The MAK Collection for Occupational Health and Safety

Trichloroethene, 1,1,1-trichloroethane, 1,1,2,2-tetrachloroethane and tetrachloroethene – Determination of trichloroacetic acid in urine using headspace-gas chromatography-mass spectrometry

Biomonitoring Method – Translation of the German version from 2017

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Keywords: trichloroethene; 1,1,1-trichloroethane; 1,1,2,2-tetrachloroethane; tetrachloroethene; trichloroacetic acid; TCA; urine; headspace-GC-MS

Citation Note: Will W, Bader M, Berger-Preiss E, Göen T, Hartwig A, MAK Commission. Trichloroethene, 1,1,1-trichloroethane, 1,1,2,2-tetrachloroethane and tetrachloroethene – Determination of trichloroacetic acid in urine using headspace-gas chromatography-mass spectrometry. Biomonitoring Method – Translation of the German version from 2017. MAK Collect Occup Health Saf [Original edition. Weinheim: Wiley-VCH; 2017 Jan;2(1):247-261]. Corrected republication without content-related editing. Düsseldorf: German Medical Science; 2026. https://doi.org/10.34865/bi7603e2117_w

Republished (online): 07 Aug 2026

Originally published by Wiley-VCH Verlag GmbH & Co. KGaA; https://doi.org/10.1002/3527600418.bi7603e2117

Manuscript completed: 03 Nov 2011

Published (online): 26 Jan 2017

The commission established rules and measures to avoid conflicts of interest.

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Matrix:	Urine
Hazardous substances:	Trichloroethene, 1,1,1-trichloroethane, 1,1,2,2-tetrachloroethane, tetrachloroethene
Analyt. principle:	Headspace-gas chromatography with mass spectrometric detection (HS-GC/MS)
Completed in:	November 2011

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

Hazardous substance	CAS	Parameter	CAS
Trichloroethene	79-01-6	Trichloroacetic acid (TCA)	76-03-9
1,1,1-Trichloroethane	71-55-6		
1,1,2,2-Tetrachloroethane	79-34-5		
Tetrachloroethene	127-18-4		

Summary

The described method enables the determination of trichloroacetic acid (TCA) in urine. It is based on the quantitative, thermolytic degradation of TCA into carbon dioxide and chloroform (trichloromethane) in an aqueous solution. The analyte is chloroform, which can be quantified using headspace-gas chromatography and a mass selective detector in the Selected-Ion-Monitoring-mode. For quantitation, a calibration is carried out using standard solutions in pooled urine or water which are processed and analysed in the same way as the samples.

Reliability data of the method

Trichloroacetic acid (TCA)

Within-day precision:	Standard deviation (rel)	s_w = 4.0%; 5.5% or 4.0%
	Prognostic range	u = 8.9%; 12.5% or 9.1%
	at a spiked concentration of 0.5; 5.0 or 50 mg TCA per liter urine and where n = 10 determinations	
Day-to-day precision:	Standard deviation (rel)	s_w = 8.2%; 5.7% or 4.6%
	Prognostic range	u = 18.6%; 12.8% or 10.4%
	at a spiked concentration of 0.5; 5.0 or 50 mg TCA per liter urine and where n = 10 determinations	
Accuracy:	Recovery rate (rel)	r = 95 – 118%
	at a spiked concentration of 5 mg TCA per liter urine and where n = 10 determinations	
Detection limit:	0.01 mg TCA per liter urine	
Quantitation limit:	0.03 mg TCA per liter urine	

General information on the hazardous substances

Trichloroacetic acid is a metabolite of several chlorinated hydrocarbons which are often used as solvents, such as 1,1,1-trichloroethane, 1,1,2,2-tetrachloroethane, tetrachloroethene and above all trichloroethene [Angerer et al. 1980; Monster 1986].

