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# Dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, 1,1,1-trichloroethane, trichloroethene, and tetrachloroethene – Determination of chlorinated hydrocarbons in blood by headspace-GC-MS

## Biomonitoring Method – Translation of the German version from 2021

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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 developed and verified the presented biomonitoring method.

The analytical method described herein allows the simultaneous determination of dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, 1,1,1-trichloroethane, trichloroethene, and tetrachloroethene in blood. For determination, the blood samples are injected into sealed headspace sample vials and equilibrated at 50 °C for one hour in a headspace-autosampler. Afterwards, an aliquot is withdrawn from the sample headspace and is transferred to the gas chromatograph and analysed by mass spectrometry. Calibration standards are prepared in sheep blood and processed analogously to the samples to be analysed.

# 1 Characteristics of the method

**Matrix** Blood

**Analytical principle** Headspace gas chromatography with mass-spectrometric detection

**Parameters and corresponding hazardous substances**

| Hazardous substance | CAS No. | Parameter | CAS No. |
|---|---|---|---|
| Dichloromethane | 75-09-2 | Dichloromethane | 75-09-2 |
| Trichloromethane | 67-66-3 | Trichloromethane | 67-66-3 |
| Tetrachloromethane | 56-23-5 | Tetrachloromethane | 56-23-5 |
| 1,2-Dichloroethane | 107-06-2 | 1,2-Dichloroethane | 107-06-2 |
| 1,1,1-Trichloroethane | 71-55-6 | 1,1,1-Trichloroethane | 71-55-6 |
| Trichloroethene | 79-01-6 | Trichloroethene | 79-01-6 |
| Tetrachloroethene | 127-18-4 | Tetrachloroethene | 127-18-4 |

## Reliability data

### Dichloromethane

Within-day precision:
Standard deviation (rel.) $s_w$ = 8.80% or 7.61%
Prognostic range $u$ = 20.3% or 17.6%
at a spiked concentration of 87.9 µg or 238 µg dichloromethane per litre of blood and n = 9 determinations

Day-to-day precision:
Standard deviation (rel.) $s_w$ = 9.92%
Prognostic range $u$ = 21.6%
at a spiked concentration of 94.5 µg dichloromethane per litre of blood and n = 13 determinations

Accuracy:
Recovery rate (rel.) $r$ = 88.7%, 91.8%, or 97.6%
at a spiked concentration of 14.1 µg, 81.3 µg, or 706 µg dichloromethane per litre of blood and n = 8 determinations

Detection limit: 1.0 µg dichloromethane per litre of blood

Quantitation limit: 3.0 µg dichloromethane per litre of blood

### Trichloromethane

Within-day precision:
Standard deviation (rel.) $s_w$ = 9.29% or 8.94%
Prognostic range $u$ = 21.4% or 20.6%
at a spiked concentration of 23.3 µg or 101 µg trichloromethane per litre of blood and n = 9 determinations

Day-to-day precision:
Standard deviation (rel.) $s_w$ = 7.00%
Prognostic range $u$ = 15.3%
at a spiked concentration of 17.5 µg trichloromethane per litre of blood and n = 13 determinations

| | | |
|---|---|---|
| Accuracy: | Recovery rate (rel.) | $r$ = 89.0%, 91.7%, or 95.2% |
| | at a spiked concentration of 1.64 µg, 9.45 µg, or 82.1 µg trichloromethane per litre of blood and n = 8 determinations | |
| Detection limit: | 0.8 µg trichloromethane per litre of blood | |
| Quantitation limit: | 2.4 µg trichloromethane per litre of blood | |

### Tetrachloromethane

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w$ = 8.51% or 8.62% |
| | Prognostic range | $u$ = 19.6% or 19.9% |
| | at a spiked concentration of 2.99 µg or 11.6 µg tetrachloromethane per litre of blood and n = 9 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w$ = 12.9% |
| | Prognostic range | $u$ = 28.0% |
| | at a spiked concentration of 0.68 µg tetrachloromethane per litre of blood and n = 13 determinations | |
| Accuracy: | Recovery rate (rel.) | $r$ = 75.2%, 79.3%, or 88.8% |
| | at a spiked concentration of 0.338 µg, 1.94 µg, or 16.9 µg tetrachloromethane per litre of blood and n = 8 determinations | |
| Detection limit: | 0.1 µg tetrachloromethane per litre of blood | |
| Quantitation limit: | 0.3 µg tetrachloromethane per litre of blood | |

### 1,2-Dichloroethane

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w$ = 5.09% or 4.15% |
| | Prognostic range | $u$ = 11.7% or 9.57% |
| | at a spiked concentration of 7.93 µg or 138 µg 1,2-dichloroethane per litre of blood and n = 9 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w$ = 7.71% |
| | Prognostic range | $u$ = 16.8% |
| | at a spiked concentration of 9.20 µg 1,2-dichloroethane per litre of blood and n = 13 determinations | |
| Accuracy: | Recovery rate (rel.) | $r$ = 86.0%, 90.0%, or 93.9% |
| | at a spiked concentration of 3.01 µg, 17.3 µg, or 150 µg 1,2-dichloroethane per litre of blood and n = 8 determinations | |
| Detection limit: | 0.1 µg 1,2-dichloroethane per litre of blood | |
| Quantitation limit: | 0.3 µg 1,2-dichloroethane per litre of blood | |

### 1,1,1-Trichloroethane

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w$ = 9.45% or 6.06% |
| | Prognostic range | $u$ = 21.8% or 14.0% |
| | at a spiked concentration of 132 µg or 326 µg 1,1,1-trichloroethane per litre of blood and n = 9 determinations | |

| | | |
|---|---|---|
| Day-to-day precision: | Standard deviation (rel.)<br>Prognostic range<br>at a spiked concentration of 172 µg 1,1,1-trichloroethane per litre of blood and n = 13 determinations | $s_w$ = 7.43%<br>$u$ = 16.2% |
| Accuracy: | Recovery rate (rel.)<br>at a spiked concentration of 13.6 µg, 78.3 µg, or 680 µg 1,1,1-trichloroethane per litre of blood and n = 8 determinations | $r$ = 79.3%, 83.3%, or 90.9% |
| Detection limit: | 0.1 µg 1,1,1-trichloroethane per litre of blood | |
| Quantitation limit: | 0.3 µg 1,1,1-trichloroethane per litre of blood | |

