A New Approach to the Analysis of Chlorinated Paraffins by Gas Chromatography Quadrupole Time-of-Flight Mass Spectrometry

Abstract

Chlorinated paraffins (CPs) are industrial products produced and used in bulk for various purposes. However, the analysis of CPs is challenging, as they are complex mixtures of compounds and isomers. This study develops an analytical method for the analysis of short-chain CPs (SCCPs) and medium-chain CPs (MCCPs) using gas chromatography coupled with quadrupole time-of-flight high-resolution mass spectrometry operated in negative chemical ionization mode (GC-NCI-Q-TOF-HRMS). The linear relationship between chlorination and the CP total response factors was applied to quantify the CP content and the congener group distribution patterns. In a single injection, 24 SCCP formula groups and 24 MCCP formula groups were quantified. Extraction of accurate masses using TOF-HRMS allowed the SCCPs and MCCPs to be distinguished, with interference from other chemicals (for example, PCBs) being effectively avoided. The SCCP and MCCP detection limits were 24–81 ng/mL and 27–170 ng/mL, respectively. Comparison of the results with those obtained through gas chromatography coupled with low-resolution mass spectrometry operated under the same ionization mode (GC-NCI-LRMS) indicated that the developed technique was a more accurate and convenient method for the analysis of CPs in samples from a range of matrices.
Introduction

Chlorinated paraffins (CPs), also known as polychlorinated n-alkanes, have been widely used for decades in commercial products\(^1\),\(^2\),\(^3\). The commercial CP mixtures can be divided into three categories:

- Short-chain chlorinated paraffins (SCCPs) C\(_{10}\)–C\(_{13}\)
- Medium-chain chlorinated paraffins (MCCPs) C\(_{14}\)–C\(_{17}\)
- Long-chain chlorinated paraffins (LCCPs) C \(>17\).

Among these, SCCPs have drawn significant attention due to their high toxicity\(^2\); however, as MCCPs and SCCPs coexist in the environment, and MCCPs can be transformed into SCCPs through environmental processes such as combustion, the issue of MCCP analysis should also be addressed.

The quantification of CPs in environmental samples is challenging\(^4\) due to the complexity of the industrial mixtures and self-interference among the CPs. A number of different methods have been developed for the determination of SCCPs and MCCPs in a range of environmental matrices\(^5\)–\(^9\). However, these methods encounter several challenges such as high cost and the risk of interference between other chlorinated pollutants and CPs with the same nominal mass. Interference related to mass overlap between SCCP and MCCP congeners must also be addressed, and fragmentation patterns should be studied to allow more accurate quantification of CPs. With these challenges in mind, this Application Note describes a published study on the development of a novel analytical approach based on the GC-NCI-Q-TOF-HRMS system to simultaneously analyze SCCPs and MCCPs in a single injection\(^10\).

High-resolution TOF scan mode was used to directly quantify SCCPs, and avoid possible interference by MCCPs in environmental samples. Twenty-four different SCCP formula groups (C\(_{10}\)–C\(_{13}\) with 5–10 chlorine atoms) and 24 MCCP formula groups (C\(_{14}\)–C\(_{17}\) with 5–10 chlorine atoms) were analyzed by extracting accurate masses. CPs bearing fewer chlorine atoms and shorter chain lengths were also studied. Samples from a range of environmental matrices were analyzed using the developed method, proving that it is a more accurate and convenient method for the analysis of CPs in environmental samples.

Experimental

Reagents and Standards

Pesticide analytical grade solvents were purchased from J.T. Baker (Phillipsburg, NJ, USA). Solutions of the SCCP mixtures (100 ng/µL, C\(_{10}\)–C\(_{13}\) with 51 %, 55.5 %, and 63 % chlorination, 100 % purity) and MCCP mixtures (100 ng/µL, C\(_{14}\)–C\(_{17}\) with 42 %, 52 %, and 57 % chlorination, 100 % purity) in cyclohexane and \(\varepsilon\)-hexachlorocyclohexane (\(\varepsilon\)-HCH, solution in cyclohexane, 10 ng/µL, 99.9 % purity) were purchased from Dr. Ehrenstorfer GmbH (Augsburg, Germany). 1,5,5,6,6,10-Hexachlorodecane (\(^{13}\)C\(_{10}\), 100 ng/µL, solution in cyclohexane, ≥98 % purity) and 1,5,5,6,6,10-hexachlorodecane (unlabeled, 100 ng/µL in cyclohexane, ≥98 % purity) were purchased from Cambridge Isotope Laboratories (Andover, USA).

