The MAK Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Furan – Determination of furan in exhaled air by GC-MS/MS

Biomonitoring Method – Translation of the German version from 2024

C.-E. Ziener[1]
C. Otto[1]
O. Lorenz Contreras[1]
B. Roßbach[2]
K. Lüddens-Dämgen[2]
T. Göen[3,*]
A. Hartwig[4,*]
MAK Commission[5,*]

1 *Method development, Federal Institute for Occupational Safety and Health (BAuA), Nöldnerstraße 40/42, 10317 Berlin, Germany*

2 *External verification, University Medical Center of the Johannes Gutenberg University Mainz, Institute of Occupational, Social, and Environmental Medicine, Obere Zahlbacher Straße 67, 55131 Mainz, 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, Henkestraße 9–11, 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

furan; biomonitoring; end-exhaled air; GC-MS/MS; SPME

Citation Note:
Ziener C-E, Otto C, Lorenz Contreras O, Roßbach B, Lüddens-Dämgen K, Göen T, Hartwig A, MAK Commission. Furan – Determination of furan in exhaled air by GC-MS/MS. Biomonitoring Method – Translation of the German version from 2024. MAK Collect Occup Health Saf. 2024 Mar;9(1):Doc027. https://doi.org/10.34865/bi11000e9_1or

Manuscript completed:
27 Apr 2023

Publication date:
28 Mar 2024

Abstract

The working group "Analyses in Biological Materials" of the German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) developed and verified the presented method for the biomonitoring of furan exposure.

This method focuses on the determination of furan in human end-exhaled air. Samples are collected in 20-ml screw-top glass vials (headspace vials) into which the subjects exhale through a PTFE tube. The vials are then sealed using screw caps with PTFE-lined silicone septa. After enrichment of the furan from the gas phase by solid-phase microextraction (SPME), the extract is analysed by gas chromatography. Detection is performed using a triple-quadrupole mass spectrometer with electron-impact ionisation in Multiple Reaction Monitoring (MRM) mode. End-exhaled-air samples spiked with furan are used for external calibration.

The procedure has been comprehensively validated, and the reliability data have been confirmed by replication and verification of the procedure in a second, independent laboratory. Good precision and accuracy data show that the method provides reliable and accurate analytical results. The limit of quantitation of 0.06 ng furan/l end-exhaled air is sufficient to determine occupational exposure as well as exposure to furan after smoking or shortly after coffee consumption.

1 Characteristics of the method

Matrix	End-exhaled air
Analytical principle	Gas chromatography with tandem mass spectrometry (GC-MS/MS)

Parameter and corresponding hazardous substance

Hazardous substance	CAS No.	Parameter	CAS No.
Furan	110-00-9	Furan	110-00-9

Reliability data

Furan

Within-day precision:	Standard deviation (rel.) Prognostic range at a spiked concentration of 1.5 ng, 5.0 ng, or 51 ng furan per litre of end-exhaled air and n = 10 determinations	s_w = 2.2%, 2.0%, or 2.7% u = 5.0%, 4.5%, or 6.1%
Day-to-day precision:	Standard deviation (rel.) Prognostic range at a spiked concentration of 1.5 ng, 4.9 ng, or 49 ng furan per litre of end-exhaled air and n = 10 determinations	s_w = 6.3%, 7.2%, or 5.5% u = 14.3%, 16.3%, or 12.4%
Accuracy:	Recovery (rel.) at a spiked concentration of 1.5 ng, 5.0 ng, or 50 ng furan per litre of end-exhaled air and n = 10 determinations	r = 107%, 108%, or 94,8%
Limit of detection:	0.02 ng furan per litre of end-exhaled air	
Limit of quantitation:	0.06 ng furan per litre of end-exhaled air	

2 General information on furan

Furan is a five-membered aromatic oxygen heterocycle which is liquid at room temperature and boils at 31 °C, thus exhibiting high volatility. Furan is used as a raw material for the production of other substances and is industrially synthesised for this purpose (Hoydonckx et al. 2007). However, it is likewise formed from the incineration of organic materials and can be found in cigarette and wood smoke as well as in exhaust fumes from diesel and petrol engines (IARC 1995). Moreover, furan may be unintentionally formed during the processing or handling of food products under heat (Batool et al. 2021).

There are only few data available on furan toxicity in humans (Hartwig and MAK Commission 2020; NIOSH 2016). Animal studies have shown toxic effects after oral administration, especially in the liver and in the bile ducts, which led to carcinomas in long-term exposure (Hartwig and MAK Commission 2020). Furan has been classified for carcinogenicity (Category 1B) and germ cell mutagenicity (Category 2) per the CLP Regulation (European Parliament and European Council 2008), as it is presumed to be carcinogenic for humans and causes concern due to the possibility that it may induce heritable mutations in human germ cells. The Commission assumes that a non-genotoxic mode of action is of primary importance for furan, that genotoxic effects play a subordinate role, and that furan does not contribute to carcinogenic risk for workers if the MAK value is not exceeded. The Commission has therefore derived a MAK value, classifying the substance as a Category 4 carcinogen (DFG 2023; Hartwig and MAK Commission 2020).

No data on occupational exposure to furan are currently available (IARC 1995; NTP 1993). Furan has been registered as an intermediate product under the REACH regulation (ECHA 2019). Accordingly, workers are involved in the

production and use of furan in closed industrial plants, in the transfer of the substance to and from technical facilities, as well as in filling and weighing processes. Since the high volatility of furan requires handling and application to take place in closed systems, the possibility of occupational exposure first appears rather limited. Insufficiently sealed systems or leaks may however lead to toxicologically relevant exposure due to the high volatility of the substance.

Aside from the purposeful use of furan, occupational exposure may be possible in areas in which the substance arises unintentionally or is inadvertently released from products and materials. For example, furan is a known heat-related process contaminant in food products (Andres et al. 2017). As such, if the treatment or processing of food products takes place on a commercial or industrial scale, workplace exposure cannot be ruled out *a priori*. For example, an emission concentration of 170 µg furan/m^3 was measured in the exhaust air of an industrial frying unit (Moortgat et al. 1992). During the thermal preparation of various food products in a household kitchen, spot measurements of the ambient air yielded furan concentrations of up to 200 µg/m^3. The burden measured in the ambient air thereby varied depending on the food product in question as well as on the kind of preparation. Among other tests, the preparation of various coffee drinks, the toasting of different types of bread, the baking of pizza, and the preparation of potato chips were investigated (Crews 2009).

In the workplace, furan is primarily taken up by inhalation, although oral or dermal uptake is possible as well (NTP 2016). According to model calculations, dermal uptake may contribute significantly to the toxicity of furan. Accordingly, furan is designated with an "H" by the Commission (Hartwig and MAK Commission 2020). There are currently no systematic observations available on the distribution of furan throughout the human body nor on its metabolism or excretion. An inhalation study on rats showed that furan exposure leads to measurable levels of furan in the blood which increased with exposure concentrations (Kedderis et al. 1993). Based on their measured data, the authors developed a toxicokinetic model according to which about 16% of the absorbed furan is exhaled unchanged within 24 hours. This finding was quite consistent with the results of an earlier study in rats in which about 14% of the administered furan was excreted unchanged via exhaled air within 24 hours (Burka et al. 1991).

As a result, measurements of both blood and exhaled air present possibilities for the assessment of furan exposure, whereby, in a workplace context, exhaled air may be the more preferable matrix due to its non-invasive sampling procedure. Furan measurements in human blood and exhaled-air samples have already been performed in various settings; examples include the measurement of background exposure in the general population, the estimation of diet-related furan levels, or the application of chemical-analytical screening methods. Table 1 provides a summary of such studies, including information on the analytical procedure applied as well as measured concentrations. Furan concentrations measured in blood may be used to estimate expected concentrations in exhaled air using the blood-air partition coefficient for furan, which is given in the literature as 6.59 (Kedderis et al. 1993) or 6.84 (Kramer et al. 2016). Studies on the internal furan burden of occupationally exposed workers are not yet available.