### Trichloroethene

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.)<br>Prognostic range<br>at a spiked concentration of 110 µg or 221 µg trichloroethene per litre of blood and n = 9 determinations | $s_w$ = 7.78% or 9.91%<br>$u$ = 17.9% or 22.8% |
| Day-to-day precision: | Standard deviation (rel.)<br>Prognostic range<br>at a spiked concentration of 111 µg trichloroethene per litre of blood and n = 13 determinations | $s_w$ = 7.14%<br>$u$ = 15.6% |
| Accuracy: | Recovery rate (rel.)<br>at a spiked concentration of 4.80 µg, 27.6 µg, or 240 µg trichloroethene per litre of blood and n = 8 determinations | $r$ = 81.3%, 84.2%, or 84.9% |
| Detection limit: | 0.1 µg trichloroethene per litre of blood | |
| Quantitation limit: | 0.3 µg trichloroethene per litre of blood | |

### Tetrachloroethene

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.)<br>Prognostic range<br>at a spiked concentration of 88.4 µg or 486 µg tetrachloroethene per litre of blood and n = 9 determinations | $s_w$ = 9.92% or 8.77%<br>$u$ = 22.9% or 20.2% |
| Day-to-day precision: | Standard deviation (rel.)<br>Prognostic range<br>at a spiked concentration of 148 µg tetrachloroethene per litre of blood and n = 13 determinations | $s_w$ = 7.84%<br>$u$ = 17.1% |
| Accuracy: | Recovery rate (rel.)<br>at a spiked concentration of 7.91 µg, 45.6 µg, or 396 µg tetrachloroethene per litre of blood and n = 8 determinations | $r$ = 79.3%, 82.9%, or 85.6% |
| Detection limit: | 0.1 µg tetrachloroethene per litre of blood | |
| Quantitation limit: | 0.3 µg tetrachloroethene per litre of blood | |

## 2 General information on chlorinated hydrocarbons

Figure 1 depicts the structural formulas of all analytes included in the method presented herein.

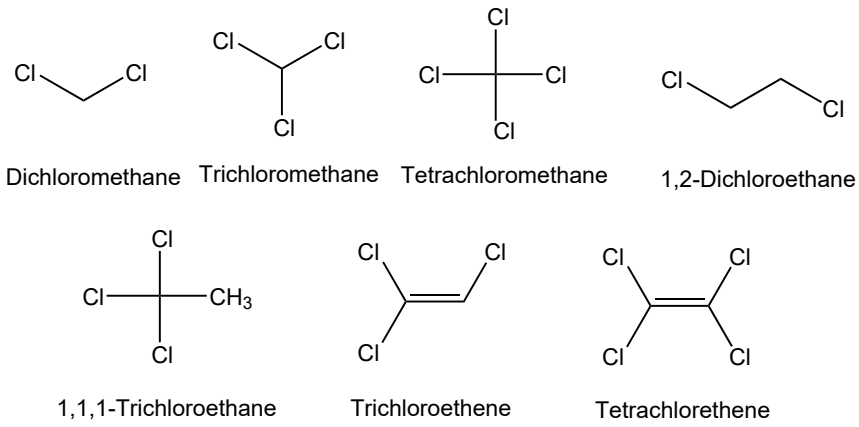


**Fig. 1** Structural formulas of the analytes dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, 1,1,1-trichloroethane, trichloroethene, and tetrachloroethene

Table 1 summarises the classifications and assessment values of the Commission for the hazardous substances of this method, which correspond with the most current List of MAK and BAT Values (DFG 2021).

**Tab. 1** Classifications and assessment values of the Commission for the chlorinated hydrocarbons determined with this method

| Hazardous substance | Maximum concentrations at the workplace | Assessment values in biological material |
|---|---|---|
| Dichloromethane | MAK: 50 ml/m³ (180 mg/m³)<br>Peak lim: II(2); Preg gr: B; Perc abs: H; Carc cat: 5 | BAT: 500 µg/l (dichloromethane in whole blood)[a]<br>EKA: cf. DFG (2021) (dichloromethane in whole blood)[a] |
| Trichloromethane | MAK: 0.5 ml/m³ (2.5 mg/m³)<br>Peak lim: II(2); Preg gr: C; Perc abs: H; Carc cat: 4 | –<br>– |
| Tetrachloromethane | MAK: 0.5 ml/m³ (3.2 mg/m³)<br>Peak lim: II(2); Preg gr: C; Perc abs: H; Carc cat: 4 | BAT: 3.5 µg/l (tetrachloromethane in whole blood)[b] |
| 1,2-Dichloroethane | MAK: –<br>Perc abs: H; Carc cat: 2 | – |
| 1,1,1-Trichloroethane | MAK: 100 ml/m³ (550 mg/m³)<br>Peak lim: II(1); Preg gr: C; Perc abs: H | BAT: 275 µg/l (1,1,1-trichloroethane in whole blood)[c] |
| Trichloroethene | MAK: –<br>Perc abs: H; Carc cat: 1; Muta cat: 3B | EKA: cf. DFG (2021) (trichloroacetic acid in urine)[b, d]<br>BAR: 0.07 mg/l (trichloroacetic acid in urine)[b, d] |
| Tetrachloroethene | MAK: 10 ml/m³ (69 mg/m³)<br>Peak lim: II(2); Preg gr: C; Perc abs: H; Carc cat: 3 | BAT: 200 µg/l (tetrachloroethene in whole blood)[e]<br>EKA: cf. DFG (2021) (tetrachloroethene in whole blood)[e] |

Abbreviations: BAR, Biologischer Arbeitsstoff-Referenzwert (biological reference value); BAT, Biologischer Arbeitsstoff-Toleranz-Wert (biological tolerance value); Carc cat, carcinogen category; EKA, Expositionsäquivalente für krebserzeugende Arbeitsstoffe (exposure equivalents for carcinogenic substances); Muta cat., germ cell mutagen category; MAK, Maximale Arbeitsplatzkonzentration (maximum workplace concentration); Peak lim, peak limitation category (excursion factor); Preg gr, pregnancy risk group; Perc abs: H, danger from percutaneous absorption

[a] Sampling time: immediately after exposure
[b] Sampling time: for long-term exposures: at the end of shift after several previous shifts
[c] Sampling time: at the beginning of the next shift, after several previous shifts
[d] Sampling time: end of exposure or end of shift
[e] Sampling time: 16 hours after end of exposure

## Dichloromethane

Dichloromethane is a colourless, highly volatile, and partly water-soluble liquid, which is used in the chemical and pharmaceutical industries as a grease solvent, extracting agent, paint stripper, and a dissolving and dilution agent, as well as a propellant. It is furthermore used for the synthesis of organic chlorine compounds (IARC 1999 e; WHO 1996; Witten et al. 1997). More than 100 000 tonnes of dichloromethane are either produced in or imported into the European Economic Area each year (ECHA 2021 e).