Instrument

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<td>Spectral acquisition rate</td>
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Sample Preparation
To test the performance of the NCI-TOF-HRMS method, samples from several environmental matrices were analyzed for both SCCPs and MCCPs. Air samples were obtained using a passive air sampler (Xpress-Application Developer, XAD). The industrial CP products were kindly provided by manufacturers. Food samples were purchased from several well-known fast food outlets. Sample pretreatment was based on the previously reported method with some minor modifications. Briefly, frozen dried samples (1 g) were mixed with diatomaceous earth (5 g), and spiked with the $^{13}$C$_{10}$-1,5,5,6,6,10-hexachlorodecane (10 ng) as surrogate internal standard and quantitative internal standard prior to accelerated solvent extraction (ASE). The extract was concentrated to approximately 1 mL by rotary evaporation. The extract was then cleaned and fractionated on a 1.5 cm silica-Florisil composite column packed with Florisil (3 g), neutral silica gel (2 g), acidic silica gel (5 g, 30 %), and anhydrous sodium sulfate (4 g) (packed from bottom to top). The column was conditioned with $n$-hexane (50 mL), and the sample was eluted with $n$-hexane (40 mL) (fraction 1 contained polychlorinated biphenyls and toxaphenes), followed by dichloromethane (50 mL) and $n$-hexane (50 mL) (fraction 2 contained CPs and HCHs). The second fraction was concentrated to approximately 2 mL by rotary evaporation, and further concentrated to close to dryness under a gentle stream of N$_2$. The fraction was then reconstituted in cyclohexane (200 µL). Prior to MS analysis, a ε-HCH (10 ng) was added as injection internal standard to determine the sample recoveries. Instrumental blanks were composed of pure cyclohexane. No CPs were observed following injection of the blanks.

Results and Discussion
Quantification Method Workflow and Auto-Integration Procedure
Figure 1 describes the workflow for the chlorination response factor-based quantification method.

In the NCI-LRMS method, manual integration was traditionally applied to compare the peak shapes and retention times with the reference standards. In the NCI-TOF-MS method, the observed extracted ion chromatography (EIC) peak was comparable to that of the standard, as high-resolution MS removed interference from the matrix. Auto integration was applied using Agilent MassHunter Quantitative Analysis B.07. The accurate masses of the SCCPs and MCCPs and quantitative and qualitative ions, along with their retention times (Table 1), were added to the method. New batch files were built, and the data files were imported. The integration results could directly transfer to customer's homemade excel table to calculate the subsequent results listed in Figure 1. The quantitative method, based on the linearity of the response factor and chlorination, compensated for the difference in response factors between the reference CP mixtures and the real samples. Figure 2 shows the linear relationship between the response factor (RF: the ratio of internal standard adjustment response to the CP content) and calculated chlorination (%) for MCCPs and SCCPs.

Figure 1. The quantification method workflow for CPs. For detailed information about the quantification method please see reference 10.
Table 1. Accurate mass of quantitative and qualitative [M-Cl]^− ions for SCCPs and MCCPs, average molecular mass, retention time, and limit of detection of each single formula group (continued next page).

<table>
<thead>
<tr>
<th>SCCP and MCCP congeners (n, z)</th>
<th>Quantitative ions</th>
<th>Qualitative ions</th>
<th>Average molecular mass</th>
<th>Retention time (min)</th>
<th>LOD (ng/mL)</th>
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<td>m/z [M-Cl]^−</td>
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Table 1. Accurate mass of quantitative and qualitative \([\text{M}-\text{Cl}]^–\) ions for SCCPs and MCCPs, average molecular mass, retention time, and limit of detection of each single formula group.

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<th>SCCP and MCCP congeners ((n, z))</th>
<th>Quantitative ions</th>
<th>Qualitative ions</th>
<th>Average molecular mass</th>
<th>Retention time (min)</th>
<th>LOD (ng/mL)</th>
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Limit of Detection (LOD) and Linearity Range

The instrumental LOD was determined as the standard deviation of the signal intensities from the five replicate injections multiplied by Student’s T-value at a 95% confidence level. In real samples, detection of a congener group was defined as both m/z values of the quantitative and qualitative ions being detected above their respective LODs, and where the LOD of the congener group was equal to the LOD of the least sensitive of the two monitored m/z values. The LOD for the SCCPs and MCCPs was defined as detection of the most abundant congener group. Results showed that the LOD of the MCCPs was in the range of 27–170 ng/mL, while that of the SCCPs was in the range of 24–81 ng/mL. Table 1 provides the LOD of each formula group. The linearity of the NCI-Q-TOF-HRMS method was determined by fitting the intensities obtained from the standard solutions of 55.5% Cl SCCP, 52% Cl MCCP, and 57% Cl MCCP mixtures against their concentrations ranging from 0.25 to 100 ng/µL using weighted linear regression. Figure 3 shows the corresponding fitting curves. It was found that the linearity ranges for both SCCP and MCCP can reach three orders of magnitude, which are higher than that of the NCI-LRMS method. This relatively good linearity performance for the CPs was due to no isomer reaching its upper limit, even at high total concentrations.