Trichloroethene

Trichloroethene is classified by the Commission in Category 1 for carcinogenic substances and in Category 3B for germ cell mutagenicity. Furthermore, trichloroethene is marked with an "H" indicating a relevant skin resorption [DFG 2016]. A summary of the toxicological classification of trichloroethene is presented in detail in the respective MAK Value Documentations [Greim 1998; Greim 2007; Greim 2008; Henschler 1977] For a biological monitoring, the Commission established an EKA-correlation for TCA and a BAR of 0.07 mg TCA per liter urine [Drexler and Hartwig 2011; Lehnert and Henschler 1994 a]. The ACGIH evaluated a BEI (Biological Exposure Index) of 15 mg TCA per liter urine for trichloroethene [ACGIH 2016].

Humans may be exposed to trichloroethene either via inhalation or by dermal resorption. After inhalative exposure, about 70 – 80% of the dose is resorbed. Here, the oxidative metabolism is the main excretion route. The main metabolite of the oxidative metabolism of trichloroethene is trichloroacetic acid (TCA). Mercapturic acids can be formed by the reductive metabolism pathway, however only in small amounts [Greim 1998; Lehnert and Henschler 1994 a].

The excretion in urine is relatively slow due to the strong plasma protein binding capacity of TCA. In 1994, the elimination half-life of TCA was stated to be 100 h [Lehnert and Henschler 1994 a]. Newer studies, investigating an exposure against chlorinated potable water, stated a half-life of 2.1 to 6.3 days (corresponding to 50 to 151 h) [Bader et al. 2004]. Therefore, a correlation of the biomonitoring results to an external exposure for a certain work day in a certain week is hardly possible. In order to assess the occupational exposure of trichloroethene in urine using the biomarker TCA, sampling should take place after several work shifts [ACGIH 2016; Csanády et al. 2010; DFG 2016].

Other chlorinated hydrocarbons

After exposure, other chlorinated hydrocarbons also cause the formation of TCA which is then excreted via urine. An overview of the toxicological classification of these substances is presented in Table 1.

Table 1 Toxicological classification of various chlorinated hydrocarbons by the Commission [DFG 2016].

Substance	MAK value [ppm (mg/m³)]	Carcinogen category	H, S designation	Biological value
1,1,1-Trichloroethane	200 (1100)	–	H	BAT value 550 µg/L blood
1,1,2,2-Tetrachloroethane	1 (7.0)	3B	H	–
Tetrachloroethene	–	3B	H	EKA in blood

The above mentioned substances are primarily exhaled unchanged after exposure, while only a small amount is metabolised in the body. For all the substances, an important metabolisation product is TCA. Due to the slow speed of metabolisation, however, only 1 – 2% of the exposure dose is excreted as TCA via urine. Based on the long elimination half-life of TCA and high individual variability, the amount of the excreted TCA does not allow a reliable correlation to the respective exposure. Therefore, TCA is only partially suitable as a biomarker for the halogenated hydrocarbons as shown in Table 1 [Henschler 1973; Lehnert and Henschler 1994 b; Lehnert and Henschler 1994 c].

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Completed in:	November 2011

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1 General principles

The described method enables the determination of trichloroacetic acid (TCA) in urine. It is based on the quantitative, thermolytic degradation of TCA into carbon dioxide and chloroform (trichloromethane) in an aqueous solution. The analyte is chloroform, which can be quantified using headspace-gas chromatography and a mass selective detector in the Selected-Ion-Monitoring-mode. For quantitation, a calibration is carried out using standard solutions in pooled urine or water which are processed and analysed in the same way as the samples.