The Commission derived a MAK value of 50 ml/m$^3$ for dichloromethane. Details on the toxicological evaluation of dichloromethane can be found in the corresponding MAK Value Documentation of the Commission (Hartwig and MAK Commission 2016) and in an IARC monograph (IARC 1999 e).

Dichloromethane intake primarily takes place via inhalation, and rarely via dermal and oral routes (ATSDR 2000). In case of uniform inhalation exposure, a concentration equilibrium arises between dichloromethane in the ambient air and in the blood. In correlation to the MAK value, the Commission derived a BAT value of 500 µg of dichloromethane per litre of whole blood. As the half-life of dichloromethane is less than one hour, sampling should take place during or immediately following exposure, two hours after the beginning of exposure at the earliest (Bolt et al. 2018 b).

Under resting conditions and at exposures within the range of the MAK value, about 70% of inhaled dichloromethane is absorbed. Of this absorbed proportion, a maximum 5% is later exhaled unchanged, and the remaining 95% is metabolised via two alternative metabolic pathways, whereby carbon monoxide or formic acid and carbon dioxide are formed (ATSDR 2000; Bolt et al. 2018 b).

The substance was classified in Group 2A (probably carcinogenic to humans) by the International Agency for Research on Cancer (IARC) (IARC 1999 e) and in Carcinogen Category 5 (genotoxic carcinogens of weak potency) by the Commission (Hartwig and MAK Commission 2016).

## Trichloromethane

Trichloromethane (chloroform) is a colourless, highly volatile liquid which displays a characteristic odour. Over 90% of trichloromethane are used as a starting material for the production of chlorodifluoromethane (HCFC 22). Trichloromethane is otherwise used as a solvent and extracting agent, as a degreaser, and is also an intermediate in the production of pesticides and dyes (INERIS 2007). Each year, 100 000–1 000 000 tonnes of trichloromethane are either produced in or imported into the European Economic Area (ECHA 2021 d). The Commission derived a MAK value of 0.5 ml/m$^3$ for trichloromethane. Details on the toxicological evaluation of trichloromethane can be found in the corresponding MAK Value Documentation of the Commission (Greim 2000) and in an IARC monograph (IARC 1999 d).

Exposure to trichloromethane occurs by inhalation and only rarely via oral or dermal routes. Following oral exposure, the maximum blood level is reached within about five minutes. Trichloromethane is primarily exhaled unchanged or in the form of carbon dioxide and is excreted in only small amounts with the urine and faeces (ATSDR 1997). Trichloromethane is metabolised in the liver by cytochrome P450 (CYP)2E1. During this process, about half of the substance is broken down into carbon dioxide, yielding phosgene and the dichloromethyl radical, among other substances, as toxic intermediates (Greim 2000).

Trichloromethane has been classified in Group 2B (possibly carcinogenic to humans) by the IARC (IARC 1999 d) and in Carcinogen Category 4 (carcinogens acting primarily by non-genotoxic mechanisms) by the Commission (Greim 2000).

## Tetrachloromethane

Tetrachloromethane is a colourless, non-flammable liquid, which displays a characteristic odour. It is used as a starting material for the production of partially halogenated chlorofluorohydrocarbons, partially halogenated hydrofluorocarbons, and hydrofluoroolefins (US EPA 2020 a). Furthermore, tetrachloromethane is applied as a solvent in the production of semiconductors and in the processing of oils, greases, and rubber (IARC 1999 c). Annually, 1000–10 000

tonnes of tetrachloromethane are either produced in or imported into the European Economic Area (ECHA 2021 c). The Commission derived a MAK value of 0.5 ml/m$^3$ for tetrachloromethane. Details on the toxicological evaluation can be found in the corresponding MAK Value Documentation of the Commission (Greim 2002) as well as in an IARC monograph (IARC 1999 c). In correlation with the MAK value, the Commission derived a BAT value of 3.5 µg of tetrachloromethane per litre of whole blood, whereby sampling should take place during or immediately following exposure, two hours after the beginning of exposure at the earliest (Bolt 2005).

For inhalation exposure, the absorption rate in humans is about 60% (US EPA 2020 a). The substance is metabolised by CYP2E1 in the liver. During this process, the trichloromethyl radical initially arises, from which carbon dioxide, trichloromethane, and hexachloroethane are formed in further processes. About 10% of the metabolised tetrachloromethane is exhaled in the form of carbon dioxide (Greim 2002). Tetrachloromethane is primarily eliminated from the body via exhaled air (with an initial elimination half-life of one to three hours) and with the faeces, whereby it is excreted only in small amounts with the urine (ATSDR 2005).

Tetrachloromethane has been classified in Group 2B (possibly carcinogenic to humans) by the IARC (IARC 1999 c) and in Carcinogen Category 4 (carcinogens acting primarily by non-genotoxic mechanisms) by the Commission (Greim 2002).

## 1,2-Dichloroethane

1,2-Dichloroethane is a clear, colourless, and oleaginous liquid. Each year, 1 000 000–10 000 000 tonnes of the substance are either produced in or imported into the European Economic Area (ECHA 2021 b). 1,2-Dichloroethane is used as a chemical intermediate and as a solvent. Furthermore, 1,2-dichloroethane is used in the synthesis of other substances, especially vinyl chloride. Small amounts are used for the production of vinylidene chloride, 1,1,1-trichloroethane, trichloroethene, tetrachloroethene, and a number of other substances (ATSDR 2001).

The intake of 1,2-dichloroethane occurs by oral, inhalative, or dermal routes (UBA 2019). Due to the danger from percutaneous absorption, the Commission has designated 1,2-dichloroethane with an "H" (Henschler 1992). Details on the toxicological evaluation of the substance can be found in the MAK Documentation (Henschler 1992) and an IARC monograph (IARC 1999 b).