Tab. 1 Furan concentrations in blood and exhaled air from persons not occupationally exposed to furan

Study collective	Sample material	Furan concentration[a)] [ng/l]	Sample collection; analytical method	Purpose of measurement	Reference
1 N (♂)	Exhaled air	1.2	Cryotrap; GC-FID/ECD/MSD	Screening for volatile substances (VOCs)	Conkle et al. 1975
54 N (35 ♂; 19 ♀)	Exhaled air	Quantifiable in 3.9% of samples (n = 387), 68% of measured values in the range of 0.1–2.9	Teflon bags, TENAX® as adsorbent, TD-GC-MS	Screening for volatile substances (VOCs)	Krotoszynski et al. 1979
2 N (1 ♂; 1 ♀)	Exhaled air	1.6–36	Tedlar bags, GC-MS	Measurement of furan levels in exhaled air within 8 min of coffee consumption	Crews 2009
22 N; 6 S (14 ♂; 14 ♀)	Blood	< 0.68 (LOD)–24.5	NTD-GC-MS	Screening for volatile substances (VOCs)	Mochalski et al. 2013
	Exhaled air	< 0.03 (LOD)–6.5	Tedlar bags, HS-SPME-GC-MS		

Tab. 1 *(continued)*

Study collective	Sample material	Furan concentration[a)] [ng/l]	Sample collection; analytical method	Purpose of measurement	Reference
2086 N; 833 S (adults)	Blood	S: 190[b)] N: < 25 (LOD)[b)]	HS-SPME-GC-MS	Measurement of furan levels in the general population	NCEH 2021

GC-FID/ECD/MSD: gas chromatography with flame-ionisation detection or electron-capture detection or mass-spectrometric detection; HS-SPME: headspace-solid-phase microextraction; LOD: limit of detection; N: non-smoker; NTD: extraction via needle-trap device; S: smoker; TD: thermal desorption; VOCs: volatile organic compounds

[a)] Concentrations given in different units in the original sources were converted to ng/l.

[b)] 95th percentile

3 General principles

The method herein described enables the determination of furan in end-expiratory exhaled air. Samples are collected in 20-ml screw-top glass vials into which the persons to be tested exhale through a PTFE tube. The vials are then sealed using screw caps with PTFE-lined silicone septa. After extraction and enrichment of the furan by SPME, which is carried out directly in the sample vials, determination is performed by GC-MS/MS. Exhaled-air samples spiked with furan are used for external calibration.

4 Equipment, chemicals, and solutions

4.1 Equipment

- Gas chromatograph with a split/splitless injector and a quadrupole mass spectrometer (e.g. triple-quadrupole mass spectrometer, Agilent GC 7890B with Agilent MS-MS 7010B, Agilent Technologies Deutschland GmbH, Waldbronn, Germany)
- Gas-chromatographic capillary column: stationary phase: polyethylene glycol; length: 30 m; inner diameter: 0.25 mm; film thickness: 0.25 µm (e.g. No. 19091N-133l, HP-INNOWax, Agilent Technologies Deutschland GmbH, Waldbronn, Germany)
- Autosampler: XYZ Robot for automated solid-phase microextraction with a station for SPME-fibre conditioning (e.g. MPS RoboticPro, GERSTEL GmbH & Co. KG, Mühlheim an der Ruhr, Germany)
- Inlet liner for SPME, straight design (unpacked), inner diameter of 0.75 mm (e.g. No. 2637505, Supelco Inc., Bellefonte, USA)
- SPME fibres made of quartz glass: fibre length of 1 cm, CAR/PDMS (Carboxen®/Polydimethylsiloxane) coating of 75 µm, cannula of 23 ga (e.g. No 57343-U, Supelco Inc., Bellefonte, USA)
- PTFE tubes, cut to size: length of 13 cm, outer diameter of 4.5 mm, inner diameter of 2.5 mm (e.g. PTFE Chemical Tubing, No. 92582, RCT Reichelt Chemietechnik GmbH + Co., Heidelberg, Germany)
- Variably adjustable single-channel pipettes (0.5–10 µl, 10–100 µl, 100–1000 µl, 0.5–5 ml) with matching pipette tips (e.g. Research® plus, Eppendorf AG, Hamburg, Germany)
- Analytical balance (e.g. Sartorius AG, Göttingen, Germany)
- Gastight 10-µl, 50-µl, 100-µl, and 250-µl microlitre syringes with fixed, bevel-tipped cannulas (e.g. 1700 Series syringes, Hamilton Bonaduz AG, Bonaduz, Switzerland)
- Gastight 10-µl, 25-µl, 50-µl, 100-µl, 250-µl, and 500-µl microlitre syringes with fixed side-port cannulas (e.g. 1700 Series syringes, Hamilton Bonaduz AG, Bonaduz, Switzerland)

- Gastight 1-ml and 5-ml syringes with fixed side-port cannulas (e.g. 1000 Series syringes, Hamilton Bonaduz AG, Bonaduz, Switzerland)
- 20-ml screw-top glass vials with assembled open-top screw caps with 1.3-mm silicone/PTFE septa (e.g. No. GHS6*-20R-SWFR16-H (replacement septa, No. GHS8-SW15FR01/14), Glastechnik Gräfenroda GmbH, Geratal, Germany)
- 10-ml screw-top glass vials with assembled open-top screw caps with PTFE-lined silicone septa (e.g. No. 093640-038-00 or No. 093640-040-00, GERSTEL GmbH & Co. KG, Mühlheim an der Ruhr, Germany)
- 1.5-ml screw-top glass vials (e.g. No. 093640-046-00, GERSTEL GmbH & Co. KG, Mühlheim an der Ruhr, Germany)
- Open-top screw caps (GPI 9-425 thread) with PTFE-lined silicone septa (e.g. No. 5182-0730, Agilent Technologies Deutschland GmbH, Waldbronn, Germany)
- 2.2-l threaded glass flasks (bottles for static gas dilutions) (e.g. No. 591190-2000, Static Dilution Bottle from KIMBLE®, DWK Life Sciences GmbH, Wertheim, Germany)
- PTFE-precision sampling valves for use with GPI 24-400 screw thread (e.g. Mininert® valves No. 33304 with replacement silicone septa No. 33310-U, Supelco Inc., Bellefonte, USA)

4.2 Chemicals

Unless otherwise specified, all chemicals must be a minimum of *pro analysi* grade.

- Furan, ≥ 98.0%, stabilised with 2,6-Di-*tert*-butyl-4-methylphenol (e.g. No. 43861-1ML, Merck KGaA, Darmstadt, Germany)
- Dimethyl sulfoxide (DMSO) for headspace analysis, ≥ 99.99% (e.g. No. HN47.1, ROTISOLV®, Carl Roth GmbH + Co. KG, Karlsruhe, Germany)
- Nitrogen 5.0 (e.g. Linde GmbH, Pullach, Germany)
- Helium 6.0 (e.g. Linde GmbH, Pullach, Germany)
- Ultra-pure water (e.g. PURELAB® flex 3, ELGA LabWater, High Wycombe, United Kingdom)

4.3 Calibration standards

It is advisable to prepare calibration standards in an air-conditioned laboratory with a room temperature of 20 °C. The exact volumes of the static dilution bottles and 20-ml screw-top glass vials are ascertained gravimetrically prior to use. To this end, the sealed bottles and vials are first weighed when empty and then again after being filled to the brim with ultra-pure water. The corresponding volume is calculated from the mass difference using water density and accounting for water temperature with an accuracy of 0.1 °C.

