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# Polychlorinated biphenyls (PCBs), hexachlorobenzene (HCB), and dichlorodiphenyltrichloroethane (DDT) – Determination of PCBs, HCB, and dichlorodiphenyldichloroethylene (DDE) in serum/plasma or whole blood by GC-MS

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

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polychlorinated biphenyls, hexachlorobenzene, dichlorodiphenyltrichloroethane, dichlorodiphenyldichloroethylene, plasma, serum, blood, whole blood, GC-MS

## 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 method presented herein enables the sensitive and specific quantification of 21 PCB congeners, HCB, and the DDT metabolite DDE in serum/plasma or whole blood. For determination, formic acid is added to serum/plasma or whole blood samples, which are shaken and thereby homogenised. The analytes are then extracted into isooctane. The silica gel-purified and concentrated extracts are quantified following capillary gas-chromatographic separation by mass-selective detection in SIM mode. Calibration standards are prepared in bovine serum and processed in the same way as the samples to be analysed. PCB 54 and selected $^{13}$C-labelled PCB congeners are used as internal standards.

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# 1 Characteristics of the method

**Matrix** Serum/plasma or whole blood

**Analytical principle** GC-MS

**Parameters and their corresponding hazardous substances**

| Hazardous substance | CAS No. | Parameter | CAS No. |
|---|---|---|---|
| 2,4,4′-Trichlorobiphenyl (PCB 28) | 7012-37-5 | PCB 28 | 7012-37-5 |
| 2,2′,5,5′-Tetrachlorobiphenyl (PCB 52) | 35693-99-3 | PCB 52 | 35693-99-3 |
| 2,3′,4,4′-Tetrachlorobiphenyl (PCB 66) | 32598-10-0 | PCB 66 | 32598-10-0 |
| 2,4,4′,5-Tetrachlorobiphenyl (PCB 74) | 32690-93-0 | PCB 74 | 32690-93-0 |
| 3,3′,4,4′-Tetrachlorobiphenyl (PCB 77) | 32598-13-3 | PCB 77 | 32598-13-3 |
| 3,4,4′,5-Tetrachlorobiphenyl (PCB 81) | 70362-50-4 | PCB 81 | 70362-50-4 |
| 2,2′,4,4′,5-Pentachlorobiphenyl (PCB 99) | 38380-01-7 | PCB 99 | 38380-01-7 |
| 2,2′,4,5,5′-Pentachlorobiphenyl (PCB 101) | 37680-73-2 | PCB 101 | 37680-73-2 |
| 2,3,3′,4,4′-Pentachlorobiphenyl (PCB 105) | 32598-14-4 | PCB 105 | 32598-14-4 |
| 2,3,4,4′,5-Pentachlorobiphenyl (PCB 114) | 74472-37-0 | PCB 114 | 74472-37-0 |
| 2,3′,4,4′,5-Pentachlorobiphenyl (PCB 118) | 31508-00-6 | PCB 118 | 31508-00-6 |
| 2′,3,4,4′,5-Pentachlorobiphenyl (PCB 123) | 65510-44-3 | PCB 123 | 65510-44-3 |
| 3,3′,4,4′,5-Pentachlorobiphenyl (PCB 126) | 57465-28-8 | PCB 126 | 57465-28-8 |
| 2,2′,3,4,4′,5′-Hexachlorobiphenyl (PCB 138) | 35065-28-2 | PCB 138 | 35065-28-2 |
| 2,2′,4,4′,5,5′-Hexachlorobiphenyl (PCB 153) | 35065-27-1 | PCB 153 | 35065-27-1 |
| 2,3,3′,4,4′,5-Hexachlorobiphenyl (PCB 156) | 38380-08-4 | PCB 156 | 38380-08-4 |
| 2,3,3′,4,4′,5′-Hexachlorobiphenyl (PCB 157) | 69782-90-7 | PCB 157 | 69782-90-7 |
| 2,3′,4,4′,5,5′-Hexachlorobiphenyl (PCB 167) | 52663-72-6 | PCB 167 | 52663-72-6 |
| 3,3′,4,4′,5,5′-Hexachlorobiphenyl (PCB 169) | 32774-16-6 | PCB 169 | 32774-16-6 |
| 2,2′,3,4,4′,5,5′-Heptachlorobiphenyl (PCB 180) | 35065-29-3 | PCB 180 | 35065-29-3 |
| 2,3,3′,4,4′,5,5′-Heptachlorobiphenyl (PCB 189) | 39635-31-9 | PCB 189 | 39635-31-9 |
| Hexachlorobenzene (HCB) | 118-74-1 | HCB | 118-74-1 |
| Dichlorodiphenyltrichloroethane (DDT; 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane) | 50-29-3 | Dichlorodiphenyldichloroethylene (DDE; 1-chloro-4-[2,2-dichloro-1-(4-chlorophenyl)ethenyl]benzene) | 72-55-9 |

## Reliability data

### PCB 28

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 4.7\%$ |
| | Prognostic range | $u = 12.1\%$ |
| | at a spiked concentration of 0.4 µg PCB 28 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 4.5\%$ |
| | Prognostic range | $u = 10.0\%$ |
| | at a spiked concentration of 0.4 µg PCB 28 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 99\%$ |
| | at a nominal concentration of 0.4 µg PCB 28 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 28 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 28 per litre of serum | |

### PCB 52

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 2.8\%$ |
| | Prognostic range | $u = 7.2\%$ |
| | at a spiked concentration of 0.4 µg PCB 52 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 3.1\%$ |
| | Prognostic range | $u = 6.9\%$ |
| | at a spiked concentration of 0.4 µg PCB 52 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 97\%$ |
| | at a nominal concentration of 0.4 µg PCB 52 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 52 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 52 per litre of serum | |

## PCB 66

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 4.7\%$ |
| | Prognostic range | $u = 12.1\%$ |
| | at a spiked concentration of 0.4 µg PCB 66 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 2.6\%$ |
| | Prognostic range | $u = 5.8\%$ |
| | at a spiked concentration of 0.4 µg PCB 66 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 100\%$ |
| | at a nominal concentration of 0.4 µg PCB 66 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 66 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 66 per litre of serum | |

## PCB 74

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 4.0\%$ |
| | Prognostic range | $u = 10.3\%$ |
| | at a spiked concentration of 0.4 µg PCB 74 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 2.5\%$ |
| | Prognostic range | $u = 5.6\%$ |
| | at a spiked concentration of 0.4 µg PCB 74 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 100\%$ |
| | at a nominal concentration of 0.4 µg PCB 74 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 74 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 74 per litre of serum | |

## PCB 77

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 4.2\%$ |
| | Prognostic range | $u = 10.8\%$ |
| | at a spiked concentration of 0.4 µg PCB 77 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 2.0\%$ |
| | Prognostic range | $u = 4.5\%$ |
| | at a spiked concentration of 0.4 µg PCB 77 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 95\%$ |
| | at a nominal concentration of 0.4 µg PCB 77 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 77 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 77 per litre of serum | |

## PCB 81

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 4.0\%$ |
| | Prognostic range | $u = 10.3\%$ |
| | at a spiked concentration of 0.4 µg PCB 81 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 1.9\%$ |
| | Prognostic range | $u = 4.2\%$ |
| | at a spiked concentration of 0.4 µg PCB 81 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 96\%$ |
| | at a nominal concentration of 0.4 µg PCB 81 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 81 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 81 per litre of serum | |

## PCB 99

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 5.1\%$ |
| | Prognostic range | $u = 13.1\%$ |
| | at a spiked concentration of 0.4 µg PCB 99 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 3.2\%$ |
| | Prognostic range | $u = 7.1\%$ |
| | at a spiked concentration of 0.4 µg PCB 99 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 97\%$ |
| | at a nominal concentration of 0.4 µg PCB 99 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 99 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 99 per litre of serum | |

## PCB 101

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 3.2\%$ |
| | Prognostic range | $u = 8.2\%$ |
| | at a spiked concentration of 0.4 µg PCB 101 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 3.4\%$ |
| | Prognostic range | $u = 7.6\%$ |
| | at a spiked concentration of 0.4 µg PCB 101 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 96\%$ |
| | at a nominal concentration of 0.4 µg PCB 101 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 101 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 101 per litre of serum | |

## PCB 105

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 5.9\%$ |
| | Prognostic range | $u = 15.2\%$ |
| | at a spiked concentration of 0.4 µg PCB 105 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 2.5\%$ |
| | Prognostic range | $u = 5.6\%$ |
| | at a spiked concentration of 0.4 µg PCB 105 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 95\%$ |
| | at a nominal concentration of 0.4 µg PCB 105 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 105 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 105 per litre of serum | |

## PCB 114

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 3.7\%$ |
| | Prognostic range | $u = 9.5\%$ |
| | at a spiked concentration of 0.4 µg PCB 114 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 1.9\%$ |
| | Prognostic range | $u = 4.2\%$ |
| | at a spiked concentration of 0.4 µg PCB 114 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 97\%$ |
| | at a nominal concentration of 0.4 µg PCB 114 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 114 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 114 per litre of serum | |

## PCB 118

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 5.0\%$ |
| | Prognostic range | $u = 12.8\%$ |
| | at a spiked concentration of 0.4 µg PCB 118 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 2.0\%$ |
| | Prognostic range | $u = 4.5\%$ |
| | at a spiked concentration of 0.4 µg PCB 118 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 96\%$ |
| | at a nominal concentration of 0.4 µg PCB 118 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 118 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 118 per litre of serum | |

## PCB 123

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 5.1\%$ |
| | Prognostic range | $u = 13.1\%$ |
| | at a spiked concentration of 0.4 µg PCB 123 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 2.7\%$ |
| | Prognostic range | $u = 6.0\%$ |
| | at a spiked concentration of 0.4 µg PCB 123 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 98\%$ |
| | at a nominal concentration of 0.4 µg PCB 123 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 123 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 123 per litre of serum | |

## PCB 126

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 4.9\%$ |
| | Prognostic range | $u = 12.6\%$ |
| | at a spiked concentration of 0.4 µg PCB 126 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 1.9\%$ |
| | Prognostic range | $u = 4.2\%$ |
| | at a spiked concentration of 0.4 µg PCB 126 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 96\%$ |
| | at a nominal concentration of 0.4 µg PCB 126 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 126 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 126 per litre of serum | |

## PCB 138

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 4.7\%$ |
| | Prognostic range | $u = 12.1\%$ |
| | at a spiked concentration of 0.4 µg PCB 138 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 3.9\%$ |
| | Prognostic range | $u = 8.7\%$ |
| | at a spiked concentration of 0.4 µg PCB 138 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 95\%$ |
| | at a nominal concentration of 0.4 µg PCB 138 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 138 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 138 per litre of serum | |

## PCB 153

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 3.4\%$ |
| | Prognostic range | $u = 8.7\%$ |
| | at a spiked concentration of 0.4 µg PCB 153 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 4.4\%$ |
| | Prognostic range | $u = 9.8\%$ |
| | at a spiked concentration of 0.4 µg PCB 153 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 95\%$ |
| | at a nominal concentration of 0.4 µg PCB 153 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 153 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 153 per litre of serum | |

## PCB 156

| | | |
|---|---|---|
| Within-day precision | Standard deviation (rel.) | $s_w = 4.5\%$ |
| | Prognostic range | $u = 11.6\%$ |
| | at a spiked concentration of 0.4 µg PCB 156 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 2.2\%$ |
| | Prognostic range | $u = 4.9\%$ |
| | at a spiked concentration of 0.4 µg PCB 156 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 95\%$ |
| | at a nominal concentration of 0.4 µg PCB 156 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 156 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 156 per litre of serum | |

## PCB 157

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 4.3\%$ |
| | Prognostic range | $u = 11.1\%$ |
| | at a spiked concentration of 0.4 µg PCB 157 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 1.1\%$ |
| | Prognostic range | $u = 2.5\%$ |
| | at a spiked concentration of 0.4 µg PCB 157 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 96\%$ |
| | at a nominal concentration of 0.4 µg PCB 157 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 157 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 157 per litre of serum | |