2 Equipment, chemicals and solutions

2.1 Equipment

- Gas chromatograph with headspace sampler, mass spectrometer (MSD) and data processing system
- Gas chromatographic column: length: 50 m; inner diameter: 0.32 mm; film thickness: 1 µm; stationary phase: 14% cyanopropyl-phenyl-86% dimethylpolysiloxane (e.g. Optima™ 1701 by Macherey-Nagel)
- Liner without glass wool (e.g. Agilent)
- Analytical balance (e.g. Sartorius)
- Microliter pipettes, variable between 100 and 1000 µL (e.g. Eppendorf)
- Several volumetric flasks and beakers (e.g. Brand)
- 20 mL headspace vials (e.g. Macherey-Nagel)

2.2 Chemicals

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

- Trichloroacetic acid (e.g. Merck, No. 1.00807.0100)
- Ultrapure water (e.g. from Milli-Q-System)
- Helium 4.9 (e.g. Air Liquide)

2.3 Calibration standards

- Stock solution TCA (1000 mg/L)
  100 mg trichloroacetic acid are weighed into a 100 mL volumetric flask and made up to the mark with ultrapure water.
- Spiking solution I (SL I, 10 mg/L)
  1000 µL of the TCA stock solution are pipetted into a 100 mL volumetric flask and made up to the mark with ultrapure water.
- Spiking solution II (SL II, 0.5 mg/L)
  5000 µL of the spiking solution I are pipetted into a 100 mL volumetric flask and made up to the mark with ultrapure water.
- Spiking solution III (SL III, 0.01 mg/L)
  2000 µL of the spiking solution II are pipetted into a 100 mL volumetric flask and made up to the mark with ultrapure water.

All stock and spiking solutions are stored at −20°C. Under these conditions, all the solutions are stable for at least 2 years without significant losses.

The calibration standards are prepared in water or pooled urine from unexposed persons of the general population. For preparation, 100 µL pooled urine or water are pipetted into 20 mL headspace vials and spiked using the three spiking solutions for TCA, according to the pipetting-scheme in Table 2. As a result, calibration standards are obtained with a TCA concentration of 0.05 – 100 mg TCA per liter urine (relating to the used sample volume of 100 µL each, respectively) and directly analysed. Water or pooled urine is used as a blank. During the evaluation of the method, no significant differences in the slope of the calibration curve could be observed between calibration standards in water or pooled urine.

Table 2 Pipetting scheme for the calibration standards.

Calibration standard	Water or pooled urine [µL]	Volume of spiking solution	Added water [µL]	TCA Concentration [mg/L]
1	100	500 µL SL III	500	0.05
2	100	1000 µL SL III	–	0.10
3	100	100 µL SL II	900	0.50
4	100	200 µL SL II	800	1.0
5	100	1000 µL SL II	–	5.0
6	100	100 µL SL I	900	10.0
7	100	500 µL SL I	500	50.0
8	100	1000 µL SL I	–	100

3 Specimen collection and sample preparation

The urine samples are collected in sealable plastic containers and stored at −20°C. Stored in this way, the urine is stable for at least six months.

Before analysis, the urine samples are thawed in a water bath at 40°C and then thoroughly mixed. An aliquot of 100 µL is pipetted into a 20 mL headspace vial, diluted with 1000 µL of water and analysed via headspace-GC/MS.

4 Operational parameters

The analysis was carried out via gas chromatography with a headspace sampler, a mass selective detector (MSD) and a data processing system.

4.1 Gas chromatography

Capillary column:	Stationary phase::	Optima™ 1701 (14% cyanopropyl-phenyl 86% dimethylpolysiloxane)
	Length:	50 m
	Inner diameter:	0.32 mm
	Film thickness:	1 µm
Temperatures:	Headspace oven:	95°C (120 min)
	Column:	Initial temperature 40°C, 4 min isothermal, then increase at a rate of 10°C/min to 100°C, then increase at a rate of 30°C/min to 200°C, 3 min at final temperature
	Injector:	250°C
	Transfer line:	280°C
Carrier gas:	Helium 4.9	
	Flow rate:	1.0 mL/min
Injection volume:	500 µL from the vapor phase	
	Split: 10:1	

4.2 Mass spectrometry

Ionisation mode:	Electron impact ionisation (EI)
Ionisation energy:	70 eV
Dwell time:	50 ms
Solvent delay:	7 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, 500 µL of the vapour phase of each sample are injected into the GC/MS-system, after sample heating for 2 h at 95°C in the headspace unit. The identification of the analyte is based on the retention time and characteristic ion traces. Using the stated instrument settings (see Section 4), the retention time is 7,1 min for trichloromethane as a characteristic degradation product of TCA. The detection is carried out using the ion traces $m/z = 83$ (quantifier) and $m/z = 47$ (qualifier). Two quality control samples and a blank value, consisting of bidest. water, are included in each analytical run.