- Stock gas (8.5 mg furan/l)
  A cap with a precision-sampling valve is screwed onto a 2.2-liter dilution bottle which has been purged with nitrogen. In the bottle thus prepared, 20 µl of furan are injected using a gastight syringe. The determination of the injected furan mass is thereby carried out by differential weighing of the syringe using an analytical balance (mass of the filled syringe minus the mass of the emptied syringe after injection). The gas mixture which arises by complete evaporation of the furan is equilibrated in the dark at room temperature for at least six hours or overnight. The stock gas is freshly prepared on each day of use.
- Spiking gas I (18.2 µg furan/l)
  A cap with a precision-sampling valve is screwed onto a 2.2-liter dilution bottle which has been purged with nitrogen. A gastight syringe (side-port cannula) is used to extract and discard 4.7 ml of gas from the sealed, gastight bottle thus prepared. The gastight syringe is then used to inject 4.7 ml of the stock gas. The gas is equilibrated for at least one hour at room temperature, avoiding direct sunlight. Spiking gas I is freshly prepared on each day of use.

- Spiking gas II (0.91 µg furan/l)
  A cap with a precision-sampling valve is screwed onto a 2.2-liter dilution bottle which has been purged with nitrogen. A gastight syringe (side-port cannula) is used to extract and discard 235 µl of gas from the sealed, gastight bottle thus prepared. The gastight syringe is then used to inject 235 µl of the stock gas. The gas is equilibrated for at least one hour at room temperature, avoiding direct sunlight. Spiking gas II is freshly prepared on each day of use.

Calibration standards are prepared in 20-ml screw-top glass vials into which exhaled air has been placed. The person who provides the exhaled air should not be occupationally exposed to furan, should not smoke, and should not have consumed coffee in the last 20 minutes. Filling the vials with exhaled air is carried out as specified in the directions on specimen collection of exhaled air (see Section 5). To prepare the intended furan concentrations in the screw-top glass vials, the required spiking-gas volumes are injected into the briefly opened 20-ml screw-top glass vials using a gastight syringe (side-port cannula). The otherwise possible injection of the spiking-gas volume through the septum may lead to non-reproduceable furan adsorption onto the septum material at the puncture site.

The silicone septa of the precision-sampling valves must be exchanged after every three injections. Table 2 provides representative spiking schemes for the preparation of calibration standards for the determination of furan in exhaled air. Three possible sets of calibration standards in the lower, medium, and upper calibration ranges are given. In order to verify the absence of a blank value in the exhaled air, an unspiked exhaled-air sample is included in the analysis.

The given spiking scheme assumes a weighed-in furan quantity of 18.8 mg, a dilution-bottle volume of 2.2 l, and that each of the 20-ml screw-top glass vials has a volume of 19.5 ml. Users of the method must use gravimetrically ascertained masses and volumes to calculate the furan concentrations in the calibration standards.

Tab. 2 Spiking scheme for the preparation of calibration standards for the determination of furan in exhaled air

Calibration standard[a)]	Volume of screw-top glass vial[b)] [ml]	Volume of spiking gas II [µl]	Volume of spiking gas I [µl]	Furan concentration [ng/l]
L0		–	–	0.0
L1		5	–	0.23
L2		15	–	0.70
L3	19.5	25	–	1.2
L4		35	–	1.6
L5		45	–	2.1
L6		55	–	2.6
M0		–	–	0.0
M1		65	–	3.0
M2		80	–	3.7
M3	19.5	95	–	4.4
M4		110	–	5.1
M5		125	–	5.8
M6		140	–	6.5

Tab. 2 *(continued)*

Calibration standard[a)]	Volume of screw-top glass vial[b)] [ml]	Volume of spiking gas II [µl]	Volume of spiking gas I [µl]	Furan concentration [ng/l]
U0		–	–	0.0
U1		–	5	4.7
U2		–	20	18.7
U3	19.5	–	35	32.7
U4		–	50	46.7
U5		–	65	60.7
U6		–	80	74.6

[a)] Examples of various concentration ranges: L – lower; M – medium; U – upper
[b)] Filled with exhaled air before spiking

5 Specimen collection, assessment of sample integrity, and sample preparation

5.1 Specimen collection

To avoid contamination, exhaled-air sampling must take place in a furan-free environment. A risk of contamination is present not only at workplaces with possible furan exposure, but also in environments in which coffee is prepared or which contain cigarette smoke. A 20-ml screw-cap glass vial, an assembled open-top screw cap with septum, and a PTFE tube are used to collect a sample of end-exhaled air. The glass vial selected for this purpose is characterised by a small opening with a cross-section of 10 mm, and the relatively large, hexagonal screw cap is robust and allows for easy handling. The person to be tested should breathe normally, hold the breath for five seconds, and then exhale as completely as possible through the PTFE tube, which leads the stream of exhaled air into the screw-top glass vial. The glass is then rapidly sealed gastight with the screw cap (see Figure 1). Two directly consecutive exhaled-air samples should be taken from each person to be tested. If possible, these samples should be analysed within one week. Even though the samples can be transported without cooling, they should be stored in the laboratory in a cool, dark place (see Section 12).

Fig. 1 Collection of an exhaled-air sample: a) 20-ml screw-top glass vial, assembled open-top screw cap with PTFE-lined septum, and PTFE tube, b) specimen collection, and c) sealed, gastight 20-ml screw-top glass vial containing the exhaled-air sample

5.2 Assessment of sample integrity

Sample integrity must be verified, especially when specimen collection takes place without supervision. Exhaled-air samples exhibit characteristic amounts of water and carbon dioxide which can be used to assess their integrity (Ziener 2014). Exhaled air exits the body at about 35 °C and a relative humidity of 100%. Since the ambient temperature at the time of sample collection is generally much lower, moisture inevitably condenses in the sampling vials (see Figure 1c). As such, sample vials can be checked for visible condensation. A more laborious although more reliable option is the gravimetric determination of condensate mass, the evaluation of which can be based on experience and self-determined tolerance ranges. Samples without condensate or with unusually small condensate masses are considered questionable.

Moreover, the carbon dioxide contained in the samples can be measured simultaneously with furan. The CO_2 signal can be semi-quantitatively assessed by comparison with the carbon-dioxide signal of an ambient-air sample, a furan calibration standard, or other exhaled-air samples. As an example, Figure 2 shows a chromatogram of an ambient-air sample compared with a typical exhaled-air sample. As expected, the exhaled-air sample yields a considerably larger carbon-dioxide measurement signal when compared with the ambient-air sample. An exact quantification of the carbon-dioxide concentrations is possible via calibration with test gas. Samples with carbon-dioxide concentrations at the level of the ambient air should be considered questionable.