## PCB 167

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 4.1\%$ |
| | Prognostic range | $u = 10.5\%$ |
| | at a spiked concentration of 0.4 µg PCB 167 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 1.6\%$ |
| | Prognostic range | $u = 3.6\%$ |
| | at a spiked concentration of 0.4 µg PCB 167 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 96\%$ |
| | at a nominal concentration of 0.4 µg PCB 167 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 167 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 167 per litre of serum | |

## PCB 169

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 5.7\%$ |
| | Prognostic range | $u = 14.6\%$ |
| | at a spiked concentration of 0.4 µg PCB 169 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 1.1\%$ |
| | Prognostic range | $u = 2.5\%$ |
| | at a spiked concentration of 0.4 µg PCB 169 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 96\%$ |
| | at a nominal concentration of 0.4 µg PCB 169 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 169 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 169 per litre of serum | |

## PCB 180

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 4.6\%$ |
| | Prognostic range | $u = 11.8\%$ |
| | at a spiked concentration of 0.4 µg PCB 180 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 4.1\%$ |
| | Prognostic range | $u = 9.1\%$ |
| | at a spiked concentration of 0.4 µg PCB 180 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 94\%$ |
| | at a nominal concentration of 0.4 µg PCB 180 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 180 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 180 per litre of serum | |

## PCB 189

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 4.7\%$ |
| | Prognostic range | $u = 12.1\%$ |
| | at a spiked concentration of 0.4 µg PCB 189 per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 3.8\%$ |
| | Prognostic range | $u = 8.5\%$ |
| | at a spiked concentration of 0.4 µg PCB 189 per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 98\%$ |
| | at a nominal concentration of 0.4 µg PCB 189 per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg PCB 189 per litre of serum | |
| Quantitation limit: | 0.015 µg PCB 189 per litre of serum | |

## HCB

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 2.0\%$ |
| | Prognostic range | $u = 5.1\%$ |
| | at a spiked concentration of 0.4 µg HCB per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 2.7\%$ |
| | Prognostic range | $u = 6.0\%$ |
| | at a spiked concentration of 0.4 µg HCB per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 96\%$ |
| | at a nominal concentration of 0.4 µg HCB per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg HCB per litre of serum | |
| Quantitation limit: | 0.015 µg HCB per litre of serum | |

**DDE**

| | | |
|---|---|---|
| Within-day precision: | Standard deviation (rel.) | $s_w = 3.8\%$ |
| | Prognostic range | $u = 9.8\%$ |
| | at a spiked concentration of 0.4 µg DDE per litre of serum and n = 6 determinations | |
| Day-to-day precision: | Standard deviation (rel.) | $s_w = 4.7\%$ |
| | Prognostic range | $u = 10.5\%$ |
| | at a spiked concentration of 0.4 µg DDE per litre of serum and n = 12 determinations | |
| Accuracy: | Recovery rate (rel.) | $r = 95\%$ |
| | at a nominal concentration of 0.4 µg DDE per litre of serum and n = 12 determinations | |
| Detection limit: | 0.005 µg DDE per litre of serum | |
| Quantitation limit: | 0.015 µg DDE per litre of serum | |

# 2 General information on the hazardous substances

## Polychlorinated biphenyls (PCBs)

Polychlorinated biphenyls (PCBs) were first synthesised in 1881 by chlorinating biphenyl and have been produced industrially since 1929. This chemical synthesis always results in mixtures of substances that can theoretically consist of up to 209 different PCB congeners which differ in both the number and arrangement of chlorine atoms in the molecule. Usually, about 130–140 different congeners are formed during technical production. Depending on the degree of chlorination, PCBs are light-coloured, viscous liquids, which are mainly characterised by excellent thermal stability and low dielectric constants (UBA 1999). The congener composition of some commercially available PCB mixtures was specified by Frame et al. (1996). Internationally, a simplified distinction is made between the low-chlorinated, more volatile, degradable congeners (≤ 5 chlorine atoms) and the higher-chlorinated, more persistent congeners (≥ 6 chlorine atoms). Figure 1 shows the 21 PCB congeners that can be determined using this analytical method.

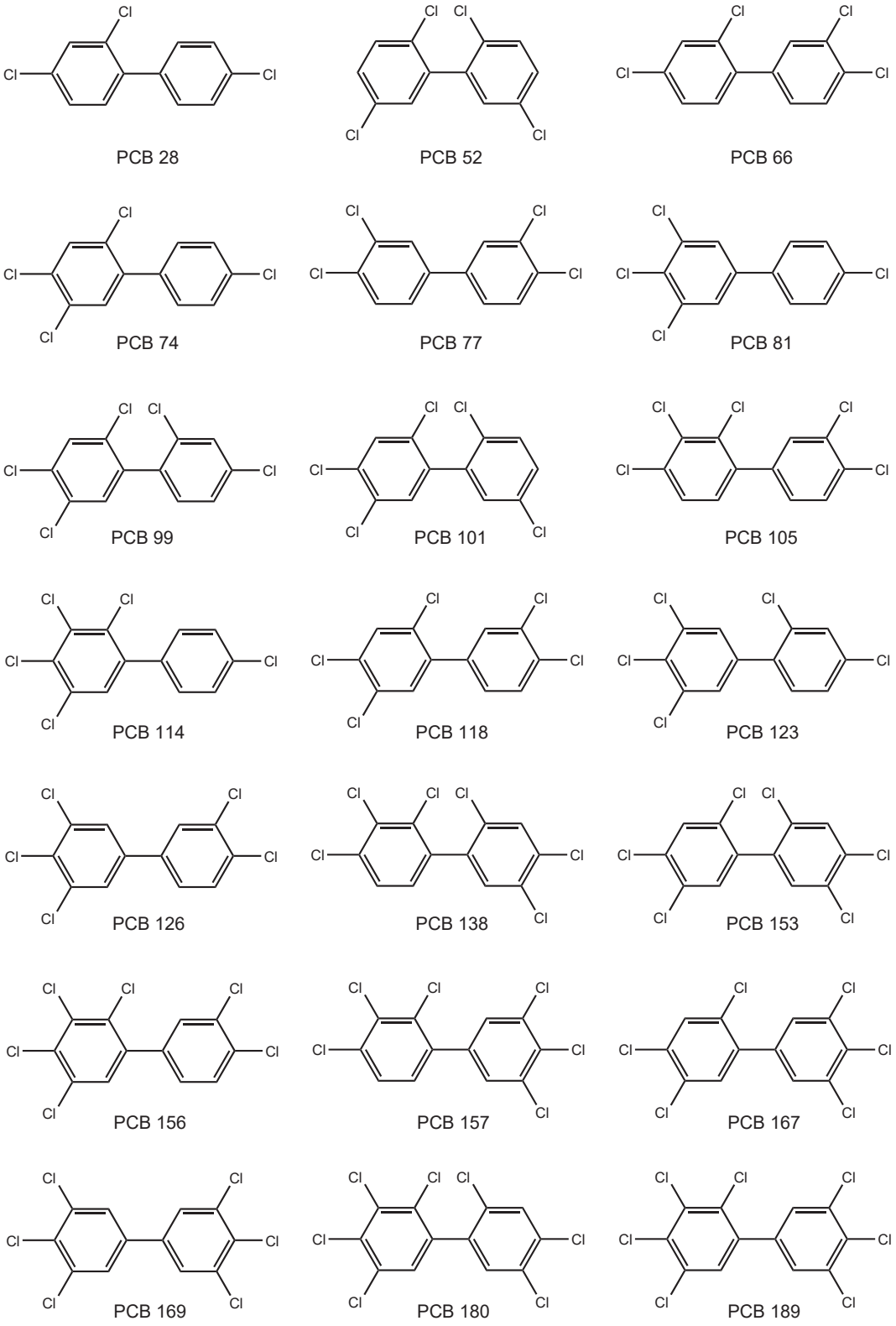


**Fig. 1** Structural formulas of the 21 PCB congeners that can be determined using this method

The Commission has classified the group of PCBs as Category 4 carcinogens and derived a MAK value of 3 µg/m³, determined as the sum of the indicator congeners PCB 28, PCB 52, PCB 101, PCB 138, PCB 153, and PCB 180, multiplied by a factor of five. The PCBs are classified as Category 5 germ cell mutagens and have been designated with an "H" (danger from percutaneous absorption). In addition, PCBs have been classified in Pregnancy Risk Group B (DFG 2020). Further information regarding the prerequisites for classification in Pregnancy Risk Group C can be found in the Commission's BAT Value Documentation on PCBs (Brinkmann et al. 2019). The IARC (International Agency for Research on Cancer) has classified PCBs as carcinogenic to humans (Group 1) (IARC 2016). For details on the toxicological evaluation of PCBs, please refer to the Commission's respective MAK Value Documentations (Greim 1994; Hartwig and MAK Commission 2016 a, b; Henschler 1978).

The high lipophilicity of PCBs in combination with their great stability and consequent low (microbial) degradation rate causes especially higher-chlorinated PCBs to accumulate in all environmental compartments. As PCBs are metabolised very slowly even in animals, they accumulate in fatty tissue and affect humans through the food chain, where they accumulate once more. The extent of their accumulation in fatty tissue is determined by the chemical stability and position of the chlorine atoms in the molecule (UBA 1999). Based on the accumulation in fatty tissue, the individual PCB congeners have different half-lives in blood, ranging from several months to decades, depending on the duration and level of exposure as well as on the number of chlorine substituents and the position of the chlorine atoms in the molecule (Brown et al. 1989; Ryan et al. 1993; Schettgen et al. 2012 a; Seegal et al. 2011; Yakushiji et al. 1984).

Food is the main source of exposure to PCBs in individuals who are not occupationally exposed to PCBs. In particular, animal-based foods with a high fat content are considered one of the main sources of exposure to PCBs in the general population (UBA 1999). This dietary intake results in age-related background exposure, which mainly affects the higher-chlorinated PCB congeners (≥ 6 chlorine atoms) and which has been quantified in various studies (Schettgen et al. 2011; UBA 1999, 2003, 2009).

The high persistence of PCBs led to a ban on PCB production in the U.S. at the end of the 1970s. The manufacture, sale, import, and export of PCB-containing products was finally banned in Germany in 1989 under the German *Gefahrstoffverordnung* (Ordinance on Hazardous Substances). The Stockholm Convention on Persistent Organic Pollutants (POP) came into effect in 2004, banning the production and subsequent use of PCBs worldwide. As a result of this ban, residual PCBs are now the main sources of exposure to PCBs in the workplace. PCBs were used in closed systems as hydraulic fluids in mining, as coolants in transformers, and as dielectrics in capacitors. "Open" applications of PCBs include the formerly common use as plasticisers and flame retardants in paints, paint resins, and plastics; as in lubricants and cutting oils; as additives in sealants, cements, fillers; as flame protection coating of pressboards; and as heat-exchange fluids (UBA 1999).

In addition to inhalation, the main routes of exposure for persons occupationally exposed to PCBs are dermal absorption and possible peroral ingestion. A lack of workplace hygiene, under certain circumstances, can cause PCBs to be transferred into the domestic environment and lead to additional internal exposure in relatives (Kaifie et al. 2019; Schettgen et al. 2012 b). PCBs can be readily absorbed through the skin. Recent studies show that especially lower-chlorinated PCB congeners (≤ 5 chlorine atoms) can penetrate the skin quickly and effectively compared with higher-chlorinated congeners (Dennerlein et al. 2013).

The use of PCBs in the construction of buildings leads to indoor air pollution due to degassing from PCB-containing materials. However, due to the different vapour pressures of the individual congeners, this pollution is mainly caused by the more volatile low-chlorinated PCB congeners (≤ 5 chlorine atoms) (Meyer et al. 2013).