In a study with rats, the applied dose was almost completely excreted within 48 hours, whereby thiodiacetic acid and thiodiacetic acid sulfoxide represented the main metabolites in urine at about 85%. A significantly lower proportion of less than 10% was exhaled in the form of carbon dioxide (Reitz et al. 1982). 1,2-Dichloroethane is metabolised either by CYP2E1-oxidation to the reactive 2-chloroacetaldehyde or by immediate reaction with glutathione, whereby a reactive episulfonium ion is formed (UBA 2019).

1,2-Dichloroethane has been assigned to Group 2B (possibly carcinogenic to humans) by the IARC (IARC 1999 b) and has been designated by the Commission as a Category 2 carcinogen (substances that are considered to be carcinogenic to humans) (Henschler 1992).

## 1,1,1-Trichloroethane

1,1,1-Trichloroethane is a colourless, volatile liquid, which was used in metal degreasing and as a solvent in, for example, adhesives, paints, and varnishes. Furthermore, 1,1,1-trichloroethane was used as a coolant and lubricant and is also a chemical intermediate in the production of 1,1-dichloroethene (WHO 1992). 1,1,1-Trichloroethane is registered under the REACH Regulation and is manufactured in and / or imported to the European Economic Area for intermediate use only (ECHA 2021 a). The Commission derived a MAK value of 100 ml/m$^3$ for 1,1,1-trichloroethane. Details on the toxicological evaluation of 1,1,1-trichloroethane can be found in the respective MAK Value Documentation of the Commission (Hartwig and MAK Commission 2019) as well as in an IARC monograph (IARC 1999 a). In correlation with the MAK value, the Commission derived a BAT value of 275 µg/l of 1,1,1-trichloroethane per litre of whole blood,

whereby sampling should take place during or immediately following exposure, two hours after the start of shift at the earliest (Bolt et al. 2019).

1,1,1-Trichloroethane is quickly absorbed after inhalation. Dermal or oral uptake of the substance is also possible (WHO 1992). 1,1,1-Trichloroethane is primarily exhaled unchanged, whereby the elimination proceeds exponentially. The half-lives of the initial, intermediate, and final phases are about 1–9 hours, 6–20 hours, and > 26 hours, respectively (IARC 1999 a). Only about 10% of the substance is metabolised by CYP enzymes. During metabolism, 2,2,2-trichloroethanol glucuronide and trichloroacetic acid predominantly arise and both substances are excreted with the urine (Hartwig and MAK Commission 2019). As a result of the low metabolism rate of 1,1,1-trichloroethane, it is assumed that external airborne exposure shows a linear correlation with the blood level (Bolt et al. 2019).

1,1,1-Trichloroethane has been assigned to Group 3 (not classifiable as to its carcinogenicity to humans) by the IARC (WHO 1992). 1,1,1-Trichloroethane is not carcinogenic in animal studies and has not been assigned to a Carcinogen Category by the Commission (Hartwig and MAK Commission 2019).

## Trichloroethene

Trichloroethene is a colourless, non-flammable liquid, which displays a characteristic chloroform-like odour. It is primarily used as a solvent for the cleaning and degreasing of metals and as a raw material for the production of fluorinated hydrocarbons and fluorinated polymers (IARC 2014 b). Moreover, trichloroethene is used as an extracting agent for fats, oils, and waxes, as well as in the processing of textiles. Trichloroethene is also a common component of adhesives, paints, lacquers, paint strippers, pesticides, and cold metal cleaners (ATSDR 2019). More than 10 000 tonnes of the substance are either produced in or imported into the European Economic Area each year (ECHA 2021 f). Details on the toxicological evaluation can be found in the corresponding MAK Value Documentation published by the Commission (Greim 1998), as well as in an IARC monograph (IARC 2014 b).

Following exposure, a proportion of inhaled trichloroethene is exhaled unchanged. The substance is then metabolised via two different metabolic pathways, whereby the oxidative metabolic pathway is the primary route. The main metabolites trichloroethanol and trichloroacetic acid are excreted with the urine. Moreover, reactive metabolites are formed by glutathione. The elimination kinetics of trichloroethene become clearly distinct in terms of either short-term or long-term exposure, as trichloroethene enters deeper compartments during chronic exposure and accumulates in the body (Bolt 1994).

Trichloroethene has been assigned to Group 1 (carcinogenic to humans) by the IARC (IARC 2014 b), and to Carcinogen Category 1 (substances that cause cancer in humans) by the Commission (Greim 1998).

## Tetrachloroethene

Tetrachloroethene is a colourless, non-flammable liquid, which is used in the production of chlorofluorocarbons, as a solvent in dry-cleaning and in metal-degreasing. Furthermore, tetrachloroethene is used in paint removers, printing inks, and paper coatings (IARC 2014 a; NTP 2016; US EPA 2020 b). The Commission derived a MAK value of 10 ml/m$^3$ for tetrachloroethene. Details on the toxicological evaluation of tetrachloroethene can be found in the respective MAK Value Documentation of the Commission (Hartwig 2014) as well as in an IARC monograph (IARC 2014 a). In correlation to the MAK value, the Commission derived a BAT value of 200 µg of tetrachloroethene per litre of whole blood, whereby sampling should take place 16 hours after the end of exposure (Bolt et al. 2018 a).

Tetrachloroethene is quickly absorbed after inhalation, dermal contact, or oral intake, and is subsequently metabolised in small amounts (1–3%) to trichlorometabolites, especially trichloroacetic acid, which are then excreted with the urine. The majority of the absorbed tetrachloroethene is, however, exhaled unchanged (Hartwig 2014). For subjects who were exposed to tetrachloroethene via inhalation for several days, accumulation of the substance in the body was observed. Furthermore, the concentration in the blood increased over several days. The half-life of tetrachloroethene is about

25 hours (IARC 2014 a). Even at low levels of exposure, a linear correlation exists between blood levels and external exposure (Bolt et al. 2018 a).

Tetrachloroethene was classified in Group 2A (probably carcinogenic to humans) by the IARC (IARC 2014 a) and in Carcinogen Category 3 (suspected carcinogen) by the Commission (Hartwig 2014).