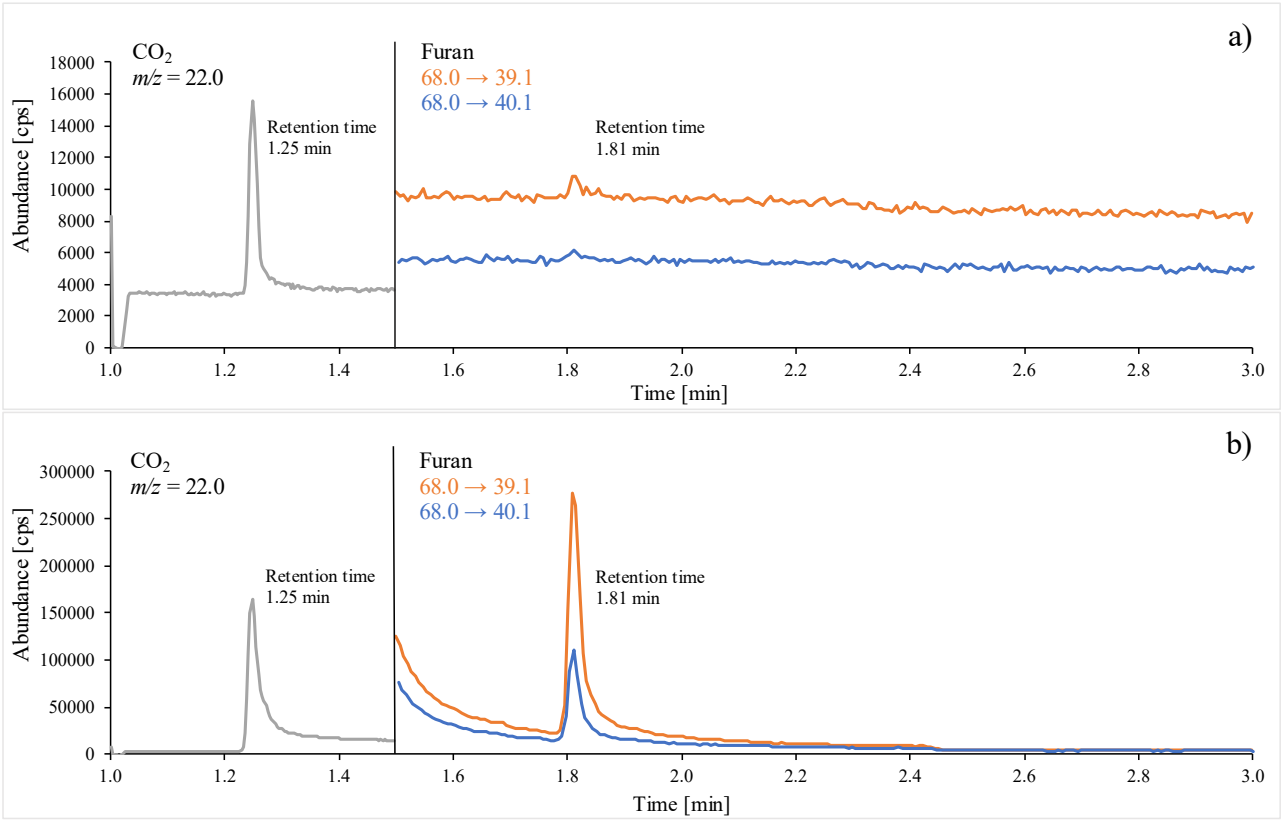

Fig. 2 Chromatograms of furan analyses with simultaneous carbon-dioxide measurement: a) chromatogram of an ambient-air sample, carbon-dioxide concentration of about 0.04%; b) chromatogram of an exhaled-air sample from a smoker, carbon-dioxide concentration of about 4%

The mass-spectrometric parameters (see Section 6.3) must be expanded to include carbon-dioxide measurement. Prior to the window for furan detection, a window for the detection of carbon dioxide is established according to Table 3.

Tab. 3 Mass-spectrometric settings for the measurement of carbon dioxide in exhaled air

Analyte	Retention time [min]	Detection mode	Ion [*m/z*]
Carbon dioxide	1.25	MS1 SIM	22[a)]

[a)] The verifiers of the method measured the carbon dioxide on the ion trace *m/z* 44.

5.3 Sample preparation

Samples are measured without any further manual workup.

6 Operational parameters

Analytical determination was carried out using a device configuration comprised of a gas chromatograph with a tandem mass spectrometer as well as an SPME unit.

6.1 Solid-phase microextraction (SPME)

Extraction location:	Sample tray of the autosampler
Extraction time:	10 min
Extraction temperature:	Room temperature (20 °C)
Bake-out of the SPME fibre:	In the conditioning station under nitrogen at 300 °C: after several hours of idle time before the start of an analytical run for 60 min, within an analytical run immediately before each extraction for 8 min each (pre-bake-out)

6.2 Gas chromatography

Capillary column:	Stationary phase:	Polyethylene glycol
	Length:	30 m
	Inner diameter:	0.25 mm
	Film thickness:	0.25 µm
Temperatures:	Column:	Initial temperature of 45 °C, isothermal for 3 min; 100 °C for 2 min after each sample
	Injector:	200 °C
	Transfer line:	200 °C
Carrier gas:	Helium 6.0	Flow rate: 1.0 ml/min, constant
Injection:	Split injection	Split ratio 1 : 10
SPME fibre:	Sample injection via thermal desorption	Desorption time: 1 min

6.3 Mass spectrometry

Ionisation mode:	Electron-impact ionisation (EI)
Ionisation energy:	70 eV
Source temperature:	230 °C
Quadrupole temperature:	150 °C

Quenching gas: Helium (4 ml/min)

Collision gas: Nitrogen (1.5 ml/min)

Collision energy: see Table 4

Detection mode: Multiple Reaction Monitoring (MRM)

The settings given above are instrument-specific and must be ascertained and, if necessary, adjusted by the user of the method.

Tab. 4 Retention time and detected mass transitions for the determination of furan in exhaled air

Analyte	Retention time [min]	Mass transition [*m/z*]		Status	Collision energy [eV]
		Precursor ion (Q1)	Product ion (Q3)		
Furan	1.81	68.0	39.1	Quantifier	23
		68.0	40.1	Qualifier	13

7 Analytical determination

Furan is enriched using solid-phase microextraction, which is carried out per automation in the 20-ml screw-top glass vials, and then transferred on the SPME fibre into the injection port of the gas-chromatograph, where it is thermally desorbed. Gas-chromatographic separation of the sample is carried out on the analytical column. The time courses of the mass transitions utilised (Table 4) are recorded in MRM mode of the triple-quadrupole mass spectrometer. The retention time given in Table 4 is only intended as a point of reference. The user must ensure the separation performance of the column used and the resulting retention behaviour of the analyte. Both consecutively obtained samples from a person (see Section 5) are analysed. The mean value of the two determinations is used to calculate the analytical result. Figure 3 shows chromatograms of native exhaled-air samples of a non-smoker and a smoker as an example.