To assess internal exposure to PCBs in the workplace, the Commission has derived a biological tolerance value (BAT, *Biologischer Arbeitsstoff-Toleranzwert*) of 15 µg/l plasma, as a sum parameter for the indicator congeners PCB 28, PCB 52, PCB 101, PCB 138, PCB 153, and PCB 180 (Rettenmeier et al. 2017). In addition, the Commission has established biological reference values (BAR, *Biologischer Arbeitsstoff-Referenzwert*) for the general population's

background exposure to the low-chlorinated PCB indicator congeners (Kraus and Rettenmeier 2019; see Table 1). Due to the long half-lives of PCBs, there are no restrictions as to the time of sampling.

**Tab. 1** Biological reference values for low-chlorinated PCBs

| Indicator congener | BAR [µg/l plasma] |
|---|---|
| PCB 28 | 0.02 |
| PCB 52 | < 0.01 |
| PCB 101 | < 0.01 |

Knowledge of the general population's background exposure is an essential prerequisite for the assessment of possible additional exposure to higher-chlorinated PCBs in the context of (previous) occupational or environmental exposure. The temporal trend of internal exposure to higher-chlorinated PCBs (PCB 138, PCB 153, PCB 180) in the German adult population was surveyed annually by the UBA (*Umweltbundesamt*; German Environment Agency) between 1997 and 2010. For all three indicator PCBs, a significant decrease in the measured levels was observed over time (UBA 2016).

The internal exposure of a very large collective of the general population to HCB, DDE, and higher-chlorinated PCBs was investigated when applying this method (see Table 2). These plasma samples were collected from individuals residing in Germany (North Rhine-Westphalia and Hesse) and were sampled between September 2010 and March 2014. Although not strictly representative in the sense of an environmental survey, these data provide an updated basis for the assessment of individual human biomonitoring data (Schettgen et al. 2015).

**Tab. 2** Age-related background exposure in the German general population to HCB, DDE, PCB 138, PCB 153, and PCB 180 between 2010 and 2014 (according to Schettgen et al. 2015)

| Age [years] | 6–10 (n = 102) | 11–17 (n = 499) | 18–25 (n = 157) | 26–35 (n = 710) | 36–45 (n = 400) | 46–55 (n = 525) | 56–65 (n = 357) |
|---|---|---|---|---|---|---|---|
| **HCB [µg/l plasma]** | | | | | | | |
| Median | 0.05 | 0.06 | 0.08 | 0.08 | 0.11 | 0.14 | 0.20 |
| **95$^{th}$ percentile** | **0.10** | **0.11** | **0.15** | **0.15** | **0.22** | **0.42** | **0.68** |
| Maximum | 0.12 | 0.27 | 0.19 | 0.55 | 0.99 | 1.2 | 3.4 |
| **DDE [µg/l plasma]** | | | | | | | |
| Median | 0.18 | 0.18 | 0.24 | 0.30 | 0.45 | 0.64 | 0.94 |
| **95$^{th}$ percentile** | **1.24** | **0.74** | **0.85** | **1.20** | **1.74** | **3.3** | **4.7** |
| Maximum | 3.5 | 9.1 | 3.1 | 22.5 | 10.0 | 30.4 | 37.3 |
| **PCB 138 [µg/l plasma]** | | | | | | | |
| Median | 0.05 | 0.09 | 0.12 | 0.15 | 0.24 | 0.39 | 0.56 |
| **95$^{th}$ percentile** | **0.22** | **0.23** | **0.25** | **0.33** | **0.53** | **0.93** | **1.3** |
| Maximum | 0.37 | 0.40 | 0.58 | 0.71 | 1.1 | 1.7 | 4.0 |

**Tab. 2** *(continued)*

| Age [years] | 6–10 (n = 102) | 11–17 (n = 499) | 18–25 (n = 157) | 26–35 (n = 710) | 36–45 (n = 400) | 46–55 (n = 525) | 56–65 (n = 357) |
|---|---|---|---|---|---|---|---|
| **PCB 153 [µg/l plasma]** | | | | | | | |
| Median | 0.06 | 0.13 | 0.17 | 0.21 | 0.37 | 0.63 | 0.92 |
| **95$^{th}$ percentile** | **0.32** | **0.35** | **0.38** | **0.49** | **0.79** | **1.4** | **1.9** |
| Maximum | 0.57 | 0.58 | 0.84 | 0.89 | 1.6 | 2.7 | 5.5 |
| **PCB 180 [µg/l plasma]** | | | | | | | |
| Median | 0.03 | 0.07 | 0.10 | 0.14 | 0.29 | 0.57 | 0.87 |
| **95$^{th}$ percentile** | **0.19** | **0.25** | **0.29** | **0.34** | **0.65** | **1.2** | **1.9** |
| Maximum | 0.43 | 0.65 | 0.40 | 0.77 | 1.4 | 4.6 | 9.1 |

For the toxicological evaluation of PCBs, the dioxin-like congeners are of particular importance. As these twelve congeners contain either no or only one chlorine atom in the *ortho* position of the biphenyl bond, these congeners can adopt a coplanar, dioxin-like spatial structure and thus develop effects toxicologically similar to those of tetrachlorodibenzodioxin (TCDD).

In order to assess the different potencies of these dioxin-like congeners, the WHO has evaluated toxic equivalency factors (TEFs) for these PCB congeners, taking into account the relative potency of each congener with respect to 2,3,7,8-TCDD (TEF = 1) (van den Berg 2006). Table 3 gives an overview of the dioxin-like PCB congeners and their corresponding toxic equivalence factors.

**Tab. 3** Overview of dioxin-like PCB congeners and their toxic equivalence factors (TEFs)

| PCB congener | IUPAC name | Molar mass [g/mol] | TEF |
|---|---|---|---|
| PCB 77 | 3,3′,4,4′-Tetrachlorobiphenyl | 292.0 | 0.0001 |
| PCB 81 | 3,4,4′,5-Tetrachlorobiphenyl | 292.0 | 0.0003 |
| PCB 105 | 2,3,3′,4,4′-Pentachlorobiphenyl | 326.4 | 0.00003 |
| PCB 114 | 2,3,4,4′,5-Pentachlorobiphenyl | 326.4 | 0.00003 |
| PCB 118 | 2,3′,4,4′,5-Pentachlorobiphenyl | 326.4 | 0.00003 |
| PCB 123 | 2′,3,4,4′,5-Pentachlorobiphenyl | 326.4 | 0.00003 |
| PCB 126 | 3,3′,4,4′,5-Pentachlorobiphenyl | 326.4 | 0.1 |
| PCB 156 | 2,3,3′,4,4′,5-Hexachlorobiphenyl | 360.9 | 0.00003 |
| PCB 157 | 2,3,3′,4,4′,5′-Hexachlorobiphenyl | 360.9 | 0.00003 |
| PCB 167 | 2,3′,4,4′,5,5′-Hexachlorobiphenyl | 360.9 | 0.00003 |
| PCB 169 | 3,3′,4,4′,5,5′-Hexachlorobiphenyl | 360.9 | 0.03 |
| PCB 189 | 2,3,3′,4,4′,5,5′-Heptachlorobiphenyl | 395.3 | 0.00003 |

First data on background levels of dioxin-like PCBs in the German general population were obtained using this method on plasma samples of a collective from 2004 and published (Schettgen et al. 2011).

## HCB and DDT

Organochlorine compounds such as hexachlorobenzene (HCB) and the well-known insecticide dichlorodiphenyltrichloroethane (DDT) have been banned worldwide since 2004 under the 2001 Stockholm Convention. Both com-

pounds and dichlorodiphenyldichloroethylene (DDE) (see Figure 2), as metabolite of DDT, are highly persistent in the environment, and have been linked to endocrine and reproductive toxicity effects in various epidemiological studies (Chevrier et al. 2008; Longnecker et al. 2007).

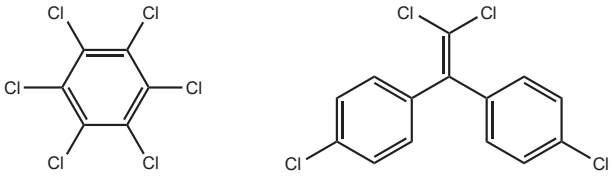


**Fig. 2** Structural formulas of HCB and DDE

HCB was formerly used as a fungicide for sowing grains as well as in pyrotechnics. Despite the ban on its use, exposure to HCB in the workplace is still possible as HCB is formed in large quantities during the production of chlorinated solvents (Greim 2001; IARC 2001). In addition, as a persistent substance, HCB is degraded very slowly in the environment; its biodegradation half-life spans across decades (IARC 2001).

HCB has been classified as a Category 4 carcinogen and designated with an "H" (danger from percutaneous absorption) by the Commission (DFG 2020). The IARC has classified HCB as possibly carcinogenic to humans (Group 2B). For details on the toxicological evaluation of HCB, please refer to the respective MAK Value Documentations and the IARC monograph (Greim 2001, 2002; IARC 2001).

HCB is a very lipophilic substance that accumulates in fatty tissue, and has a biological half-life in humans of two to eight years (Greim 2001; IARC 2001). With respect to occupational exposure, inhalation and percutaneous absorption are the main routes of uptake. Biotransformation of HCB takes place primarily in the liver, with pentachlorophenol being formed as the main metabolite in both humans and animals. In addition, HCB is metabolised into a variety of other chlorophenols and chlorobenzenes. The metabolites are excreted primarily with the faeces and urine (IARC 2001; Lewalter and Reuter 2005; Schumacher-Wittkopf and Lehnert 1995). The Commission recommends the determination of HCB in serum or plasma for the biomonitoring of HCB and has established a BAT value of 150 µg/l for HCB. Due to the long half-life of HCB, sampling time is not restricted (Lewalter and Reuter 2005).

DDT had been applied worldwide as an insecticide for a long time until its usage was significantly restricted or banned in most Western industrialised countries in the early 1970s due to toxicological concerns. Today, the production and use of DDT is only permitted in exceptional cases to control disease-transmitting insects, especially the vectors of malaria. DDT is very persistent in the environment. The biodegradation half-lives of DDT and its metabolites are about 30 years in soil. In bodies of water, these half-lives are even longer (IARC 2018).

For DDT, the Commission has established a MAK value of 1 mg/m$^3$ and a designation with "H" (danger of percutaneous absorption) (DFG 2020). The IARC has classified DDT as probably carcinogenic to humans (Group 2A). For details on the toxicological evaluation of DDT, please refer to the IARC monograph (IARC 2018).

DDT is readily absorbed via inhalative, dermal, and oral route. Due to its high lipophilicity, DDT accumulates primarily in fatty tissue. The biological half-life of DDT in humans is estimated to be about five years. The half-life of the metabolite DDE is even longer at about nine years (IARC 2018). The high persistence of both substances leads to an age-dependent accumulation in fatty tissue, which is reflected in both blood and plasma concentrations.

Since the two pesticides were banned in Germany many years ago (HCB: 1981; DDT: 1972 (West), 1991 (East)), the concentrations of both substances in the environment have declined significantly. The prolonged use of DDT in

Eastern Germany has led to an increased internal exposure to the metabolite DDE in the East German population, which is also reflected in the reference values of the German Environment Agency (UBA 2003, 2009). However, due to the general decline in exposure, the reference values established at that time can no longer be reliably used to assess current exposure (see Table 2).

# 3 General principles

The method presented herein enables the sensitive and specific quantification of 21 PCB congeners, HCB, and the DDT metabolite DDE in serum/plasma or whole blood. For determination, formic acid is added to serum/plasma or blood samples, which are shaken and thereby homogenised. The analytes are then extracted into isooctane. The silica gel-purified and concentrated extracts are quantified following capillary gas-chromatographic separation by mass-selective detection in SIM mode. Calibration standards are prepared in bovine serum and processed in the same way as the samples to be analysed. PCB 54 and selected $^{13}$C-labelled PCB congeners are used as internal standards (ISTD).