# 3 General principles

The analytical method described herein allows the simultaneous determination of dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, 1,1,1-trichloroethane, trichloroethene, and tetrachloroethene in blood. For determination, the blood samples – filled into sealed headspace sample vials – are equilibrated at 50 °C for one hour in a headspace autosampler. Afterwards, an aliquot is withdrawn from the sample headspace and injected into the GC-MS-system. The analytes are seperated by gas chromatography and analysed by mass spectrometry. Calibration standards are prepared in sheep blood and processed analogously to the samples to be analysed.

# 4 Equipment, chemicals, and solutions

## 4.1 Equipment

- Gas chromatograph with a mass-spectrometric detector (e.g. Agilent 5890 A with Agilent 5975 C, Agilent Technologies Germany GmbH & Co. KG, Waldbronn, Germany)
- Headspace autosampler (e.g. TurboMatrix HS 40 Trap, PerkinElmer Inc., Rodgau, Germany)
- Capillary gas-chromatography column: 6% cyanopropyl/phenyl, 94% polydimethylsiloxane, 60 m × 0.32 mm × 1.8 µm (e.g. Agilent VF 624ms, Agilent Technologies Germany GmbH & Co. KG, Waldbronn, Germany)
- Analytical balance (e.g. Sartorius AG, Göttingen, Germany)
- Roller mixer (e.g. VWR International GmbH, Darmstadt, Germany)
- 20-ml headspace vials (e.g. No. 5183-4474, Agilent Technologies Germany GmbH & Co. KG, Waldbronn, Germany)
- Aluminium crimp caps with Teflon-lined butyl septa (e.g. No. 5183-4479, Agilent Technologies Germany GmbH & Co. KG, Waldbronn, Germany)
- Crimper (e.g. No. 5191-5615, Agilent Technologies Germany GmbH & Co. KG, Waldbronn, Germany)
- 25-µl microlitre syringe (e.g. No. 80465, Hamilton Bonaduz AG, Bonaduz, Switzerland)
- Variably adjustable pipettes (10–100 µl and 100–1000 µl) with matching pipette tips (e.g. Research® plus, Eppendorf AG, Hamburg, Germany)
- 25-ml volumetric flasks (e.g. VWR International GmbH, Darmstadt, Germany)
- EDTA Monovettes® for blood collection (e.g. Sarstedt AG & Co. KG, Nümbrecht, Germany)

## 4.2 Chemicals

Unless otherwise specified, all chemicals must be at least *pro analysi* grade.

- Ethanol (e.g. No. 100983, Merck KGaA, Darmstadt, Germany)
- Dichloromethane (e.g. No. 107020, Merck KGaA, Darmstadt, Germany)

- Trichloromethane (e.g. No. 102432, Merck KGaA, Darmstadt, Germany)
- Tetrachloromethane (e.g. No. 319961, Merck KGaA, Darmstadt, Germany)
- 1,2-Dichloroethane (e.g. No. 113713, Merck KGaA, Darmstadt, Germany)
- 1,1,1-Trichloroethane (e.g. No. EHERCA17738300, VWR International GmbH, Darmstadt, Germany)
- Trichloroethene (e.g. No. 251402, Merck KGaA, Darmstadt, Germany)
- Tetrachloroethene (e.g. No. 270393, Merck KGaA, Darmstadt, Germany)
- Ultra-pure water (e.g. No. 115333, Merck KGaA, Darmstadt, Germany)
- Sheep blood with EDTA (e.g. Fiebig Nährstofftechnik GbR, Idstein-Niederauroff, Germany)

## 4.3 Calibration standards

- Stock solution
  10 ml of ethanol are added to a 25-ml volumetric flask and 688 mg of dichloromethane, 75 mg of trichloromethane, 12.5 mg of tetrachloromethane, 125 mg of 1,2-dichloroethane, 688 mg of 1,1,1-trichloroethane, 250 mg of trichloroethene, and 375 mg of tetrachloroethene are weighed out into the flask. Alternatively, the corresponding volumes of the pure substances may be added using a microlitre syringe (see Section 11). The flask is then made up to the mark with ethanol. The solution is thoroughly mixed.
- Spiking solution
  100 µl of the stock solution are pipetted into a 25-ml volumetric flask. The flask is then made up to the mark with ethanol. The solution is thoroughly mixed.

The stock and spiking solutions are stable for one year when refrigerated at 4 °C.

The calibration standards are prepared in sheep blood. 2-ml aliquots of sheep blood are placed into 20-ml headspace vials, which are sealed with aluminium crimp caps with Teflon-lined butyl septa. The aliquots of the spiking solution listed in Table 2 are added through the septum using the 25-µl syringe (microlitre syringe).

**Tab. 2** Pipetting scheme for the preparation of calibration standards for the determination of chlorinated hydrocarbons in blood

| Calibration standard | Volume of blood [µl] | Volume of spiking solution [µl] |
|---|---|---|
| 0 | 2000 | 0 |
| 1 | 2000 | 1 |
| 2 | 2000 | 2 |
| 3 | 2000 | 4 |
| 4 | 2000 | 7 |
| 5 | 2000 | 10 |
| 6 | 2000 | 15 |
| 7 | 2000 | 20 |

The calibration standards thus prepared are placed on the roller mixer for one hour and can be used directly thereafter for analysis. Table 3 shows the resulting analyte concentrations in the calibration solutions.

**Tab. 3** Analyte concentrations in the calibration standards for the determination of chlorinated hydrocarbons in blood

| Calibration standards | Dichloromethane/ 1,1,1-Trichloroethane [µg/l] | Trichloro-methane [µg/l] | Tetrachloro-methane [µg/l] | 1,2-Dichloro-ethane [µg/l] | Trichloro-ethene [µg/l] | Tetrachloro-ethene [µg/l] |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 55 | 6 | 1 | 10 | 20 | 30 |
| 2 | 110 | 12 | 2 | 20 | 40 | 60 |
| 3 | 220 | 24 | 4 | 40 | 80 | 120 |
| 4 | 385 | 48 | 7 | 70 | 140 | 210 |
| 5 | 550 | 60 | 10 | 100 | 200 | 300 |
| 6 | 825 | 90 | 15 | 150 | 300 | 450 |
| 7 | 1100 | 120 | 20 | 200 | 400 | 600 |

# 5 Specimen collection and sample preparation

Approximately 5 ml of whole blood are drawn from the cubital vein using an EDTA-containing Monovette®. 2 ml of this blood sample are then immediately injected into a sealed headspace vial. The samples are stored at –18 °C until analysis. Prior to analysis, the samples are thawed at room temperature and thoroughly mixed. The samples can be used directly thereafter for analysis.