The given retention time is intended as a rough guide only. Users of the method must ensure proper separation performance of the used GC column that may influence the resulting retention behaviour of the analyte. The chromatograms of two urine samples, spiked with TCA, are displayed in Figures 1 and 2 (see addendum).

6 Calibration

The calibration standards in pooled urine or water (see Section 2.3) are analysed in the same way as the urine samples according to Sections 4 and 5. Calibration graphs are obtained by plotting the analyte peak areas of the calibration standards against the spiked concentration. The linearity of the calibration curve was confirmed in the range between the detection limit and a TCA level of 100 mg/L. In general, it is sufficient to carry out a single-point calibration.

7 Calculation of the analytical results

The TCA level of a urine sample is determined based on the peak area of trichloromethane. Using the calibration function corresponding to the analytical run (see Section 6), the TCA concentration in mg/L urine is obtained. Blank values are considered by subtraction.

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, two urine samples with a known and constant TCA concentration are analysed in each

analytical run as quality control samples. As the material for quality control is not commercially available, it must be prepared in the laboratory.

For that purpose, pooled urine is spiked with a defined amount of TCA, aliquoted in gas-tight vials and stored at –20°C. The TCA level of the control samples should lie in the decision-relevant concentration range. The nominal value and the tolerance ranges of the quality control samples are determined in a pre-analytical period (one analysis of the control material on 20 different days) [Bader et al. 2010].

9 Evaluation of the method

9.1 Precision

For determining the within-day precision, pooled urine samples with a spiked TCA concentration of 0.5 mg/L, 5.0 mg/L or 50 mg/L, respectively, were prepared and analysed. Based on the 10-fold determination of these urine samples the within-day precision was calculated (see Table 3).

The same material was used for the calculation of the precision from day-to day. The samples were prepared and analysed on 10 different days. The resulting precision data are also documented in Table 3.

Table 3 Within-day precision and precision from day-to-day for the determination of TCA in urine (n = 10).

	Concentration [mg/L]	Standard deviation (rel) [%]	Prognostic range [%]
Within-day precision	0.5	4.0	8.9
	5.0	5.5	12.5
	50	4.0	9.1
Day-to-day precision	0.5	8.2	18.6
	5.0	5.7	12.8
	50	4.6	10.4

9.2 Accuracy

Recovery tests were carried out in order to determine the accuracy of the method. Here, pooled urine was spiked with TCA (0.5 mg/L, 5.0 mg/L or 50 mg/L) and analysed using a single-point calibration at 5 mg/L. Pearson correlation coefficients of constantly >0.999 showed good linearity within the concentration range. The relative recovery rate was found to range between 95 – 118%.

With slight changes, the described method was used for determining TCA in urine (at the beginning with GC/ECD) from 1989 until 2009 in all 38 round robins for toxicological analyses in biological material on behalf of the German Society for

Occupational and Environmental Medicine. The results have always been in the reference range except for two years (in 1996 and 1999).

9.3 Detection limits and quantitation limits

The detection limit was estimated using the 3-fold signal to noise-ratio. The quantitation limit was determined analogously (9-fold signal to noise-ratio). Thus, the detection limit and the quantitation limit of TCA were calculated to be 0.01 mg/L and 0.03 mg/L, respectively.

9.4 Sources of error

It has to be considered that in some cases the formation of TCA may be influenced by medication (e.g. by chloral hydrate).