# 4 Equipment, chemicals, and solutions

## 4.1 Equipment

- Gas chromatograph with a split/splitless injector, mass-selective detector, and data-processing system (e.g. M-L Tech Mess- & Labortechnik GmbH, Hohenfels-Liggersdorf, Germany)
- 10-µl syringe for gas chromatography, preferably autosampler (e.g. Agilent Technologies Deutschland GmbH, Waldbronn, Germany)
- Capillary gas-chromatography column: HP-5MS (95%-dimethyl-5%-diphenylpolysiloxane), length: 60 m; inner diameter: 0.25 mm; film thickness: 0.25 µm (e.g. Agilent Technologies Deutschland GmbH, Waldbronn, Germany, No. 19091S-436)
- Heating and drying oven, heatable up to at least 200 °C (e.g. HORO Dr. Hofmann GmbH, Ostfildern, Germany)
- Solid-phase extraction vacuum manifold (e.g. VacElut, Agilent Technologies Deutschland GmbH, Waldbronn, Germany)
- Nitrogen evaporator (e.g. Biotage AB, Uppsala, Sweden)
- Laboratory centrifuge (e.g. Megafuge™, Heraeus Deutschland GmbH & Co. KG, Hanau, Germany)
- Laboratory shaker (e.g. Köttermann GmbH, Uetze, Germany)
- Vortex mixer (e.g. Heidolph Instruments GmbH & Co. KG, Schwabach, Germany)
- 10-ml glas vials with screw caps and PTFE septa (e.g. VWR International GmbH, Darmstadt, Germany, No. 2121670)
- 6-ml screw-neck vials with caps and aluminium-lined septa (e.g. VWR International GmbH, Darmstadt, Germany)
- 3-ml glass cartridges for solid-phase extraction (e.g. Waters GmbH, Eschborn, Germany)
- PTFE frits for the 3-ml glass cartridges (e.g. VWR International GmbH, Darmstadt, Germany, No. 7329-03)
- 1.8-ml crimp-neck vials with PTFE septa and crimp caps (e.g. MACHEREY-NAGEL GmbH & Co. KG, Düren, Germany)

- 200-µl micro-inserts for crimp-neck vials (e.g. MACHEREY-NAGEL GmbH & Co. KG, Düren, Germany)
- Glass pasteur pipettes (e.g. Eppendorf AG, Hamburg, Germany)
- Variably adjustable microlitre pipettes (e.g. Eppendorf AG, Hamburg, Germany)
- Various beakers and volumetric flasks (e.g. Brand GmbH & Co. KG, Wertheim, Germany)
- Separatory funnel (e.g. VWR International GmbH, Darmstadt, Germany)
- 250-ml amber glass bottles with ground joint (e.g. VWR International GmbH, Darmstadt, Germany)
- Serum Monovettes® (e.g. Sarstedt AG & Co. KG, Nümbrecht, Germany)

## 4.2 Chemicals

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

- PCB standard solution 1 (10 mg/l each of PCB 28, 52, 101, 138, 153, and 180 in isooctane) (e.g. PCB-Mix 1, Dr. Ehrenstorfer GmbH, Augsburg, Germany, No. L20030100IO)
- PCB standard solution 2 (10 mg/l each of PCB 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, and 189 in isooctane) (e.g. PCB-Mix 41, Dr. Ehrenstorfer GmbH, Augsburg, Germany, No. LA20034100IO)
- PCB 54 (10 mg/l in isooctane) (e.g. Dr. Ehrenstorfer GmbH, Augsburg, Germany, No. L20005400IO)
- PCB 66 (10 mg/l in isooctane) (e.g. Dr. Ehrenstorfer GmbH, Augsburg, Germany, No. L20006600IO)
- PCB 74 (10 mg/l in isooctane) (e.g. Dr. Ehrenstorfer GmbH, Augsburg, Germany, No. L20007400IO)
- PCB 99 (10 mg/l in isooctane) (e.g. Dr. Ehrenstorfer GmbH, Augsburg, Germany, No. L20009900IO)
- $^{13}C_{12}$-PCB ISTD solution 1 (1 mg/l each of $^{13}C_{12}$-PCB 105, 114, 118, 123, 156, 157, 167, and 189 in nonane) (e.g. Mono-Ortho PCB Mixture, Cambridge Isotope Laboratories, Inc., Tewksbury, USA, No. EC-4188)
- $^{13}C_{12}$-PCB ISTD solution 2 (1 mg/l each of $^{13}C_{12}$-PCB 77, 81, 126, and 169 in nonane) (e.g. Co-Planar PCB-Mix, Cambridge Isotope Laboratories, Inc., Tewksbury, USA, No. EC-4187)
- Hexachlorobenzene (e.g. Merck KGaA, Darmstadt, Germany, No. 45522)
- DDE (e.g. Merck KGaA, Darmstadt, Germany, No. 35487)
- Isooctane (e.g. Merck KGaA, Darmstadt, Germany, No. 115440)
- Petroleum benzine, boiling range 40–60 °C (e.g. Merck KGaA, Darmstadt, Germany, No. 101772)
- Formic acid, 98–100% (e.g. Merck KGaA, Darmstadt, Germany, No. 111670)
- Ethanol, absolute (e.g. Merck KGaA, Darmstadt, Germany, No. 100983)
- Methanol (e.g. Merck KGaA, Darmstadt, Germany, No. 34860)
- Acetone (e.g. Merck KGaA, Darmstadt, Germany, No. 179124)
- Ethoxyethanol (e.g. Merck KGaA, Darmstadt, Germany, No. 128082)
- Ultra-pure water (e.g. Merck KGaA, Darmstadt, Germany, No. 270733)
- Silica gel (e.g. Merck KGaA, Darmstadt, Germany, No. 60741)

- Sodium sulphate, anhydrous (e.g. Merck KGaA, Darmstadt, Germany, No. 1.06649)
- Bovine serum, sterile, inactivated (e.g. ACILA AG, Weiterstadt, Germany, No. 2203-010)
- Helium 5.0 (e.g. Linde GmbH, Pullach, Germany)

## 4.3 Solutions

- Purified formic acid

  Place 100 ml of formic acid in a 250-ml separatory funnel and add 100 ml of petroleum benzine. Shake the mixture thoroughly for five minutes. After phase separation, transfer the lower formic acid phase into a 250-ml amber glass bottle and add an overlay of fresh petroleum benzine.

  When stored at room temperature, the purified formic acid is stable for a maximum of one week.

- 0.9% sodium chloride solution

  Weigh out exactly 4.5 g of sodium chloride, place it in a 500-ml volumetric flask, and dissolve it in ultra-pure water. Make up to the mark with ultra-pure water.

  When stored at room temperature, the solution is stable for at least six months.

## 4.4 Internal standards (ISTD)

- ISTD spiking solution

  Transfer 200 µl of the commercially available starting-solution of the ISTD PCB 54 (10 mg/l in isooctane) into a 200-ml volumetric flask which has been pre-rinsed with methanol and acetone and baked out. Add 200 µl each of the solutions of the $^{13}C_{12}$-labelled PCBs (1 mg/l each in nonane). Make up to the mark with isooctane. The concentration of the ISTD PCB 54 is 10 µg/l, and that of the $^{13}C_{12}$-labelled PCBs is 1 µg/l each.

The ISTD spiking solution is stored at room temperature in a sealed 250-ml amber glass bottle with ground joint in a fume hood. Under these conditions, it is stable for at least eight weeks.

## 4.5 Calibration standards

- HCB and DDE stock solution (1000 mg/l)

  Weigh out exactly 10 mg each of HCB and DDE, place them in 10-ml volumetric flasks, and dissolve them in ethanol. Make up to the mark with ethanol.

- PCB stock solution (1 mg/l)

  Transfer 500 µl each of the two commercially available PCB standard solutions and 500 µl each of the standard solutions of PCB 66, PCB 74, and PCB 99 (10 mg/l each in isooctane) into a 5-ml volumetric flask. Make up to the mark with ethoxyethanol.

The stock solutions are stored in amber glass vials with screw caps and Teflon-lined septa at −20 °C. Under these conditions, they are stable for at least six months.

- HCB and DDE working solution 1 (100 mg/l)

  Transfer 1 ml each of the stock solutions of HCB and DDE into a 10-ml volumetric flask. Make up to the mark with ethoxyethanol.

- HCB and DDE working solution 2 (1 mg/l)

  Place approximately 30 ml of ethanol into a 50-ml volumetric flask and add 500 µl of working solution 1 using a pipette. Make up to the mark with the 0.9% sodium chloride solution.

  The solution cannot be stored and must be prepared fresh every workday.

- Spiking solution (100 µg/l)

  Pipette 2 ml of the PCB stock solution and 2 ml of HCB/DDE working solution 2 into a 20-ml volumetric flask. Make up to the mark with ethanol.

  The solution cannot be stored and must be prepared fresh every workday.

Calibration standards in a concentration range between 0.04 and 3 µg/l are prepared by diluting the spiking solution with commercially available bovine serum according to the pipetting scheme shown in Table 4. The bovine serum used is included as a blank. In addition, a reagent blank consisting of purified formic acid is included in each analytical run.

**Tab. 4** Pipetting scheme for the preparation of calibration standards in bovine serum

| Calibration standard | Spiking solution [µl] | Final volume [ml] | Analyte conc. [µg/l] |
|---|---|---|---|
| 0 | 0 | 25 | 0 |
| 1 | 10 | 25 | 0.04 |
| 2 | 25 | 25 | 0.10 |
| 3 | 75 | 25 | 0.30 |
| 4 | 250 | 25 | 1.0 |
| 5 | 750 | 25 | 3.0 |

The calibration standards are aliquoted (2.2 ml each) into 6-ml screw-neck vials and can be stored at −20 °C for at least six months without any loss of analytes.

# 5 Specimen collection and sample preparation

All glassware is rinsed thoroughly with methanol and acetone prior to use and then baked out in a heating and drying oven at 170 °C for at least 16 hours. Care must be taken throughout the analysis to avoid carryover or contamination. For this reason, only properly cleaned glassware should be used and multipette tips should never be used more than once.

## 5.1 Specimen collection

Using a disposable blood-collection system with an anticoagulant additive (e.g. EDTA-K Monovettes®), approximately 5–8 ml blood are drawn by slow aspiration, preferably from the arm vein. If the analysis is performed in plasma, the latter must be obtained by centrifugation (10 minutes at 3500 × *g*) within 24 hours of blood collection.

In order to avoid substance losses by adsorption, the blood or plasma sample should be transferred to a (pre-rinsed and baked out) 6-ml screw-neck vial using a heated pasteur pipette shortly after sampling. The sample can then be stored at −20 °C for at least two years without any loss of analytes. If this cannot be done immediately, the blood sample can be stored in the refrigerator at 4 °C for a maximum of two days.

## 5.2 Sample preparation

For conditioning, the silica gel is activated in a glass bottle for at least 24 hours at 170 °C in a heating and drying oven. Prior to use, the glass bottle is removed and the silica gel is allowed to cool to room temperature.

Before analysis, the blood or plasma samples are thawed at room temperature and thoroughly mixed. Into a 10-ml screw-neck vial, 2 ml of the sample are pipetted, and 2 ml of purified formic acid are added. The sample is then briefly vortex-mixed and 1000 µl of the ISTD spiking solution, which is also used as an extraction solution, are added using a multipette. Afterwards, the vial is sealed, the solution is briefly vortex-mixed, and then shaken for 10 minutes on the laboratory shaker at maximum speed. The subsequent phase separation is performed by centrifugation (10 minutes, 1300 × *g*).

To prepare the silica-gel columns, the 3-ml glass cartridges are rinsed with methanol and acetone, and baked out in a heating and drying oven at 170 °C. After cooling, a PTFE frit is inserted into the column and the column is filled with approximately 700 mg of the conditioned silica gel. A spatula tip of sodium sulphate is then added to the silica gel. The column is first washed with 5 ml of petroleum benzine, then 900 µl of the organic sample phase is transferred onto the column using a baked-out pasteur pipette. Subsequently, the analytes are eluted with 10 ml of petroleum benzine into a new, baked-out 10-ml screw-neck vial. If necessary, the pump of the vacuum manifold can be switched on for a short time.