Figure 2. Linear relationship between the response factor (RF: the ratio of internal standard adjustment response and the CPs content) and calculated chlorination (%) for MCCPs and SCCPs. A) Standard curve of SCCPs at 10 ng/µL (different chlorination obtained by mixing 51.5% Cl, 55.5% Cl, and 63% Cl SCCP standards). B) Standard curve of MCCPs at 10 ng/µL (different chlorination obtained by mixing 42% Cl, 52% Cl, and 57% Cl MCCP standards).

Figure 3. A) Linearity of 55.5% Cl SCCP mixtures (0.25–100 ng/µL). B) Linearity of 52% Cl MCCP mixtures (0.25–100 ng/µL). C) Linearity of 57% Cl MCCP mixtures (0.25–100 ng/µL).
**Accuracy and Repeatability**

Accuracy was calculated as the ratio between the average measured concentration (n = 5) and the reference SCCP and MCCP mixture standards at different chlorination percent (51.5 % Cl SCCP, 55.5 % Cl SCCP, 63 % Cl SCCP, 52 % Cl MCCP and 57 % Cl MCCP). Table 2 shows the results.

With the NCI-TOF-MS method, the relative accuracies for SCCPs and MCCPs can be acquired within the range of 86–124 % and 114–129 %, respectively. When using the binary mixture standards of SCCP and MCCP, larger positive bias was observed than that for the single mixture standard.

Repeatability can be determined by the standard deviation of repeated injections (n = 18, spiked at 1, 10, and 100 ng/L of both 55 % Cl SCCP and 52 % Cl MCCP) over a single day (intra-day) and across several days (inter-day). The relative standard deviations (RSDs) of SCCP for the inter-day injections obtained by NCI-TOF-MS at the three concentration levels were 2.55 %, 1.95 %, and 3.58 %, respectively. For the MCCP, the corresponding RSDs were 12.3 %, 7.37 %, and 0.97 %, respectively.

### Influence of Resolution in CP Analysis

The relationship between resolution and deviation of mass (DM) is defined by Equation 1.

$$\text{Resolution} = \frac{M}{\text{DM}}$$

Equation 1.  

M is the m/z ratio of the fragment ions, DM is the mass distance between two adjacent peaks.

### Table 2. Accuracy and repeatability of the NCI-TOF-HRMS method.

<table>
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<tr>
<th>Performance test</th>
<th>Reference conc. (ng/µL)</th>
<th>Calculated conc. (± error) (ng/µL)</th>
<th>Accuracy</th>
<th>Binary mix</th>
<th>Reference conc. (ng/µL)</th>
<th>Calculated conc. (± error) (ng/µL)</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCCP Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51 % Cl SCCP</td>
<td>5.00</td>
<td>4.30 (±0.41)</td>
<td>86 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55 % Cl SCCP</td>
<td>10.00</td>
<td>10.00 (±0.19)</td>
<td>100 %</td>
<td>55 % Cl SCCP and 57 % Cl MCCP (1:1, v/v 20 ng/µL)</td>
<td>10.00</td>
<td>12.43 (±4.6)</td>
<td>124 %</td>
</tr>
<tr>
<td>63 % Cl SCCP</td>
<td>10.00</td>
<td>12.05 (±0.14)</td>
<td>120 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MCCP Test</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>52 % Cl MCCP</td>
<td>10.00</td>
<td>12.13 (±0.89)</td>
<td>121 %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>57 % Cl MCCP</td>
<td>10.00</td>
<td>11.36 (±0.71)</td>
<td>114 %</td>
<td>55 % Cl SCCP and 57 % Cl MCCP (1:1, v/v 20 ng/µL)</td>
<td>10.00</td>
<td>12.89 (±0.27)</td>
<td>129 %</td>
</tr>
</tbody>
</table>

Accuracy is defined as the percentage ratio of the calculated concentration of CPs and the reference concentration of CPs.