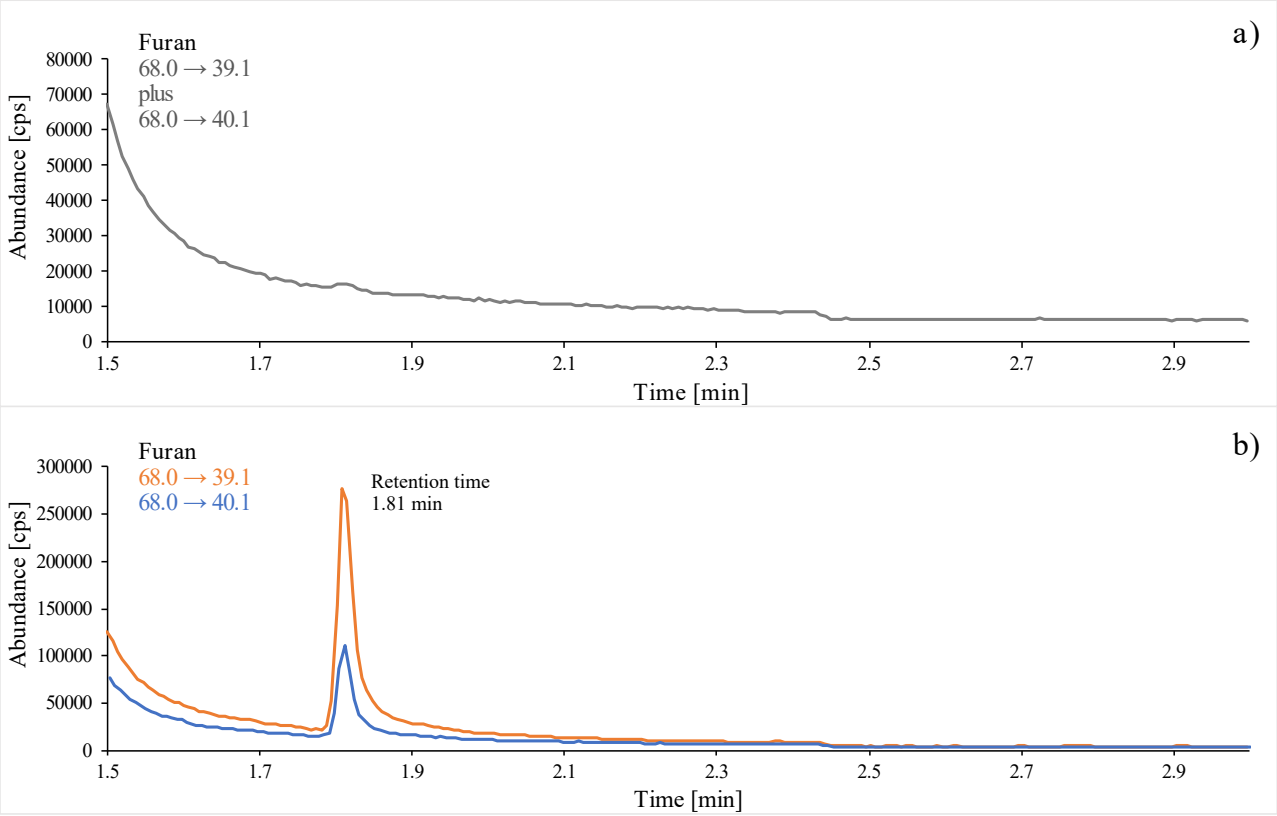

Fig. 3 Chromatograms of native exhaled-air samples: a) furan concentration < limit of quantitation; non-smoker without occupational furan exposure, at least 20 min since last coffee consumption; the sum of the ion transitions *m/z* 68.0 → 39.1 and *m/z* 68.0 → 40.1 is depicted; b) furan concentration = 7.2 ng/l; smoker without occupational furan exposure, at least 20 min since last coffee consumption; the ion transition *m/z* 68.0 → 39.1 is depicted as well as the ion transition *m/z* 68.0 → 40.1

8 Calibration

Calibration samples are included as part of each analytical run and the calibration curve is newly calculated. For this process, the calibration standards are prepared as described in Section 4.3 and analysed by GC-MS/MS. The calibration curve is generated by plotting the peak areas of furan against the corresponding analyte concentrations. The calibration curves were linear in all three concentration ranges given in Table 2. The slope and axis intercept of the calibration curve are calculated by linear regression. Figure 4 shows an example of a calibration curve for the determination of furan in exhaled air.

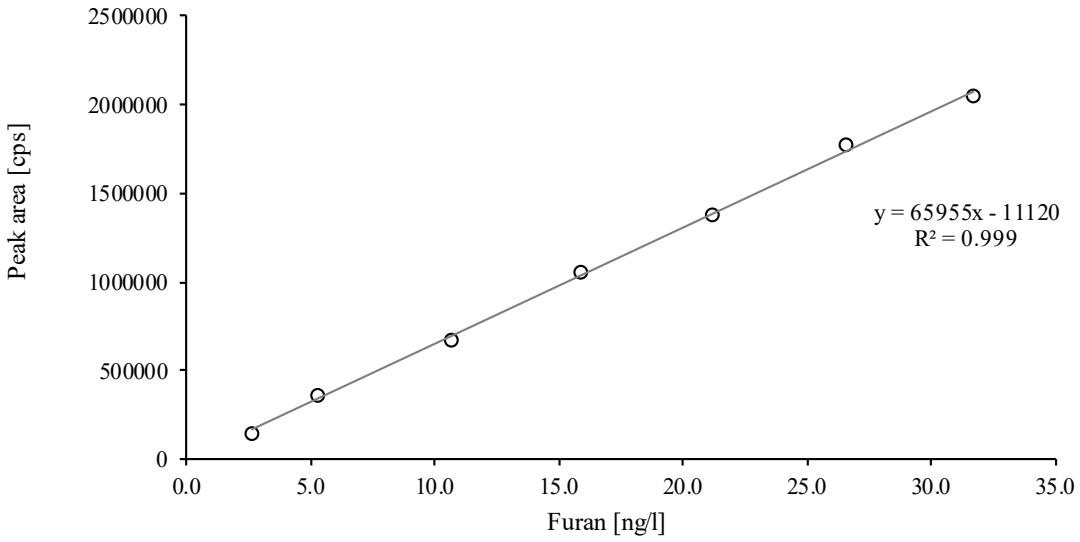

Fig. 4 Calibration curve for the determination of furan in exhaled air – the selected concentration range of 2.6 ng/l to 31.7 ng/l is suitable for the measurement of furan exposure levels typical for smokers

9 Calculation of the analytical results

The calculation of the furan concentrations in exhaled-air samples is carried out using the calibration function of the analytical run in question (Section 8). Using the evaluation software of the GC-MS/MS system, the furan peak areas are determined, inserted into the calibration function and the analyte concentration is calculated in ng/l. Any blank value which arises must be subtracted from the analytical results.

If the measured value lies outside of the selected calibration range, the calibration range must be expanded as it is not possible to dilute the sample in question.

10 Standardisation and quality control

Quality assurance of the analytical results is carried out as stipulated in the guidelines of the *Bundesärztekammer* (German Medical Association) and in a general chapter published by the Commission (Bader et al. 2010; Bundesärztekammer 2014).

For quality control, at least one control sample is included in each analytical run. Since suitable control material is not commercially available, it must be prepared in the in-house laboratory. For this purpose, the furan concentration of the control samples must lie within the concentration range relevant for assessment. The nominal value and tolerance ranges of the quality-control material are ascertained as part of a pre-analytical period (Bader et al. 2010).

The quality-control material is prepared independently from the calibration standards by an alternative procedure. As an example, the following instructions describe the preparation of control samples with a concentration of 4.8 ng furan per litre of exhaled air.

- Stock solution I (3760 mg furan/l)
  Using a pipette, 4980 µl DMSO are placed into a 10-ml screw-top glass vial. The glass vial is sealed using a screw cap with septum and weighed. Subsequently, 20 µl furan are injected through the septum into the glass vial using

a gastight syringe. The furan sample weight is ascertained by differential weighing. Stock solution I is stable for at least eight weeks when stored in the refrigerator at 4 °C.

- Stock solution II (188 mg furan/l)
  Using a pipette, 4750 µl DMSO are placed into a 10-ml screw-top glass vial. The glass vial is sealed using an open-top screw cap with septum. Subsequently, 250 µl of Stock solution I are injected through the septum into the glass vial using a microlitre syringe.
- Stock solution III (0.94 mg furan/l)
  Using a pipette, 4975 µl DMSO are placed into a 10-ml screw-top glass vial. The glass vial is sealed using a screw cap with septum. Subsequently, 25 µl of Stock solution II are injected through the septum into the glass vial using a microlitre syringe.
- Spiking solution (18.8 µg furan/l)
  Using a pipette, 980 µl of ultra-pure water are placed into a 1.5-ml screw-top glass vial. The glass vial is sealed using a screw cap with septum. Subsequently, 20 µl of Stock solution III are injected through the septum into the glass vial using a microlitre syringe.
- Control samples (4.8 ng furan/l)
  A person without occupational exposure to furan places exhaled air in 20-ml screw-top glass vials (see Section 5), the volumes of which have been determined gravimetrically (see Section 4.3). The enclosed mass of water – the breath condensate – is ascertained for each sample by differential weighing. Subsequently, the amount of water in the 20-ml screw-top glass vials is standardised by the addition of ultra-pure water using a microlitre pipette – for example, up to a total 50 mg per 20-ml screw-top glass vial. Using a microlitre syringe, 5 µl of the spiking solution are then injected into the briefly opened 20-ml screw-top glass vial.