The eluate is then evaporated to approximately 1 ml under a gentle stream of nitrogen. The sample solution is transferred to a 1.8-ml crimp-neck vial using a baked-out Pasteur pipette. Subsequently, the solution is further reduced to about 100 µl under a stream of nitrogen. As a keeper, 40 µl of isooctane are then added and the sample is transferred into a micro-insert, where it is further evaporated to approximately 30 µl. For each evaporation step, it is recommended to mark reference vials with the correct final volume and place them next to the sample vials to serve as a comparison. The crimp-cap vial is sealed and can then be used for analysis by GC-MS.

# 6 Operational parameters

## 6.1 Gas chromatography

| | | |
|---|---|---|
| Capillary column: | Stationary phase: | HP 5-MS (95%-dimethyl-5%-diphenylpolysiloxane) |
| | Length: | 60 m |
| | Inner diameter: | 0.25 mm |
| | Film thickness: | 0.25 µm |
| Temperatures: | Column: | Initial temperature 80 °C, 1.5 min isothermal; increase at a rate of 25 °C/min to 120 °C; 1.5 min isothermal; increase at a rate of 15 °C/min to 234 °C; then increase at a rate of 2 °C/min to 250 °C, then increase at a rate of 7 °C/min to 310 °C, 13 minutes at final temperature |
| | Injector: | 265 °C |
| | Transfer line: | 310 °C |
| Carrier gas: | Helium 5.0 | |
| Flow rate: | 1.0 ml/min, constant | |
| Injection: | 1 µl splitless, split valve opened after 1.5 min | |

## 6.2 Mass spectrometry

| | |
|---|---|
| Ionisation mode: | Electron ionisation (EI) |
| Ionisation energy: | 70 eV |
| Dwell time: | 50–100 ms |
| Electron multiplier: | 2400–2600 V |
| Detection mode: | SIM (single ion monitoring) |
| Parameter-specific settings: | see Table 5 |

**Tab. 5** Parameter-specific settings and retention times of analytes and ISTDs

| Analyte | Retention time [min] | Quantifier ion [*m/z*] | Qualifier ion [*m/z*] | Quantifier $^{13}C_{12}$-ISTD [*m/z*] |
|---|---|---|---|---|
| HCB | 14.56 | 284 | 286 | – |
| PCB 54 (ISTD) | 15.89 | 292 | 290 | – |
| PCB 28 | 16.14 | 256 | 258 | – |
| PCB 52 | 16.92 | 292 | 290 | – |
| PCB 74 | 18.48 | 292 | 290 | – |
| PCB 66 | 18.71 | 292 | 290 | – |
| PCB 101 | 19.39 | 326 | 328 | – |
| PCB 99 | 19.58 | 326 | 328 | – |
| 4,4′-DDE | 20.32 | 246 | 318 | – |
| PCB 81 | 20.37 | 292 | 290 | 304 |
| PCB 77 | 20.72 | 292 | 290 | 304 |
| PCB 123 | 21.49 | 326 | 328 | 338 |
| PCB 118 | 21.56 | 326 | 328 | 338 |
| PCB 114 | 22.00 | 326 | 328 | 338 |
| PCB 153 | 22.31 | 360 | 362 | – |
| PCB 105 | 22.52 | 326 | 328 | 338 |
| PCB 138 | 23.30 | 360 | 362 | – |
| PCB 126 | 23.62 | 326 | 328 | 338 |
| PCB 167 | 24.23 | 360 | 362 | 372 |
| PCB 156 | 25.02 | 360 | 362 | 372 |
| PCB 157 | 25.20 | 360 | 362 | 372 |
| PCB 180 | 25.53 | 394 | 396 | – |
| PCB 169 | 26.21 | 360 | 362 | 372 |
| PCB 189 | 27.36 | 394 | 396 | 406 |

All settings are instrument-specific and must be adjusted individually by the user. The parameters given are therefore intended as cursory guidance only. All other parameters must be optimised in accordance with the manufacturer's specifications.

# 7 Analytical determination

For the analytical determination, 1 µl each of the samples prepared as described in Section 5.2 is injected into the GC-MS system. Identification of the analytes is based on their retention times and characteristic ion traces. At least two quality-control samples and one reagent blank are included in each analytical run. The temporal profiles of the ion traces shown in Table 5 are recorded in SIM mode.

The retention times given in Table 5 are intended only as a point of reference. Users must ensure proper separation performance of the capillary column and the consequent retention behaviour of the analytes. Figures 3 to 8 show representative chromatograms of a processed standard in bovine serum.

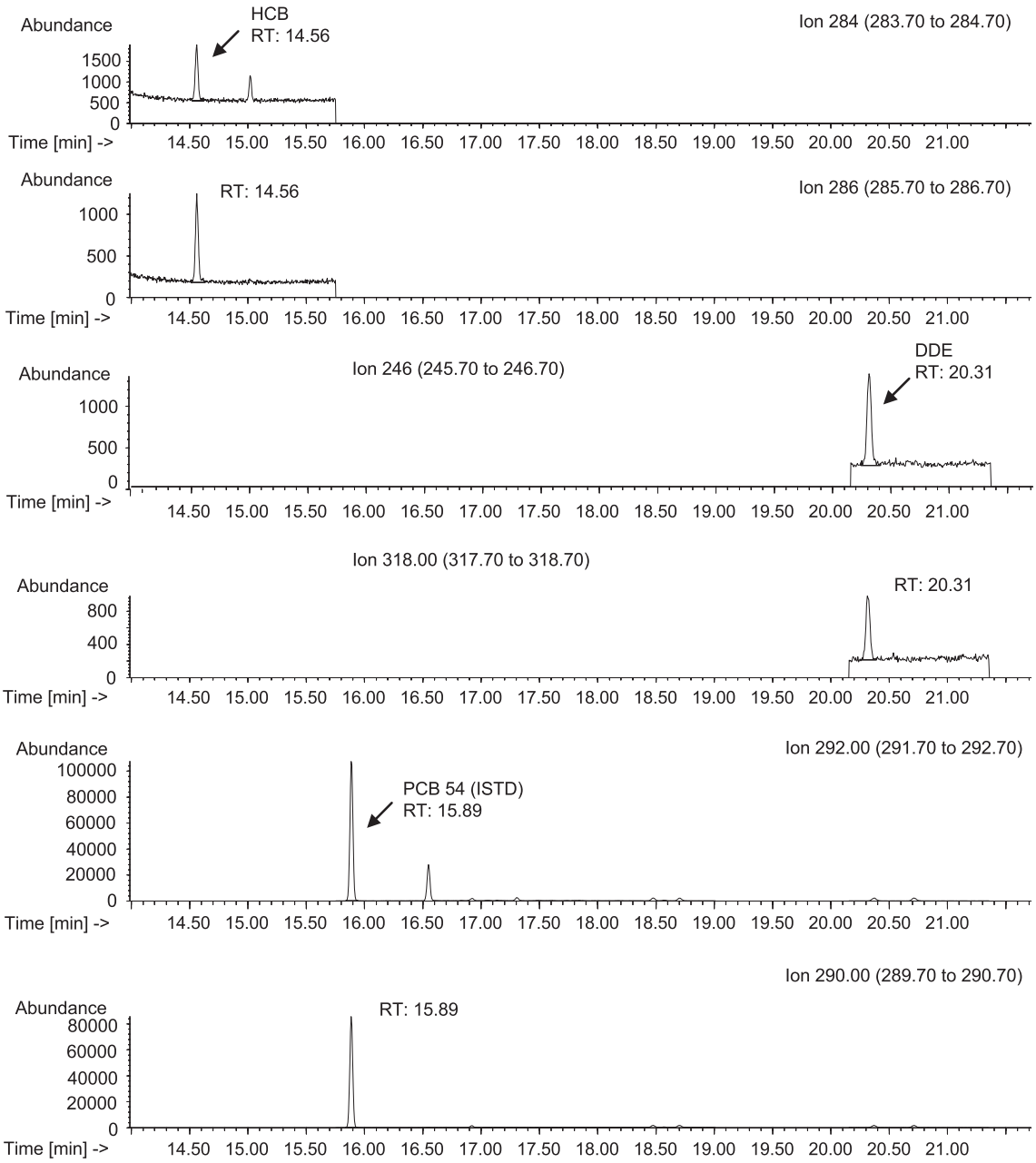


**Fig. 3** Chromatogram of a processed standard in bovine serum with a spiked concentration of 0.04 µg/l (HCB, DDE) and PCB 54 (ISTD)

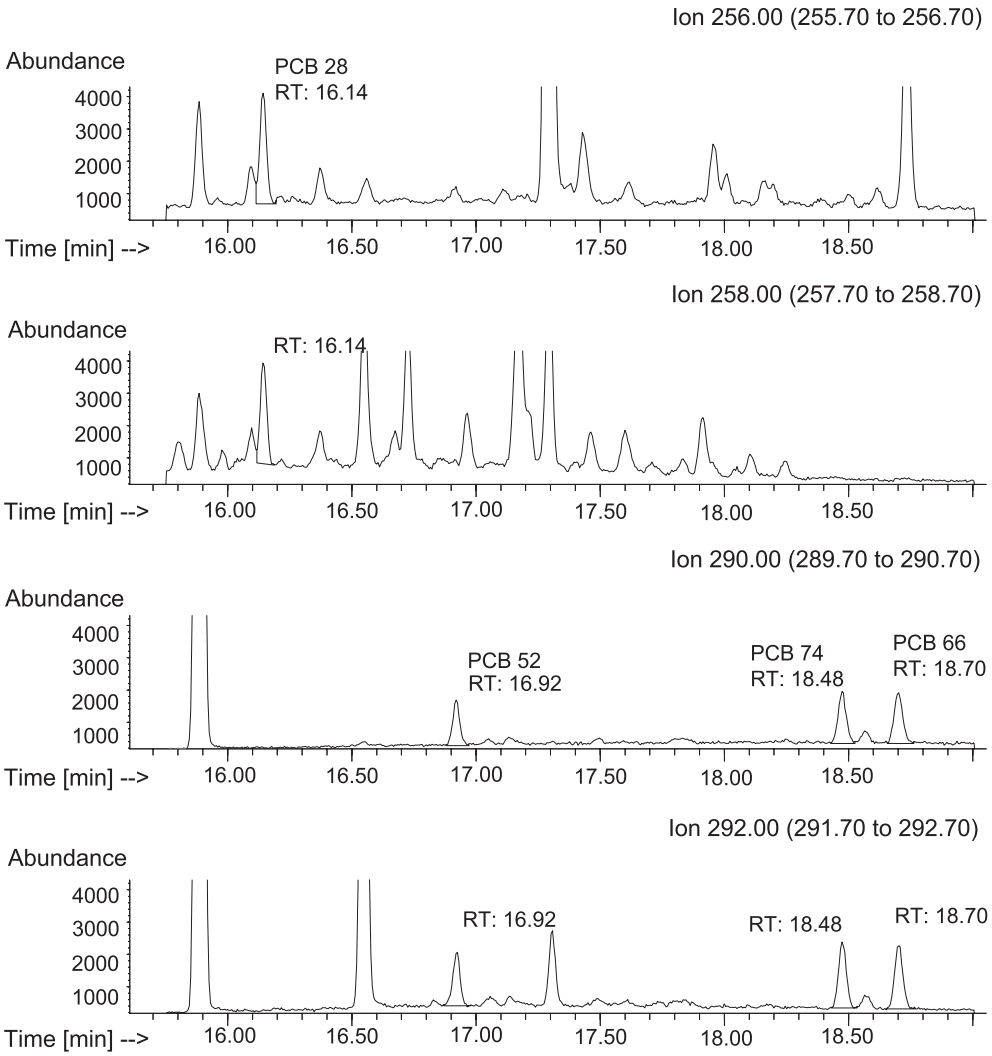


**Fig. 4** Chromatogram of a processed standard in bovine serum with a spiked concentration of 0.04 µg/l (PCB 28, PCB 52, PCB 66, and PCB 74)