In order to determine TCA levels in the lower calibration range it is recommended to use a separate calibration curve (0.05 – 5 mg/L).

10 Discussion of the method

At a temperature just below 100°C aqueous TCA solutions decompose quantitatively under the release of carbon dioxide, allowing the described, easy-to-use method. The analyte is the decomposition product trichloromethane (chloroform) which can be quantified in the Selected-Ion-Monitoring-mode using GC/MS. According to our experiences, a comparable sensitivity can also be reached using GC/ECD. The sensitivity of the described GC/MS method is designed for biomonitoring studies of occupationally exposed individuals. The mean TCA background level in the general population is known to be well below 0.01 mg/L urine [Drexler and Hartwig 2011] and results from by-products of water chlorination [Bader et al. 2004; Froese et al. 2002; Zhang et al. 2009]. Thus, using the presented method, the TCA excretion of the general population can only be partially determined. A lower limit of detection may be achieved using higher urine volumes or measuring undiluted samples, put in the headspace-vials. An even greater increase of sensitivity should be achieved using headspace samplers which allow the injection of larger sample volumes on the analytical column. The authors could confirm this presumption after carrying out first test runs with a respective headspace sampler. Subsequently, detection limits which are significantly below 1 µg/L urine are within the realms of possibility.

A former photometric method for the determination of TCA is also based on the decarboxylation of TCA. Here, however, the decarboxylation takes place in alkaline solution, followed by the formation of a red chromophor derived from trichloromethane and pyridine (Fujiwara-reaction) that is measured at 530 nm

[Eben et al. 1985; Pekari and Aitio 1985]. A revised method, which was originally published in the DGF method collection in 1976, achieves a detection limit of 3 mg/L urine [Eben et al. 1985]. With some modifications, the sensitivity can be further improved to 5 µmol/L urine (corresponding to about 0.8 mg/L urine) [Pekari and Aitio 1985]. However, the photometric methods are only applicable in cases of occupational exposure to chlorinated hydrocarbons which are metabolised to TCA. In a recent field study with occupationally exposed persons, the detection limit of this photometric method is stated to be 1 µg/L urine [Furuki et al. 2000], without mentioning further method details. However, using this technique, such sensitivity does not seem plausible. The actual detection limit is probably 1 mg/L urine, especially as all the other reported results in this study were in the range of mg/L.

An overview of chromatographic methods for TCA in different media (water, body fluids and tissues) is given by Delinsky et al. (2005) and Johns et al. (2005). Here, the focus lies on gas chromatography with mass selective detection after derivatisation of TCA to a methyl ester [Delinsky et al. 2005], whereas the esterification can also be integrated into a headspace-method [Johns et al. 2005]. Next to this, other chromatographic techniques (HPLC, capillary electrophoresis) are used. The advantages of these methods, where TCA is determined as such and not after decarboxylation, are (depending on the method): TCA and other substances and/or metabolites, as e.g. dichloroacetic acid, trichloroethanol and chloral hydrate can be quantified simultaneously and quantitation limits below 1 µg/L are often achievable. The disadvantage lies in a clearly increased effort regarding sample preparation and determination compared to the here described headspace-method.