Stock solutions II and III, the spiking solution, and the control samples should be prepared directly before use. The preparation of the quality-control material is summarised in Table 5, assuming a furan sample weight of 18.8 mg.

Tab. 5 Representative spiking scheme for the preparation of quality-control material for the determination of furan in exhaled air

Material	Advance placement of	Addition of	Furan concentration
Stock solution I	4980 µl DMSO	20 µl furan	3760 mg/l
Stock solution II	4750 µl DMSO	250 µl Stock solution I	188 mg/l
Stock solution III	4975 µl DMSO	25 µl Stock solution II	0.94 mg/l
Spiking solution	980 µl ultra-pure water	20 µl Stock solution III	18.8 µg/l
Quality-control material	19.5 ml furan-free exhaled air and ultra-pure water to standardise the mass of water	5 µl spiking solution	4.8 ng/l

11 Evaluation of the method

The reliability of this method was confirmed by comprehensive validation as well as by replication and verification in a second, independent laboratory.

11.1 Precision

Within-day precision

For the determination of within-day precision, exhaled-air samples were spiked with 1.5 ng furan/l, 5.0 ng furan/l, and 50 ng or 51 ng furan/l. Both procedures described in Section 4.3 and 10 were used to prepare ten samples per concentration, which were then analysed. Ten exhaled-air samples from a smoker, taken successively within eight minutes, were analysed as well. In this case, the smoker had last smoked a cigarette about 40 min before sampling.

The precision data obtained for each sample set are presented in Table 6. The within-day precision data determined in the smoker samples reflect both the analytical precision and the precision of sample collection in the field. The precision data given under "Characteristics of the method" in Section 1 refer to the exhaled-air samples spiked as described in Section 4.3

Tab. 6 Within-day precision for the determination of furan in exhaled air (n = 10)

Furan concentration [ng/l]	Standard deviation (rel.) s_w [%]	Prognostic range u (P = 95%) [%]
Spiked exhaled-air samples – prepared according to Section 4.3		
1.5	2.2	5.0
5.0	2.0	4.5
51.0	2.7	6.1
Spiked exhaled-air samples – prepared according to Section 10		
1.5	2.8	6.3
5.0	2.0	4.5
50.0	2.0	4.5
Native exhaled-air samples – smoker		
7.2	6.4	14.5

$u = s_w \times t_p$ (t_p – Student factor, two-tailed, at n–1 and P = 95%: 2.262) (Bader et al. 2010)

Day-to-day precision

For the determination of day-to-day precision, exhaled-air samples were spiked with 1.5 ng furan/l, 4.9 ng furan/l, or 49 ng furan/l. On the first day of analysis, the procedure described in Section 4.3 was used to prepare 20 samples for each concentration, which were stored in the dark at room temperature (about 20 °C) until measurement. Two samples per concentration were analysed on ten different days. The respective day-to-day precision data were calculated from the mean values of the two samples and are given in Table 7. These values have been influenced by furan losses from sample storage as described in Section 11.5, such that these data underestimate the analytical precision.

Tab. 7 Day-to-day precision for the determination of furan in exhaled air (n = 10)

Spiked concentration [ng/l]	Standard deviation (rel.) s_w [%]	Prognostic range u (P = 95%) [%]
1.5	6.3	14.3
4.9	7.2	16.3
49.0	5.5	12.4

$u = s_w \times t_p$ (t_p – Student factor, two-tailed, at n–1 and P = 95%: 2.262) (Bader et al. 2010)

11.2 Accuracy

Recovery tests were performed to check the accuracy of the method. To this end, exhaled-air samples were spiked with 1.5 ng furan/l, 5.0 ng furan/l, or 50 ng furan/l. Using the procedure described in Section 10, ten samples per concentration were prepared and analysed. The relative recoveries thus obtained are summarised in Table 8.

Tab. 8 Mean relative recovery for the determination of furan in exhaled air (n = 10)

Spiked concentration [ng/l]	Recovery (rel.) *r* [%]	
	Mean	Range
1.5	107	102–113
5.0	108	105–111
50.0	94.8	92.0–97.0

11.3 Matrix effects

To check for matrix effects, the verifiers of the method prepared two sets of calibration standards and performed a comparative analysis. Pure, dry nitrogen was placed in 20-ml headspace vials in one set, while the other set used exhaled air; both sets were then spiked with furan. Analysis of the samples spiked in a concentration range of 0.9–92.0 ng furan/l yielded the calibration curves depicted in Figure 5. For the exhaled-air matrix, there was about a 30% reduction in the slope of the calibration curve. As a result, the use of matrix-adjusted calibration standards is considered essential to ensure the accuracy of the measured values.

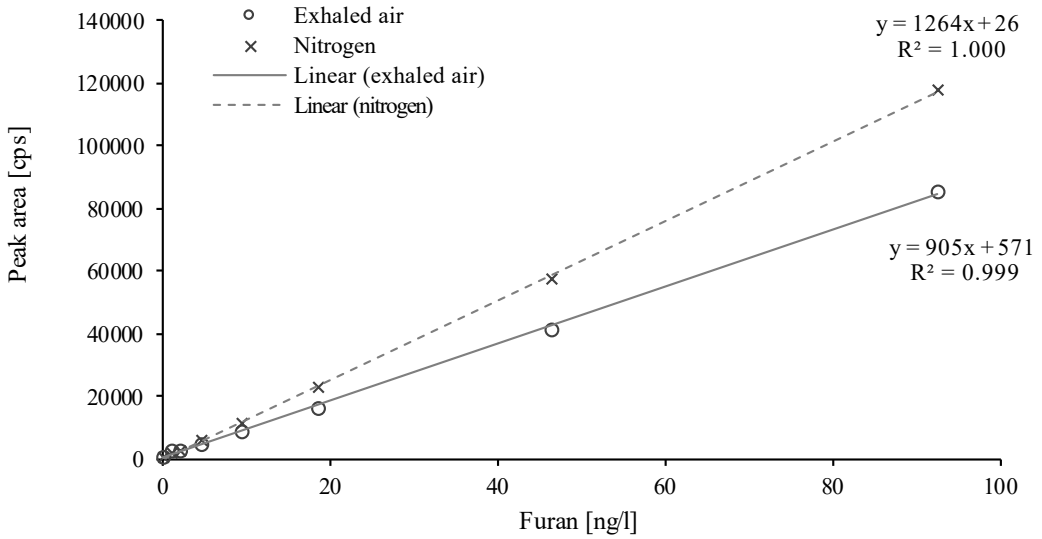

Fig. 5 Calibration curves prepared in pure, dry nitrogen or in exhaled air

11.4 Limits of detection and quantitation

The limits of detection and quantitation (Table 9) were ascertained according to the calibration-curve approach of DIN 32645 (DIN 2008). To this end, a calibration curve was generated in the range of the expected limits of detection and quantitation. The calibration points were equidistant; the lowest and highest concentrations differed by a factor of 10. The samples used for the determination of the detection and quantitation limits were prepared by spiking exhaled air as described in Section 4.3.