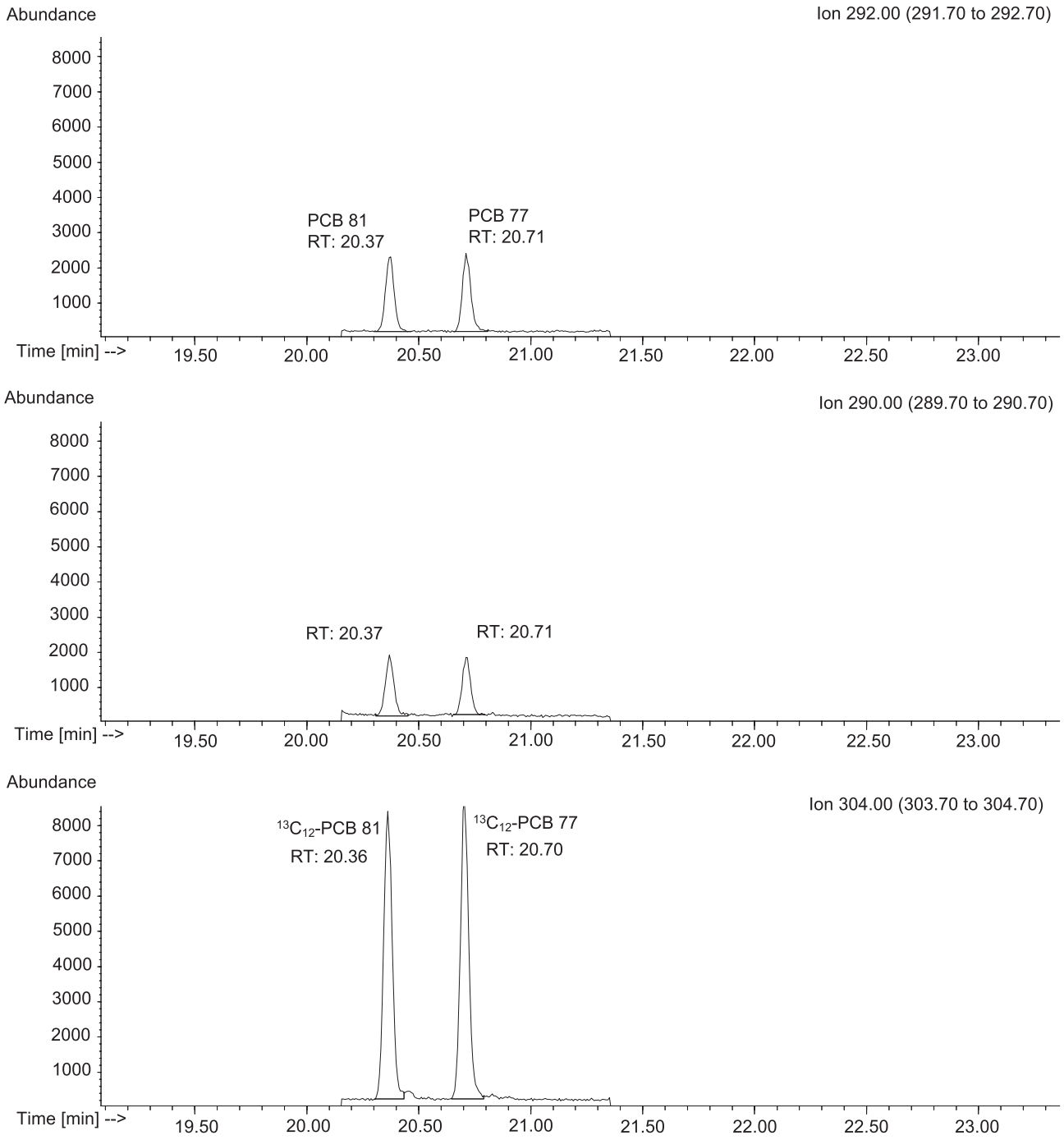


**Fig. 5** Chromatogram of a processed standard in bovine serum with a spiked concentration of 0.04 µg/l (PCB 77, PCB 81) and $^{13}C_{12}$-PCB 81, $^{13}C_{12}$-PCB 77 (ISTD)

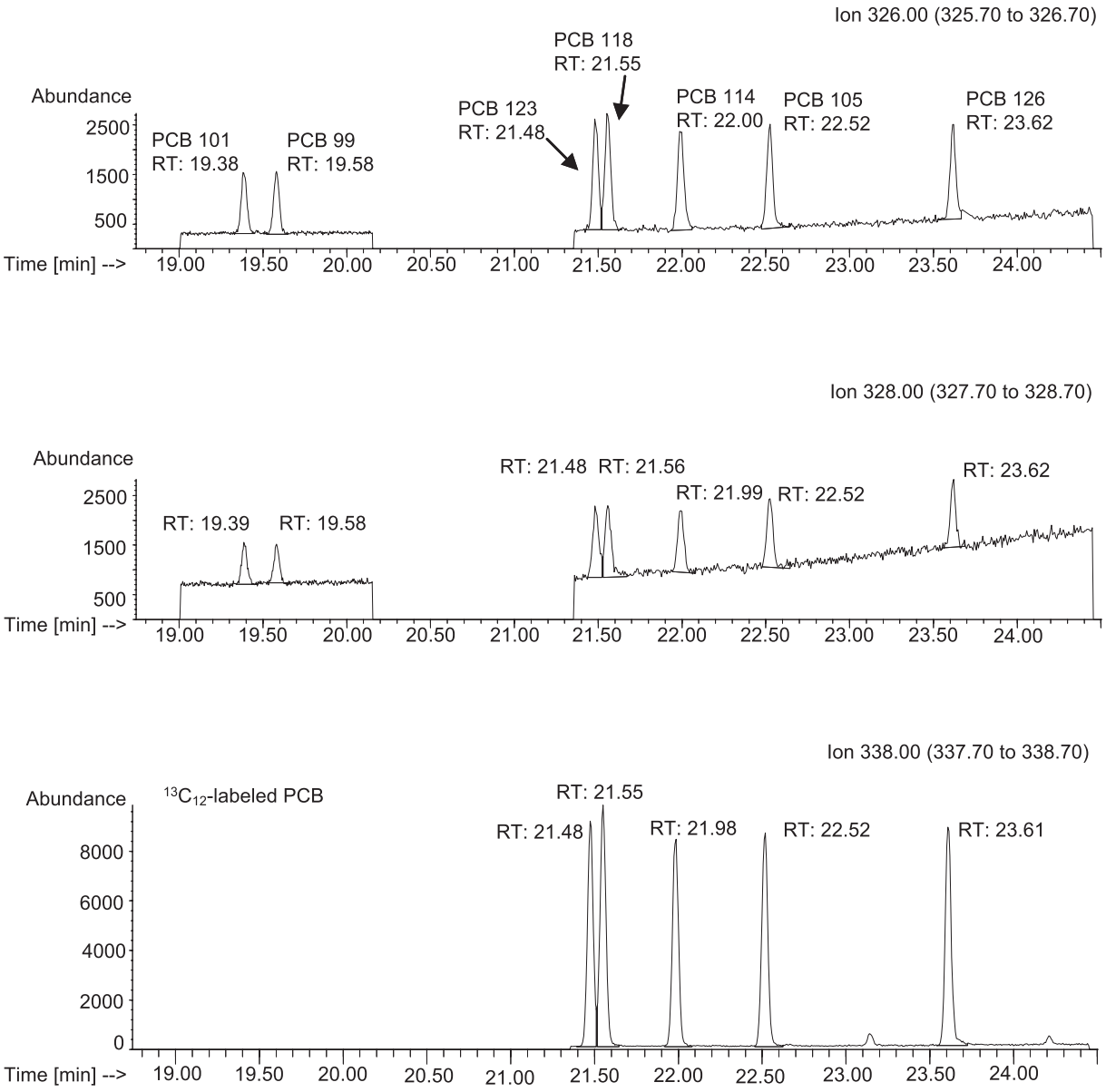


**Fig. 6** Chromatogram of a processed standard in bovine serum with a spiked concentration of 0.04 µg/l (PCB 99, PCB 101, PCB 105, PCB 114, PCB 118, PCB 123, PCB 126) and $^{13}C_{12}$-labeled PCB (ISTD)

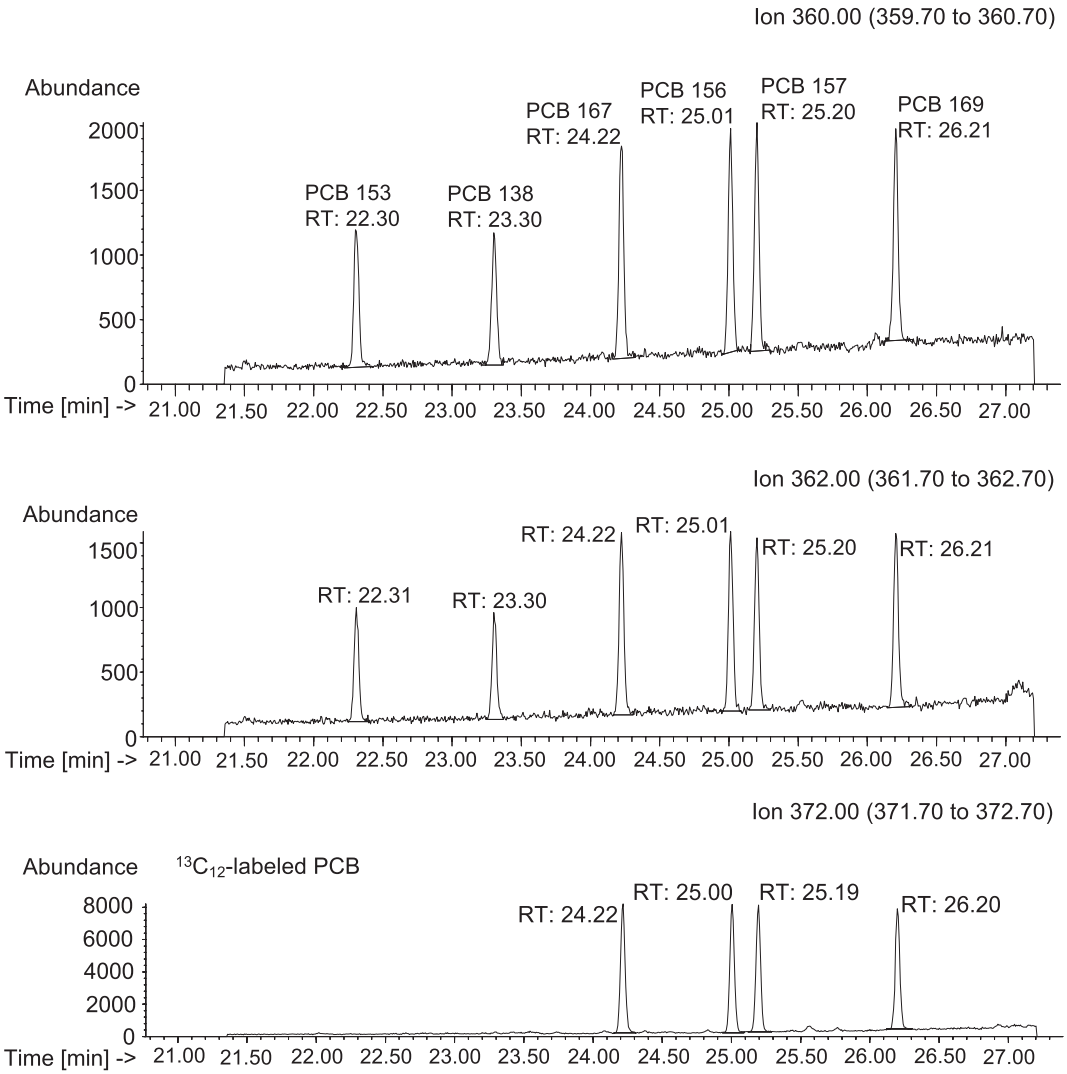


**Fig. 7** Chromatogram of a processed standard in bovine serum with a spiked concentration of 0.04 µg/l (PCB 138, PCB 153, PCB 156, PCB 157, PCB 167, PCB 169) and $^{13}C_{12}$-labeled PCB (ISTD)