# 6 Operational parameters

Analysis was performed using a gas chromatograph coupled with a headspace injector, a mass-selective detector (MSD), and a data-processing system.

## 6.1 Headspace autosampler

| | |
|---|---|
| Equilibration time: | 60 min at 50 °C |
| Temperature of the transfer line to the GC: | 110 °C |
| Needle temperature: | 70 °C |
| Pressure build-up: | 16.5 psi for 0.5 min |
| Injection time: | 0.08 min |

## 6.2 Gas chromatography

| | | |
|---|---|---|
| Capillary column: | Stationary phase: | VF 624ms (6% cyanopropyl/phenyl, 94% polydimethylsiloxane) |
| | Length: | 60 m |
| | Inner diameter: | 0.32 mm |
| | Film thickness: | 1.8 µm |

| | | |
|---|---|---|
| Temperatures: | Headspace oven: | 50 °C (60 min) |
| | Column: | Initial temperature of 45 °C, hold for 10 min, increase at a rate of 5 °C/min to 110 °C, hold for 3 min, then increase at a rate of 35 °C/min to 220 °C, 5 min at final temperature |
| | Injector: | 130 °C |
| | Transfer line: | 280 °C |
| Carrier gas: | Helium 5.0 | |
| | Flow rate: 1.2 ml/min, constant | |
| Injection: | Split 1 : 5 | |

## 6.3 Mass spectrometry

| | |
|---|---|
| Ionisation mode: | Electron impact ionisation (EI) |
| Ionisation energy: | 70 eV |
| Source temperature: | 230 °C |
| Quadrupole temperature: | 150 °C |
| Dwell time: | 50 ms |
| Detection mode: | Single Ion Monitoring (SIM) |

All parameters are intended only as a rough guide and, if necessary, must be optimised in accordance with the manufacturer's specifications for the utilised instrumentation.

# 7 Analytical determination

For the analytical determination of the blood samples prepared as described in Section 5, an aliquot of the gas phase above the sample is injected into the GC-MS system after heating the sample for one hour at 50 °C in the headspace sampler oven. Identification of the analytes is based on their retention times and characteristic ion traces. The time courses of the ion traces shown in Table 4 are recorded in SIM mode. A reagent blank consisting of ultra-pure water is included in each analytical run.

**Tab. 4** Retention times and detected ion traces of the analytes for the determination of chlorinated hydrocarbons in blood

| Analyte | Retention time [min] | Ion traces [*m/z*] | |
|---|---|---|---|
| | | Quantifier | Qualifier |
| Dichloromethane | 9.57 | 84 | 86 |
| Trichloromethane | 15.11 | 83 | 85 |
| Tetrachloromethane | 16.09 | 117 | 119 |
| 1,2-Dichloroethane | 16.97 | 62 | 98 |
| 1,1,1-Trichloroethane | 15.62 | 97 | 99 |
| Trichloroethene | 18.83 | 130 | 132 |
| Tetrachloroethene | 24.37 | 166 | 164 |

The retention times given are intended only as cursory guidance. Users must ensure proper separation performance of the capillary column used and the resulting retention behaviour of the analytes. Figure 2 shows a chromatogram of a blood sample spiked with the analytes.

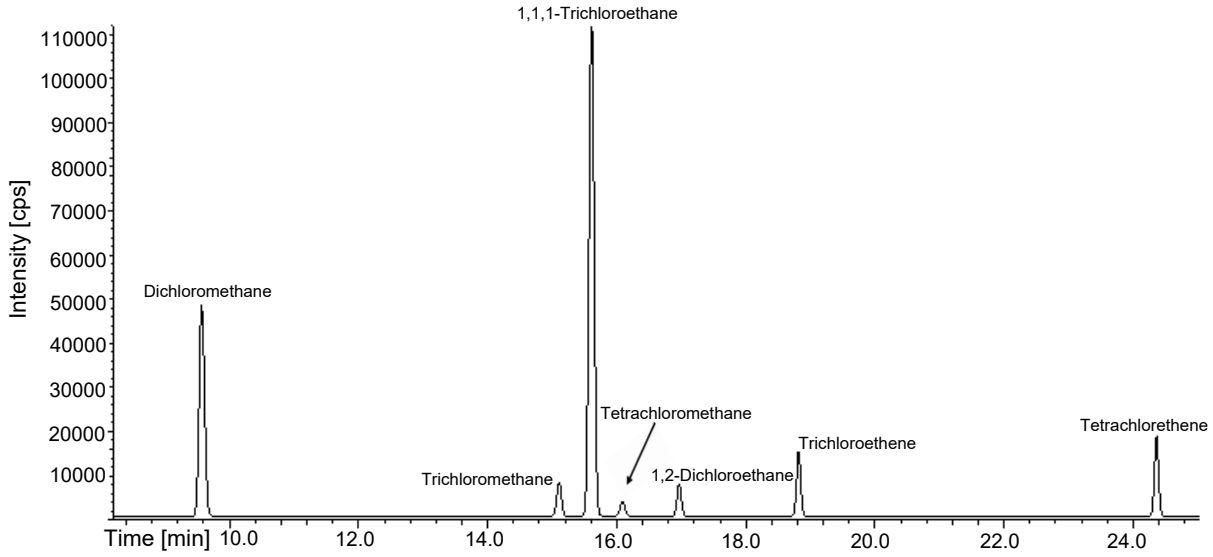


**Fig. 2** Chromatogram of a blood sample spiked with the analytes dichloromethane (395 µg/l), trichloromethane (46.0 µg/l), tetrachloromethane (9.45 µg/l), 1,2-dichloroethane (84.2 µg/l), 1,1,1-trichloroethane (381 µg/l), trichloroethene (134 µg/l), and tetrachloroethene (221 µg/l)

# 8 Calibration

The calibration standards (see Section 4.3) are analysed analogously to the blood samples according to Sections 6 and 7. Calibration curves are obtained by plotting the peak areas of the respective analytes against their spiked concentrations. Figure 3 shows representative calibration curves for the seven analytes; the curves are linear in the selected concentration range.