Tab. 9 Limits of detection and quantitation for the determination of furan in exhaled air

Analyte	Limit of detection [ng/l]	Limit of quantitation [ng/l]
Furan	0.02	0.06

11.5 Storage stability of exhaled-air samples

To assess the storage stability of exhaled-air samples, storage tests were performed at various temperatures (4 °C, 20 °C, and 35 °C) over a period of seven days. To this end, exhaled-air samples were taken from three individuals without occupational exposure to furan. Using 20-ml screw-top glass vials, 24 consecutive exhaled-air samples were taken from each person three times (see Section 5), such that a total of 216 samples were available as matrix material. Per Section 4.3, 63 samples from one individual were spiked with furan (21 samples for each concentration level of 1.5 ng furan/l, 5.0 ng furan/l, or 50 ng furan/l exhaled air). The furan analyses were carried out on Day 0 (preparation day) as well as after four and seven days. Three samples from each person, storage temperature, and concentration level were analysed. In parallel to the spiked samples, unspiked samples were analysed to check for the absence of blank values (n = 9 per person).

The results of these storage tests are presented in Table 10. According to the data, the furan concentrations of the stored samples tended to decrease with the storage period and with increasing storage temperature. At a storage period of four days and a storage temperature of 35 °C, analyte losses were at a maximum 16%. As such, samples may generally be transported without being cooled, even at summerlike temperatures. After a storage period of seven days, the samples stored in the refrigerator at 4 °C exhibited the lowest analyte losses at a maximum 14%. For this reason, samples should be cooled at 4 °C, if possible, until analysis, and analysis should take place as soon as possible after sample collection or at least within one week.

The possibility of measurement results which underestimate furan concentrations must be noted alongside storage times in the test report.

Tab. 10 Storage stability of exhaled-air samples: influence of storage duration and temperature on furan concentrations (n = 9 in each case)

Storage duration	Storage temperature [°C]	Mean relative recovery r ± relative standard deviation SD [%]		
		1.5 ng Furan/l	5.0 ng Furan/l	50 ng Furan/l
0 days[a)]	-	100 ± 1.6	100 ± 2.1	100 ± 1.1
4 days	4	97.0 ± 5.0	94.8 ± 2.0	91.5 ± 2.4
	20	92.6 ± 4.3	90.5 ± 1.1	88.4 ± 2.2
	35	85.3 ± 4.8	83.8 ± 3.0	86.3 ± 3.3
7 days	4	89.7 ± 4.9	85.9 ± 1.6	93.0 ± 1.0
	20	83.5 ± 5.5	79.8 ± 1.7	90.2 ± 1.0
	35	74.8 ± 3.6	72.0 ± 4.3	84.0 ± 1.5

[a)] The means of the measured concentrations on Day 0 were set as equal to 100%.

11.6 Sources of error

The handling of gaseous samples and calibration materials using gastight bottles, vials, and syringes requires close attention and care. Leakages may lead to lower precision and accuracy of the measured values. The PTFE-precision sampling valves used with the dilution bottles for the preparation of stock and spiking gases, as well as the PTFE-sealed plungers of the gastight syringes used for spiking the gases, can only be used for a limited period of time. For this reason, they must be regularly replaced. Prior experience shows that the silicone septa of the precision-sampling

valves should be replaced after every three injections and the gastight syringes – especially those with a volume of up to 100 µl – should be replaced after about 50 injections.

The Carboxen®/PDMS fibre used for solid-phase microextraction is very well-suited for furan enrichment. Since traces of furan may also be present in laboratory air, the extraction fibre should be sufficiently baked out and checked for blank values prior to use as well as after an extended interruption of an analytical run (see Section 6.1).

Regarding specimen collection and standard preparation, the use of 20-ml screw-top glass vials with assembled open-top screw caps with 1.3-mm PTFE/silicone septa, as described in Section 4.1, is recommended. The verifiers of the method found significant furan blank values when using PTFE-lined septa made of butyl rubber, especially with vials that have been rinsed with nitrogen, sealed, and stored over a few days. There were considerably lower blank values found when using the aforementioned PTFE-lined septa made of silicone. However, it is not advisable to store the sealed vials in this case either.

12 Discussion of the method

For occupational exposure to furan, the Commission has derived a maximum workplace concentration (*maximale Arbeitsplatz-Konzentration*, MAK value) of 0.056 mg/m^3 (DFG 2023). Even if there are currently no data on furan concentrations in exhaled air from workers with occupational furan exposure, the concentrations are expected to lie within this order of magnitude (up to about 60 ng/l). With a quantitation limit of 0.06 ng/l, the method hereby presented enables the specific and precise detection of furan in this concentration range. The low limit of quantitation is thereby achieved, among other factors, by the automated solid-phase microextraction prior to GC-MS/MS analysis.

The precision and accuracy of this method are very good and consistent with the published data for the trace analysis of furan and other volatile organic compounds in blood (CDC 2018; Göen et al. 2018). Blood measurements may be used as a reference here, assuming that furan in exhaled air presents a surrogate parameter for furan in blood.

Since exhaled air generally contains numerous volatile substances of low molecular weight, analyte quantification is performed with tandem mass spectrometry. The measurement signals obtained with GC-MS/MS did not show any relevant interferences from matrix components.

If only furan concentrations from smokers or after occupational or other types of exposure are to be measured, it is also possible to perform analysis by SPME-GC-MS. The verifiers of the method quantified furan in single ion monitoring (SIM) mode using the mass traces *m/z* 68 (quantifier) and *m/z* 39 (qualifier) and, with splitless sample injection, determined a quantitation limit of 0.8 ng furan/l exhaled air. Due to the lower sensitivity of the MSD, higher standard deviations were found at lower concentrations (1.5 ng furan/l and 5.0 ng furan/l) in the precision data. Moreover, during external method verification by GC-MS, an unspecific interfering peak appeared on the mass trace *m/z* 39, which presumably originated from a larger matrix molecule. This impurity could not be completely separated by adjusting the chromatographic parameters. When MS/MS was used for quantification, however, this interfering peak did not cause any problems.

Exhaled-air samples are collected in 20-ml screw-cap glass vials which can be sealed gastight. The samples are introduced, without further workup, into the analytical system. The personnel cost for laboratory analysis is thereby determined by the calibration of the procedure rather than by the number of samples – which facilitates the processing of extensive sample batches.

Instruments used Gas chromatograph with a split/splitless injector and a triple-quadrupole mass spectrometer (Agilent GC 7890B with Agilent MS-MS 7010B, Agilent Technologies Deutschland GmbH, Waldbronn, Germany), gas-chromatographic capillary column (stationary phase: polyethylene glycol, length of 30 m, inner diameter of 0.25 mm, film thickness of 0.25 µm, No. 19091N-133l, HP-INNOWax, Agilent Technologies Deutschland GmbH, Waldbronn, Germany) and an autosampler (XYZ Robot for automated solid-phase microextraction with a station for SPME-fibre conditioning, MPS RoboticPro, GERSTEL GmbH & Co. KG, Mühlheim an der Ruhr, Germany)

Notes

The method described herein for the determination of furan in exhaled air is based on a developmental project from the Federal Institute for Occupational Safety and Health, and has been published by this Institute as part of a publication (Ziener et al. 2024). The developers of this method submitted the procedure to the Senate Commission's Biomonitoring working group, of which the first author is a member, for feedback, external verification, and further development. Members of this working group replicated this method and independently confirmed its reliability.

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.

