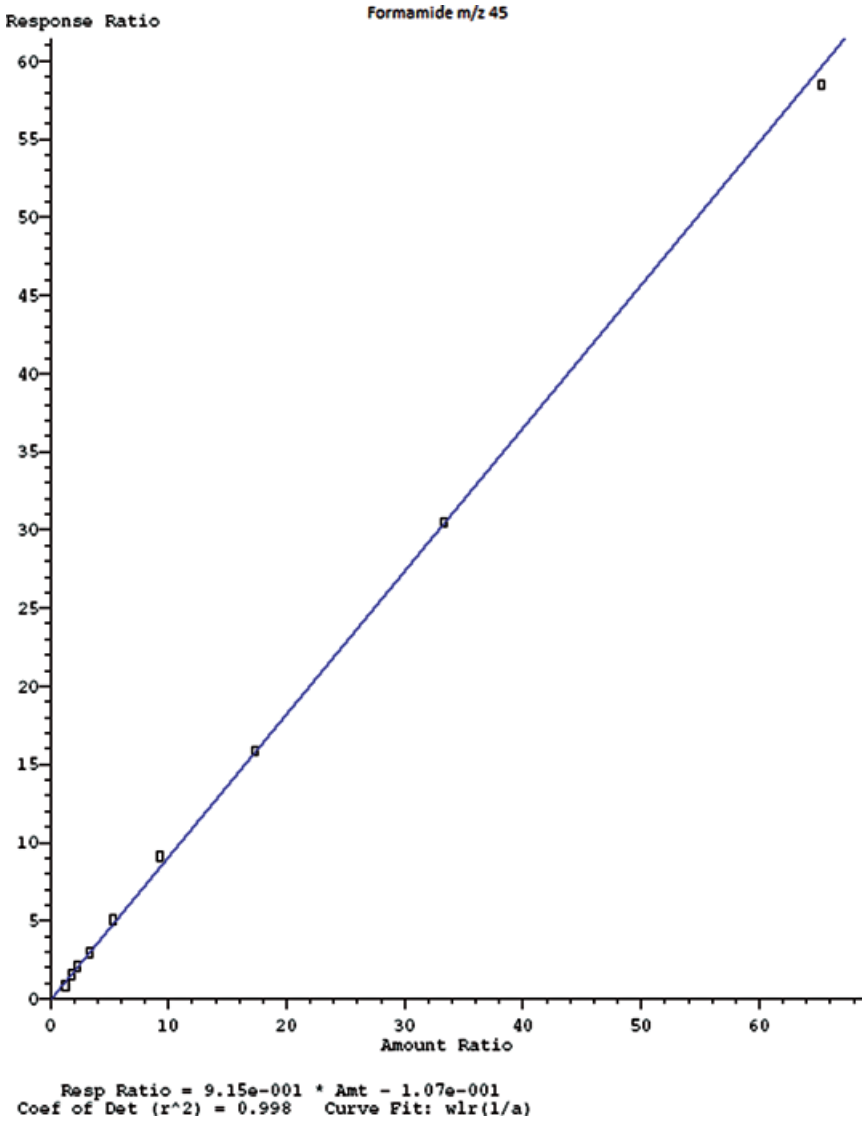

Figure 2 Calibration for formamide in urine (range 0.5–64 mg/L) relating to the internal standard $^{13}C,^{15}N$-formamide. The background level of the spiked human urine is 1.3 mg/L. The calibration points were measured in duplicate.