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12 Appendix

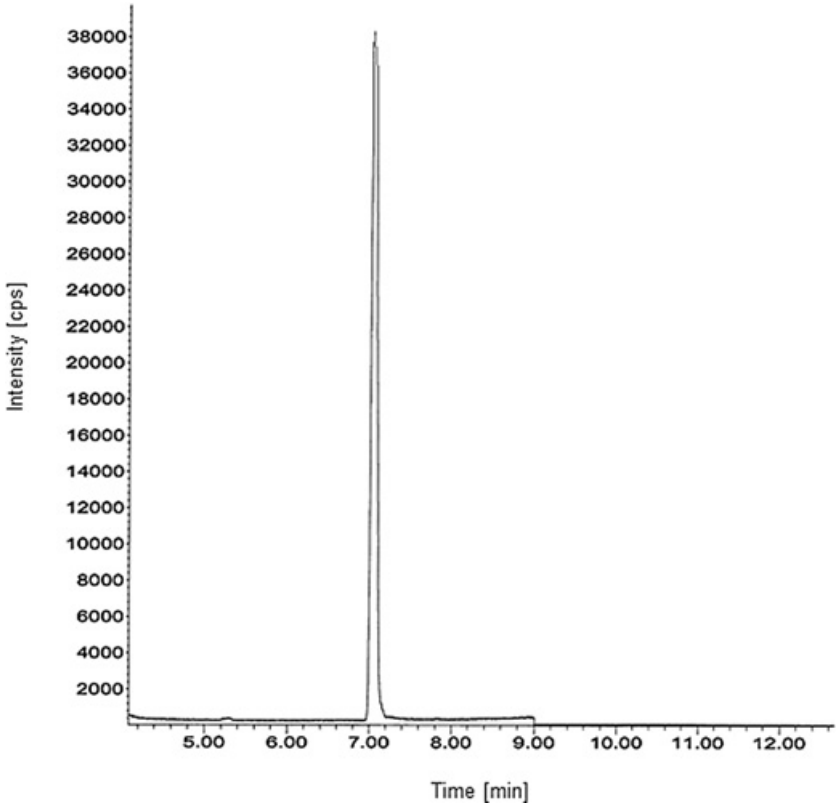

Figure 1 GC/MS chromatogram of a urine sample spiked with 1320 µg TCA per liter urine.

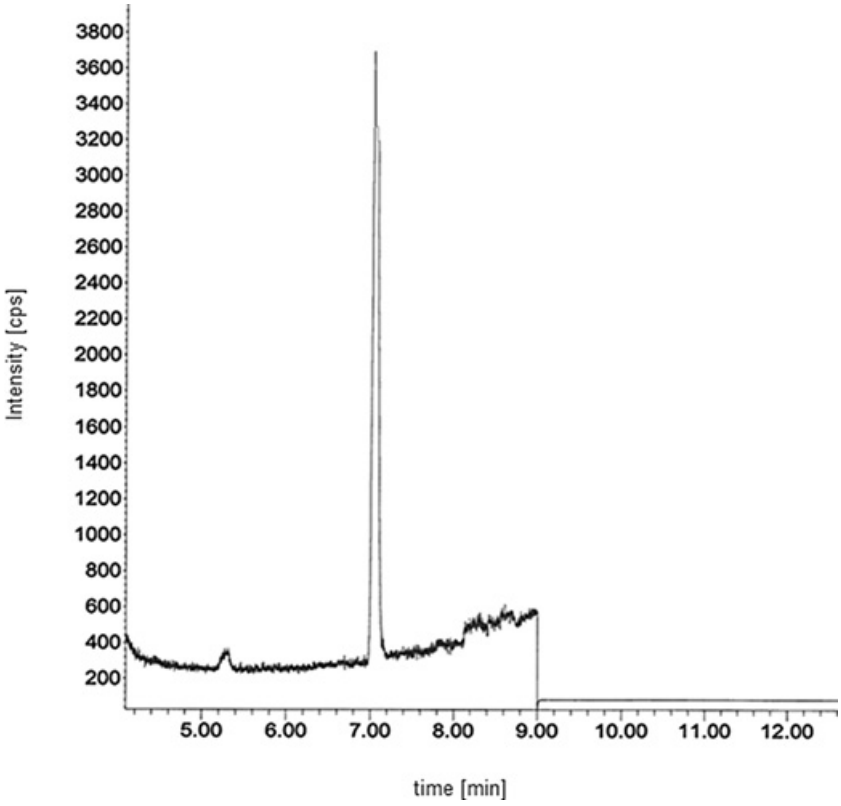

Figure 2 GC/MS chromatogram of a urine sample spiked with 132 µg TCA per liter urine.