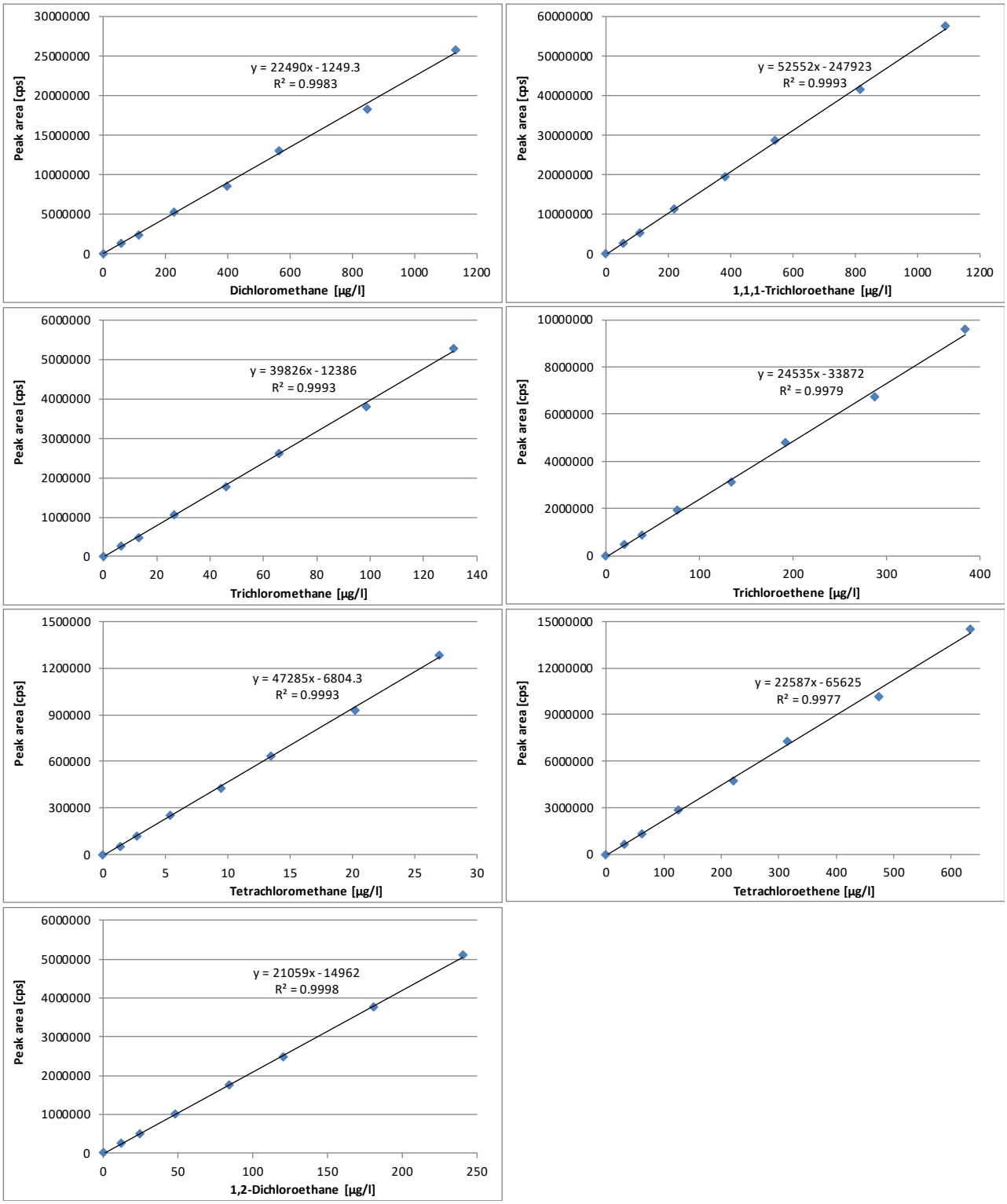


**Fig. 3** Calibration curves of the analytes dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, 1,1,1-trichloroethane, trichloroethene, and tetrachloroethene

# 9 Calculation of the analytical results

The analyte concentrations of the samples are calculated by dividing the peak area of the individual analyte by the corresponding slope of the calibration curve established according to Section 8, yielding the analyte concentrations in µg/l. Any reagent blanks must be subtracted from the analytical results.

# 10 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 special chapter published by the Commission (Bader et al. 2010; Bundesärztekammer 2014). To check precision, quality-control samples with known and constant analyte concentrations are included in each analytical run. As material for quality control is not commercially available, it must be prepared in-house by spiking sheep blood with the respective analytes at a low ($Q_{low}$) and a high ($Q_{high}$) concentration. 2-ml aliquots of the quality-control materials are aliquoted into headspace vials and frozen at –18 °C.

The nominal value and tolerance ranges (mean value ± two standard deviations) of the quality-control material are determined in a pre-analytical period (Bader et al. 2010).

# 11 Evaluation of the method

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

## 11.1 Precision

### Within-day precision

To determine within-day precision, blood samples were spiked with the analytes, processed, and analysed. The material used was the G-EQUAS RV62-5A (low concentration) and G-EQUAS RV62-5B (high concentration) material used in the interlaboratory comparisons of the German External Quality Assessment Scheme (G-EQUAS). Ninefold determination of these blood samples yielded the within-day precision data presented in Table 5.

**Tab. 5** Within-day precision for the determination of chlorinated hydrocarbons in blood (n = 9)

| Analyte | Spiked concentration [µg/l] | Standard deviation (rel.) $s_w$ [%] | Prognostic range $u$ [%] |
|---|---|---|---|
| Dichloromethane | 87.9 | 8.80 | 20.3 |
| | 238 | 7.61 | 17.6 |
| Trichloromethane | 23.3 | 9.29 | 21.4 |
| | 101 | 8.94 | 20.6 |
| Tetrachloromethane | 2.99 | 8.51 | 19.6 |
| | 11.6 | 8.62 | 19.9 |
| 1,2-Dichloroethane | 7.93 | 5.09 | 11.7 |
| | 138 | 4.15 | 9.57 |
| 1,1,1-Trichloroethane | 132 | 9.45 | 21.8 |
| | 326 | 6.06 | 14.0 |
| Trichloroethene | 110 | 7.78 | 17.9 |
| | 221 | 9.91 | 22.8 |
| Tetrachloroethene | 88.4 | 9.92 | 22.9 |
| | 486 | 8.77 | 20.2 |

### Day-to-day precision

To determine day-to-day precision, a blood sample was spiked with the analytes, processed, and analysed. The material used was the G-EQUAS RV58-5A material used in the interlaboratory comparisons of the German External Quality Assessment Scheme (G-EQUAS). Thirteenfold determination of this blood sample yielded the day-to-day precision data documented in Table 6.