References

Andres S, Schultrich K, Monien B, Buhrke T, Bakhiya N, Frenzel F, Abraham K, Schäfer B, Lampen A (2017) Erhitzungsbedingte Kontaminanten in Lebensmitteln. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 60(7): 737–744. https://doi.org/10.1007/s00103-017-2564-3

Bader M, Barr D, Göen T, Schaller KH, Scherer G, Angerer J (2010) Reliability criteria for analytical methods. Biomonitoring Method, 2010. In: Angerer J, Hartwig A, editors. The MAK-Collection for Occupational Health and Safety. Part IV: Biomonitoring Methods. Volume 12. Weinheim: Wiley-VCH. p. 55–101. Also available from https://doi.org/10.1002/3527600418.bireliabe0012

Batool Z, Xu D, Zhang X, Li X, Li Y, Chen Z, Li B, Li L (2021) A review on furan: formation, analysis, occurrence, carcinogenicity, genotoxicity and reduction methods. Crit Rev Food Sci Nutr 61(3): 395–406. https://doi.org/10.1080/10408398.2020.1734532

Bundesärztekammer (2014) Richtlinie der Bundesärztekammer zur Qualitätssicherung laboratoriumsmedizinischer Untersuchungen. Dtsch Ärztebl 111(38): A1583–A1618

Burka LT, Washburn KD, Irwin RD (1991) Disposition of [^{14}C]furan in the male F344 rat. J Toxicol Environ Health 34(2): 245–257. https://doi.org/10.1080/15287399109531564

CDC (U.S. Centers for Disease Control and Prevention) (2018) Laboratory procedure manual. Analyte: volatile organic compounds (VOCs) & trihalomethanes/MTBE. Matrix: whole blood. Method: headspace solid-phase microextraction with benchtop GC MS. Atlanta, GA: CDC. https://wwwn.cdc.gov/nchs/data/nhanes/2017-2018/labmethods/VOCWB-J-MET-508.pdf, accessed 17 Jul 2023

Conkle JP, Camp BJ, Welch BE (1975) Trace composition of human respiratory gas. Arch Environ Health 30(6): 290–295. https://doi.org/10.1080/00039896.1975.10666702

Crews C (2009) Consumer exposure to furan from heat-processed food and kitchen air. EFSA Support Publ 6(9): 1–65. https://doi.org/10.2903/sp.efsa.2009.en-30

DFG (Deutsche Forschungsgemeinschaft), editor (2023) List of MAK and BAT Values 2023. Maximum Concentrations and Biological Tolerance Values at the Workplace. Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, report 59. Düsseldorf: German Medical Science. https://doi.org/10.34865/mbwl_2023_eng

DIN (Deutsches Institut für Normung), editor (2008) DIN 32645:2008-11. Chemische Analytik - Nachweis-, Erfassungs- und Bestimmungsgrenze unter Wiederholbedingungen - Begriffe, Verfahren, Auswertung. Berlin: Beuth. https://doi.org/10.31030/1465413

ECHA (European Chemicals Agency) (2019) Furan (CAS Number 110-00-9). Registration dossier. Joint submission, first publication 17 May 2013, last modification 27 Feb 2019. https://echa.europa.eu/en/registration-dossier/-/registered-dossier/10633, accessed 08 Jan 2024

European Parliament, European Council (2008) Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (Text with EEA relevance). ABl L (353): 1–1355

Göen T, Müller J, Hoppe H-W, Hartwig A, MAK Commission (2018) Aromatic compounds in blood – Determination using headspace gas chromatography with mass spectrometric detection. Biomonitoring Method, 2018. MAK Collect Occup Health Saf 3(2): 954–974. https://doi.org/10.1002/3527600418.bi7143e2218

Hartwig A, MAK Commission (2020) Furan. MAK Value Documentation, supplement – Translation of the German version from 2017. MAK Collect Occup Health Saf 5(2): Doc034. https://doi.org/10.34865/mb11000e5_2ad

Hoydonckx HE, Van Rhijn WM, Van Rhijn W, De Vos DE, Jacobs PA (2007) Furfural and derivatives. In: Ullmann's Encyclopedia of Industrial Chemistry: John Wiley & Sons, Ltd. https://doi.org/10.1002/14356007.a12_119.pub2

IARC (International Agency for Research on Cancer) (1995) Furan. In: Dry cleaning, some chlorinated solvents and other industrial chemicals. IARC monographs on the evaluation of carcinogenic risks to humans. Volume 63. Lyon: IARC. p. 393–407. https://publications.iarc.fr/_publications/media/download/2095/e981a0a3bc62c95f6ed361ab42aa61bb6bded5db.pdf, accessed 14 Dec 2023

Kedderis GL, Carfagna MA, Held SD, Batra R, Murphy JE, Gargas ML (1993) Kinetic analysis of furan biotransformation by F-344 rats in vivo and in vitro. Toxicol Appl Pharmacol 123(2): 274–282. https://doi.org/10.1006/taap.1993.1246

Kramer C, Mochalski P, Unterkofler K, Agapiou A, Ruzsanyi V, Liedl KR (2016) Prediction of blood:air and fat:air partition coefficients of volatile organic compounds for the interpretation of data in breath gas analysis. J Breath Res 10(1): 017103. https://doi.org/10.1088/1752-7155/10/1/017103

Krotoszynski BK, Bruneau GM, O'Neill HJ (1979) Measurement of chemical inhalation exposure in urban population in the presence of endogenous effluents. J Anal Toxicol 3(6): 225–234. https://doi.org/10.1093/jat/3.6.225

Mochalski P, King J, Klieber M, Unterkofler K, Hinterhuber H, Baumann M, Amann A (2013) Blood and breath levels of selected volatile organic compounds in healthy volunteers. Analyst 138(7): 2134–2145. https://doi.org/10.1039/c3an36756h

Moortgat M, Schamp N, Van Langenhove H (1992) Assessment of odour nuisance problems in Flanders: a practical approach. In: Dragt AJ, van Ham J, editors. Studies in environmental science. Volume 51. Amsterdam: Elsevier. p. 447–452. Also available from https://doi.org/10.1016/s0166-1116(08)70729-5

NCEH (National Center for Environmental Health (U.S.). Division of Laboratory Sciences) (2021) Fourth National Report on Human Exposure to Environmental Chemicals. Updated Tables, March 2021, Volume four: analysis of chemicals found in cigarette smoke in a special sample of U.S. Adults, NHANES 2011-2016. Atlanta, GA: CDC. https://stacks.cdc.gov/view/cdc/105343/cdc_105343_DS1.pdf, accessed 05 Mar 2024

NIOSH (The National Institute for Occupational Safety and Health) (2016) Immediately dangerous to life or health (IDLH) value profile: furan. DHHS (NIOSH) Publication 2016-171. Cincinnati, OH: NIOSH. https://www.cdc.gov/niosh/docs/2016-171/pdfs/2016-171.pdf, accessed 08 Jan 2024

NTP (National Toxicology Program) (1993) Toxicology and carcinogenesis studies of furan (CAS No. 110-00-9) in F344/N rats and B6C3F1 mice (gavage studies). TR 402. Research Triangle Park, NC: NTP. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr402.pdf, accessed 08 Jan 2024

NTP (National Toxicology Program) (2016) Furan. In: 15th Report on Carcinogens. Research Triangle Park, NC: NTP. p. 1–3. https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/content/profiles/furan.pdf, accessed 17 Jul 2023

Ziener C-E (2014) Biomonitoring in Ausatemluft am Beispiel Tetrachlorethen-Exponierter. Zbl Arbeitsmed 64(6): 397–400. https://doi.org/10.1007/s40664-014-0071-z

Ziener C-E, Otto C, Lorenz Contreras O (2024) Ein Analysenverfahren zur Bestimmung von Furan in Ausatemluft für ein Biomonitoring Furan-Exponierter. b a u a: Fokus 1: 1–31. https://doi.org/10.21934/baua:fokus20240102