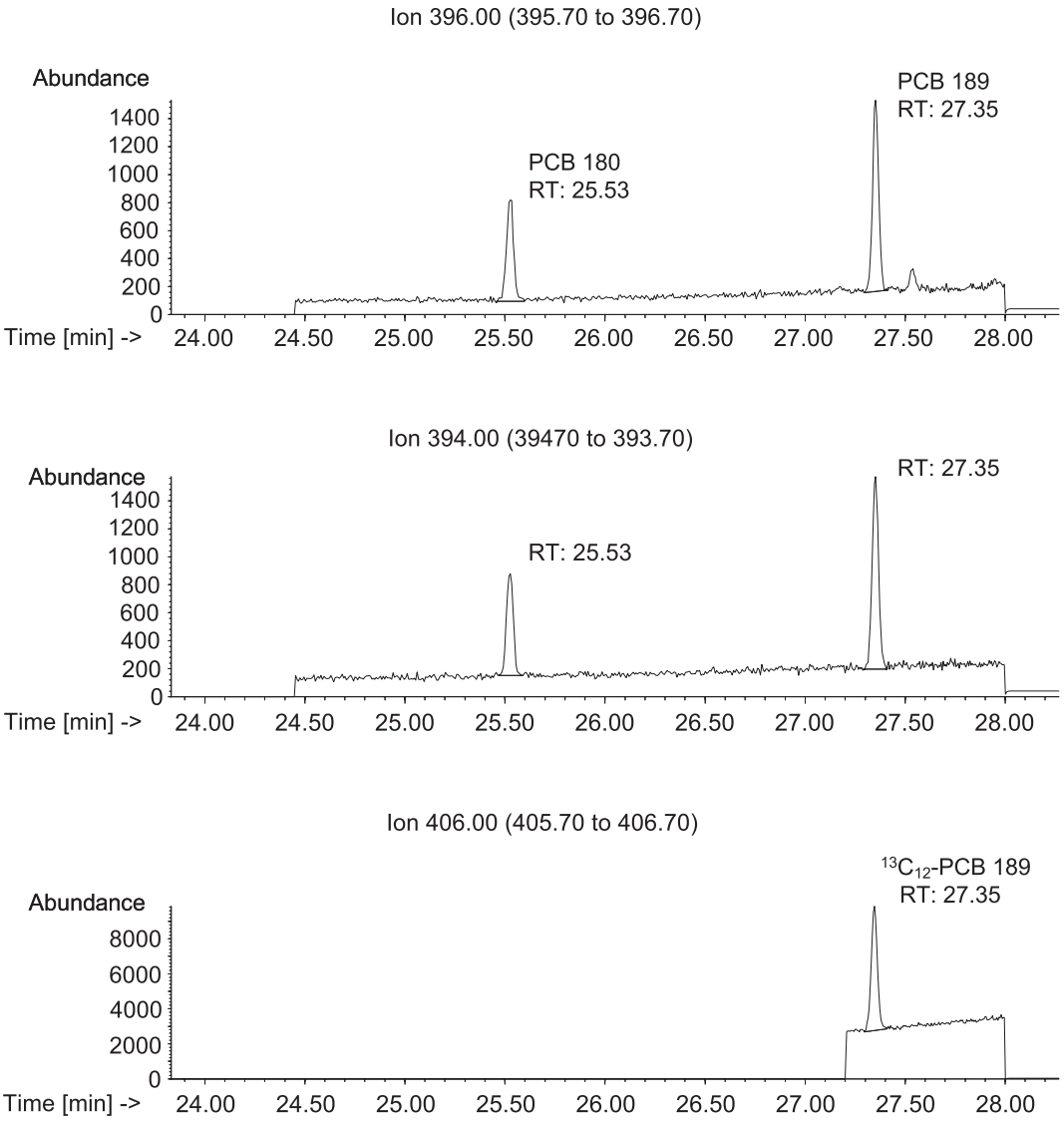


**Fig. 8** Chromatogram of a processed standard in bovine serum with a spiked concentration of 0.04 µg/l (PCB 180, PCB 189) and $^{13}C_{12}$-PCB 189 (ISTD)

# 8 Calibration

The calibration standards prepared in bovine serum (see Section 4.5) are processed in the same way as the samples according to Section 5.2 and analysed using GC-MS according to Sections 6 and 7. Calibration curves are obtained by plotting the quotients of the peak areas of the analyte and the corresponding ISTD against the concentrations of the calibration standards. PCB 54 is used as the ISTD for the indicator congeners PCB 28, 52, 101, 138, 153, and 180 as well as for HCB and DDE. For the coplanar PCBs, the $^{13}C_{12}$-labelled ISTDs are used. $^{13}C_{12}$-PCB 81 is used as the ISTD for PCB 66 and PCB 74, while $^{13}C_{12}$-PCB 123 is used for PCB 99. The slope and intercept of the calibration curves are calculated using linear regression.

The calibration functions are linear for all analytes in the specified range. Figure 9 shows calibration curves for eight of the analytes in bovine serum.

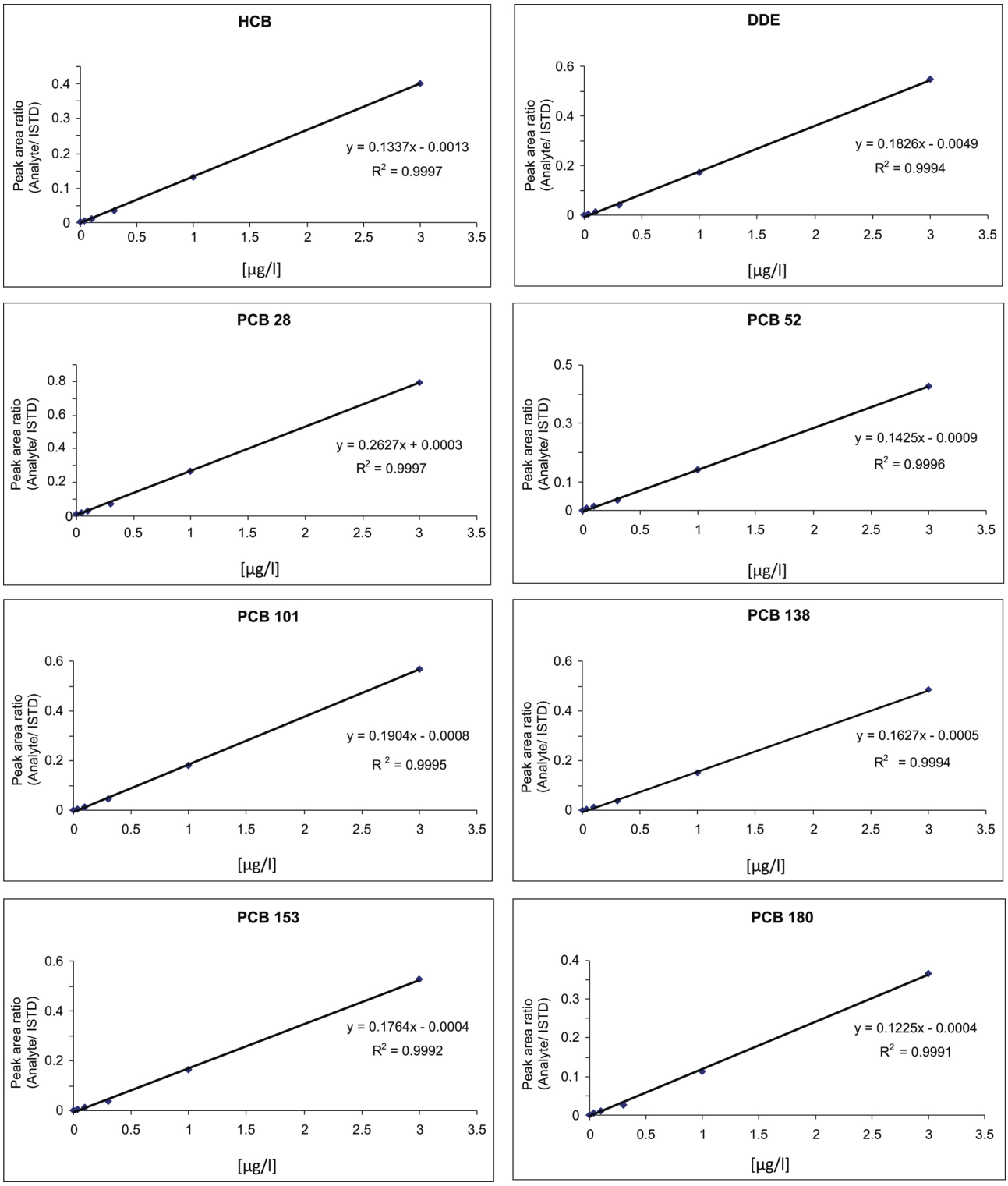


**Fig. 9** Calibration curves for HCB, DDE, PCB 28, PCB 52, PCB 101, PCB 138, PCB 153, and PCB 180, respectively, in serum

# 9 Calculation of the analytical results

The analyte concentrations in the samples are calculated by dividing the peak area of the analyte by the peak area of the corresponding ISTD. The analyte concentration of the respective analyte in µg/l of serum/plasma or whole blood can be calculated based on the quotient obtained using the calibration function pertaining to the analytical run (see Section 8).

If the bovine serum used to prepare the calibration standards shows background levels, these must be taken into account by subtraction. Any reagent blanks must also 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 general chapter published by the Commission (Bader et al. 2010; Bundesärztekammer 2014). To check precision, at least two quality-control samples with known analyte concentrations are included in each analytical run. As control material is not commercially available, it must be prepared in the laboratory by spiking bovine serum with a defined amount of the standard solutions of the analytes. The analyte concentration in this control material should be within a relevant range for the general population's background exposure. Aliquots of these samples are stored at −20 °C and are included in each analytical run as quality-control samples. The nominal value and the tolerance ranges of the quality-control material are determined in a pre-analytical period (one analysis of each control material on ten different days) (Bader et al. 2010).

# 11 Evaluation of the method

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

## 11.1 Precision

To determine within-day precision, bovine serum was spiked with a concentration of 0.4 µg/l of each analyte. These samples were processed and analysed six times in parallel. The obtained precision data are presented in Table 6.

**Tab. 6** Within-day precision data for the determination of PCBs, HCB, and DDE in serum/plasm or whole blood (n = 6)

| Analyte | Spiked concentration [µg/l] | Standard deviation $s_w$ (rel.) [%] | Prognostic range $u$ [%] |
|---|---|---|---|
| PCB 28 | 0.4 | 4.7 | 12.1 |
| PCB 52 | 0.4 | 2.8 | 7.2 |
| PCB 66 | 0.4 | 4.7 | 12.1 |
| PCB 74 | 0.4 | 4.0 | 10.3 |
| PCB 77 | 0.4 | 4.2 | 10.8 |
| PCB 81 | 0.4 | 4.0 | 10.3 |
| PCB 99 | 0.4 | 5.1 | 13.1 |
| PCB 101 | 0.4 | 3.2 | 8.2 |
| PCB 105 | 0.4 | 5.9 | 15.2 |
| PCB 114 | 0.4 | 3.7 | 9.5 |
| PCB 118 | 0.4 | 5.0 | 12.8 |
| PCB 123 | 0.4 | 5.1 | 13.1 |

**Tab. 6** *(continued)*

| Analyte | Spiked concentration [µg/l] | Standard deviation $s_w$ (rel.) [%] | Prognostic range $u$ [%] |
|---|---|---|---|
| PCB 126 | 0.4 | 4.9 | 12.6 |
| PCB 138 | 0.4 | 4.7 | 12.1 |
| PCB 153 | 0.4 | 3.4 | 8.7 |
| PCB 156 | 0.4 | 4.5 | 11.6 |
| PCB 157 | 0.4 | 4.3 | 11.1 |
| PCB 167 | 0.4 | 4.1 | 10.5 |
| PCB 169 | 0.4 | 5.7 | 14.6 |
| PCB 180 | 0.4 | 4.6 | 11.8 |
| PCB 189 | 0.4 | 4.7 | 12.1 |
| HCB | 0.4 | 2.0 | 5.1 |
| DDE | 0.4 | 3.8 | 9.8 |

Day-to-day precision was determined using the same material as was used to determine within-day precision. The serum samples were processed and analysed on twelve different days. The obtained precision data are presented in Table 7.