**Tab. 6** Day-to-day precision for the determination of chlorinated hydrocarbons in blood (n = 13)

| Analyte | Spiked concentration [µg/l] | Standard deviation (rel.) $s_w$ [%] | Prognostic range $u$ [%] |
|---|---|---|---|
| Dichloromethane | 94.5 | 9.92 | 21.6 |
| Trichloromethane | 17.5 | 7.00 | 15.3 |
| Tetrachloromethane | 0.680 | 12.9 | 28.0 |
| 1,2-Dichloroethane | 9.20 | 7.71 | 16.8 |
| 1,1,1-Trichloroethane | 172 | 7.43 | 16.2 |
| Trichloroethene | 111 | 7.14 | 15.6 |
| Tetrachloroethene | 148 | 7.84 | 17.1 |

## 11.2 Accuracy

Recovery experiments were performed to determine the accuracy of the method. To this end, blood samples were spiked with three different concentrations of the respective analytes, processed, and analysed. The relative recovery rates thus determined are presented in Table 7.

**Tab. 7** Relative recovery rates for the determination of chlorinated hydrocarbons in blood (n = 8)

| Analyte | Spiked concentration [µg/l] | Measured concentration [µg/l] | Recovery rate (rel.) $r$ [%] |
|---|---|---|---|
| Dichloromethane | 14.1 | 12.5 | 88.7 |
| | 81.3 | 74.7 | 91.8 |
| | 706 | 689 | 97.6 |
| Trichloromethane | 1.64 | 1.46 | 89.0 |
| | 9.45 | 8.67 | 91.7 |
| | 82.1 | 78.1 | 95.2 |
| Tetrachloromethane | 0.338 | 0.254 | 75.2 |
| | 1.94 | 1.54 | 79.3 |
| | 16.9 | 15.0 | 88.8 |
| 1,2-Dichloroethane | 3.01 | 2.59 | 86.0 |
| | 17.3 | 15.6 | 90.0 |
| | 150 | 141 | 93.9 |
| 1,1,1-Trichloroethane | 13.6 | 10.8 | 79.3 |
| | 78.3 | 65.3 | 83.3 |
| | 680 | 619 | 90.9 |
| Trichloroethene | 4.80 | 3.90 | 81.3 |
| | 27.6 | 23.3 | 84.2 |
| | 240 | 204 | 84.9 |
| Tetrachloroethene | 7.91 | 6.27 | 79.3 |
| | 45.6 | 37.8 | 82.9 |
| | 396 | 339 | 85.6 |

## 11.3 Limits of detection and quantitation

The limit of detection was estimated from the threefold signal-to-noise ratio and the limit of quantitation was determined analogously from the ninefold signal-to-noise ratio. The limits of detection and quantitation thus determined are presented in Table 8.

**Tab. 8** Limits of detection and quantitation for the determination of chlorinated hydrocarbons in blood

| Analyte | Detection limit [µg/l] | Quantitation limit [µg/l] |
|---|---|---|
| Dichloromethane | 1.0 | 3.0 |
| Trichloromethane | 0.8 | 2.4 |
| Tetrachloromethane | 0.1 | 0.3 |
| 1,2-Dichloroethane | 0.1 | 0.3 |
| 1,1,1-Trichloroethane | 0.1 | 0.3 |
| Trichloroethene | 0.1 | 0.3 |
| Tetrachloroethene | 0.1 | 0.3 |

## 11.4 Sources of error

When storing the blood samples in the Monovettes® used for blood collection, analyte losses occur due to their volatility. For this reason, when using this method, it is important to ensure that 2 ml of the sample are transferred into headspace vials immediately after blood collection.

The stock and the spiking solution should be kept in vials with as little headspace as possible. Because of the high volatility of the substances, a significant portion of the substance amount in storage vials will be present as vapour in the headspace. Therefore, notable substance losses can result from opening the vials, e.g. for the removal of the spiking solution, if there is a large headspace volume. As a consequence of readjustment of the partition equilibrium, these substance losses also lead to reduced concentrations of the substances in the solution.

Due to the toxicity of the substances, the stock solution of the analytes should be prepared under a fume hood. In the process of external method verification under these conditions, however, consistent weights could not be reached when preparing the stock solution by means of an analytical balance. For this reason, a volumetric dosage of the substances was used in the preparation of the stock solution. Microlitre syringes with maximum volumes of 10 or 100 µl were applied for this reason, as the necessary dosage accuracy could not be achieved with an air-displacement pipette due to the high vapour pressure of the substances. Analyte concentrations in the stock solution were calculated using the density of the pure substances.

# 12 Discussion of the method

The method presented herein permits the reliable determination of dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, 1,1,1-trichloroethane, trichloroethene, and tetrachloroethene in blood. With limits of quantitation ranging from 0.3 to 3 µg/l of blood, the method is characterised both by sensitivity and high precision. The relative standard deviations of the day-to-day precision are in the range of 7.00% to 12.9%, which can be considered good given the fact that no internal standard is used.

In general, no background levels of dichloromethane, trichloromethane, tetrachloromethane, 1,2-dichloroethane, 1,1,1-trichloroethane, trichloroethene, or tetrachloroethene are found in occupationally non-exposed persons. The detection of the analytes in blood therefore always indicates occupational exposure.

**Instruments used** Gas chromatograph with a mass-spectrometric detector (Agilent 5890 A with Agilent 5975 C, Agilent Technologies Germany GmbH & Co. KG, Waldbronn, Germany); headspace autosampler (TurboMatrix HS 40

Trap, PerkinElmer Inc., Rodgau, Germany); capillary gas-chromatography column: 6% cyanopropyl/phenyl, 94% polydimethylsiloxane, 60 m × 0.32 mm × 1.8 µm (Agilent VF 624ms, Agilent Technologies Germany GmbH & Co. KG, Waldbronn, Germany).

# Notes

### Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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