**Tab. 7** Day-to-day precision data for the determination of PCBs, HCB, and DDE in serum/plasma or whole blood (n = 12)

| Analyte | Spiked concentration [µg/l] | Standard deviation $s_w$ (rel.) [%] | Prognostic range $u$ [%] |
|---|---|---|---|
| PCB 28 | 0.4 | 4.5 | 10.0 |
| PCB 52 | 0.4 | 3.1 | 6.9 |
| PCB 66 | 0.4 | 2.6 | 5.8 |
| PCB 74 | 0.4 | 2.5 | 5.6 |
| PCB 77 | 0.4 | 2.0 | 4.5 |
| PCB 81 | 0.4 | 1.9 | 4.2 |
| PCB 99 | 0.4 | 3.2 | 7.1 |
| PCB 101 | 0.4 | 3.4 | 7.6 |
| PCB 105 | 0.4 | 2.5 | 5.6 |
| PCB 114 | 0.4 | 1.9 | 4.2 |
| PCB 118 | 0.4 | 2.0 | 4.5 |
| PCB 123 | 0.4 | 2.7 | 6.0 |
| PCB 126 | 0.4 | 1.9 | 4.2 |
| PCB 138 | 0.4 | 3.9 | 8.7 |
| PCB 153 | 0.4 | 4.4 | 9.8 |
| PCB 156 | 0.4 | 2.2 | 4.9 |
| PCB 157 | 0.4 | 1.1 | 2.5 |
| PCB 167 | 0.4 | 1.6 | 3.6 |
| PCB 169 | 0.4 | 1.1 | 2.5 |
| PCB 180 | 0.4 | 4.1 | 9.1 |
| PCB 189 | 0.4 | 3.8 | 8.5 |
| HCB | 0.4 | 2.7 | 6.0 |
| DDE | 0.4 | 4.7 | 10.5 |

## 11.2 Accuracy

To check the accuracy of the method, recovery was determined based on the day-to-day precision data. The obtained relative recovery rates are presented in Table 8.

**Tab. 8** Mean relative recovery rates for the determination of PCBs, HCB, and DDE in serum/plasma or whole blood (n = 12)

| Analyte | Spiked concentration [µg/l] | Mean recovery *r* (rel.) [%] | Range [%] |
|---|---|---|---|
| PCB 28 | 0.4 | 99 | 95–108 |
| PCB 52 | 0.4 | 97 | 93–103 |
| PCB 66 | 0.4 | 100 | 93–105 |
| PCB 74 | 0.4 | 100 | 94–102 |
| PCB 77 | 0.4 | 95 | 91–98 |
| PCB 81 | 0.4 | 96 | 92–99 |
| PCB 99 | 0.4 | 97 | 91–102 |
| PCB 101 | 0.4 | 96 | 91–103 |
| PCB 105 | 0.4 | 95 | 92–99 |
| PCB 114 | 0.4 | 97 | 95–100 |
| PCB 118 | 0.4 | 96 | 93–98 |
| PCB 123 | 0.4 | 98 | 94–104 |
| PCB 126 | 0.4 | 96 | 93–98 |
| PCB 138 | 0.4 | 95 | 91–102 |
| PCB 153 | 0.4 | 95 | 89–101 |
| PCB 156 | 0.4 | 95 | 93–99 |
| PCB 157 | 0.4 | 96 | 94–98 |
| PCB 167 | 0.4 | 96 | 94–98 |
| PCB 169 | 0.4 | 96 | 94–98 |
| PCB 180 | 0.4 | 94 | 88–103 |
| PCB 189 | 0.4 | 98 | 93–106 |
| HCB | 0.4 | 96 | 93–102 |
| DDE | 0.4 | 95 | 90–103 |

The method has also been repeatedly and successfully used in the 41st–48th G-EQUAS (German External Quality Assessment Scheme) interlaboratory surveys for the determination of indicator congeners PCB 28, 52, 101, 138, 153, and 180 as well as HCB and DDE in plasma.

## 11.3 Limits of detection and quantitation

Under the specified conditions of sample preparation and determination by gas chromatography/mass spectrometry, the detection limit for each analysed PCB congener as well as for HCB and DDE was 0.005 µg per litre of serum/plasma or whole blood. The limit of detection was estimated on the basis of a signal-to-noise ratio of 3 : 1. The limit of quantitation was calculated in the same way based on a signal-to-noise ratio of 9 : 1 and amounts to 0.015 µg per litre of serum/plasma or whole blood for each analyte.

## 11.4 Sources of error

In individual cases, interfering peaks can be expected for individual PCB congeners (especially PCB 126). During peak integration, special attention must be given to correct retention times (by comparison with $^{13}C_{12}$-ISTD) as well as to the ratio between the quantifier and qualifier ions (cf. Table 5). The quantifier/qualifier-ratio should be similar in the calibration standards and in the analysed samples. No blank values were detected for the individual analytes. Special care should be taken when cleaning and baking out glassware as well as in preparing the chemicals (purified formic acid).

The co-elution of the PCB congeners 28 and 31 (both trichlorobiphenyls), as reported in a few publications, has been tested as part of method development under the specified chromatographic conditions. Both congeners were sufficiently separated, although not to the baseline, so that a largely interference-free quantification of PCB 28 can be assumed (see Figure 10).

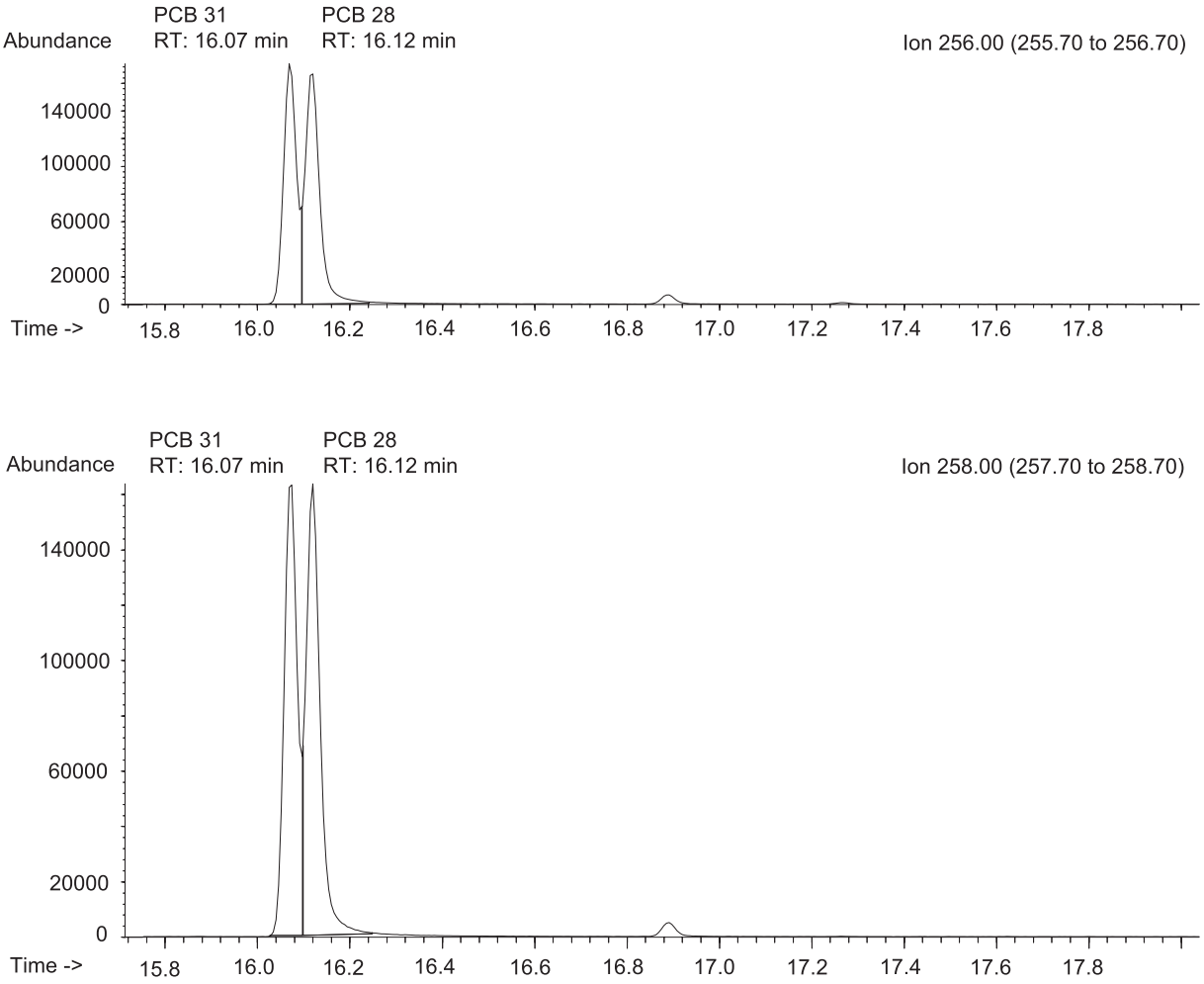


**Fig. 10** Specificity test for PCB 28: chromatogram of a standard (PCB 28 + PCB 31, each 100 µg/l in isooctane)

# 12 Discussion of the method

The method presented herein is based on the methods by Schulte et al. (1991) and Hoppe et al. (2003), which have already been published by the Commission. This method can be applied to serum, plasma, and whole blood samples. Since the analytes accumulate mainly in the plasma fraction of the blood, due to their high lipophilicity, higher concentrations and thus higher detection rates for the individual compounds are to be expected.

In contrast to the method by Hoppe et al. (2003), this method uses a longer GC column (60 m instead of 30 m). This ensures a better separation of singular interfering peaks (especially in the range of PCB 126). The introduction of mass spectrometry as a detection method has led to a significant increase in sensitivity and specificity compared to the original GC/ECD analysis (Schulte et al. 1991). Only the specific mass-spectrometric detection could enable the simultaneous determination of coplanar PCBs, which are found in much lower concentrations in the biological material than the PCB indicator congeners.

In addition to the six indicator congeners and the twelve dioxin-like PCB congeners, two tetrachlorobiphenyls (PCB 66 and PCB 74) and one pentachlorobiphenyl (PCB 99) can also be determined with this method, which may be relevant in the context of indoor exposure (Meyer et al. 2013). The method can also be extended to further relevant PCB congeners, if necessary.

In a pilot study, this method was successfully applied to plasma samples taken from 105 people of the general population grouped into seven age categories (Schettgen et al. 2011), and has meanwhile proven itself under routine conditions in numerous occupational and environmental studies (Schettgen et al. 2012 a, b, 2015). The limit of quantitation of 0.015 µg/l of serum/plasma or whole blood is sufficient to quantify these congeners in a high percentage of plasma samples.

The introduction of $^{13}C$-labelled ISTD substances for the coplanar PCB congeners significantly improved the precision of the method, as shown by the good day-to-day precision data of 1.1–3.8% for the individual congeners. As in the previous method, the ISTD PCB 54 was used for the indicator congeners. Their day-to-day precision data of 3.1–4.5% are also very satisfactory. However, isotope-labelled standard substances are now also available for a number of other PCB congeners as well as for HCB and DDE.

**Instruments used** Gas chromatograph 6890 with mass-selective detector 5975, autosampler 7683, and data-analysis system by Agilent Technologies Deutschland GmbH, Waldbronn, Germany; capillary gas-chromatography column: HP-5MS (95%-dimethyl-5%-diphenylpolysiloxane), length 60 m; inner diameter 0.25 mm; film thickness 0.25 µm by Agilent Technologies Deutschland GmbH, 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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