### Table 3. Accurate masses of MCCP and SCCP formulation groups that generated fragmentation ions with the same nominal mass, and the D-value between the two ions.

<table>
<thead>
<tr>
<th>Nominal mass</th>
<th>Formula group</th>
<th>Accurate mass</th>
<th>Formula group</th>
<th>Accurate mass</th>
<th>D-value (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>417</td>
<td>C_{10}Cl</td>
<td>416.8472</td>
<td>C_{10}Cl</td>
<td>417.0063</td>
<td>382</td>
</tr>
<tr>
<td>451</td>
<td>C_{10}Cl_{10}</td>
<td>450.8082</td>
<td>C_{10}Cl_{10}</td>
<td>450.9674</td>
<td>353</td>
</tr>
<tr>
<td>431</td>
<td>C_{10}Cl</td>
<td>430.8628</td>
<td>C_{10}Cl</td>
<td>431.0222</td>
<td>369</td>
</tr>
<tr>
<td>465</td>
<td>C_{10}Cl_{10}</td>
<td>464.8239</td>
<td>C_{10}Cl_{10}</td>
<td>464.983</td>
<td>342</td>
</tr>
<tr>
<td>445</td>
<td>C_{10}Cl</td>
<td>444.8785</td>
<td>C_{10}Cl</td>
<td>445.0376</td>
<td>358</td>
</tr>
<tr>
<td>479</td>
<td>C_{10}Cl_{10}</td>
<td>478.8395</td>
<td>C_{10}Cl_{10}</td>
<td>478.9987</td>
<td>333</td>
</tr>
</tbody>
</table>

*Part per million*
Furthermore, matrix interference was found to exist even after following thorough sample pretreatment procedures. Under the NCP-LRMS system, SIM combined the retention time window to eliminate self-interference. However, this approach did not yield satisfactory results (Figure 4). EIC at ±0.5 amu, as baseline separation of the components could not be achieved. Figure 4 shows that interference from the matrix along with CP self-interference (for example, m/z 451 generated by C_{13}Cl_{10} and C_{15}Cl_{9}) could be avoided, to a large extent, with a mass tolerance of 50 ppm upon extracting the accurate mass. In Figure 4, MCCPs were treated as interference, while SCCPs were regarded as the targets.

**Analysis of Environmental Samples and Comparison Between Two Methods**

To assess improvements in the quality of the CP environmental measurements (Figure 5), it is essential to compare the results from the current HRMS method with the LRMS method previously reported. The NCI-TOF-HRMS method was evaluated to quantify SCCPs and MCCPs in industrial products, food, and XAD-based air samples (Figure 5). The SCCP concentration ranged from 70 to 73,172 ng/g dw for the food samples. In addition, the SCCP concentration in the XAD-based air samples ranged from 0.04–29 ng/m², and finally, for the technical products, the SCCP content ranged from 54 to 1,651 ng in the CP-52 products at a concentration of 10 ppm. The SCCP contents and chlorination values obtained using the two different MS methods were also compared (Figure 5).

In the XAD-based air samples, the concentrations obtained using the NCI-TOF-HRMS method were prevalently lower than those obtained by the NCI-LRMS method, with the exception of two cases (an extremely low content (13 bz) and an extremely high content (14 dppl)). The SCCP concentrations determined by NCI-TOF-HRMS differed from those obtained by NCI-LRMS by factors of 0.19–0.92.

Conversely, the results obtained for the food samples varied due to different matrix effects. The SCCP concentrations determined by NCI-TOF-HRMS differed from those obtained by NCI-LRMS by factors of 0.16–2.55.

For the industrial CP products, the concentrations obtained using the NCI-TOF-HRMS method were generally higher than those obtained using the NCI-LRMS method, with the exception of CP8, which had a very low SCCP content. The SCCP concentrations measured by NCI-TOF-HRMS differed from those measured using NCI-LRMS by factors of 3.79–6.05.

To further investigate the reasons for the differences in results obtained using the two methods, individual formula group contents of the SCCPs obtained using both the NCI-TOF-HRMS method and the NCI-LRMS method were compared (Figure 6). This comparison showed that, in air, SCCPs containing fewer chlorine atoms and shorter chain lengths were predominant, whereas the reverse was true for the technical products. At high resolutions, the obtained content of CPs containing fewer chlorine atoms was lower. Therefore, for the lighter components found in XAD-based air samples, the content determined by NCI-TOF-HRMS was higher, while for the heavier components found in technical products, the content determined by NCI-TOF-HRMS was lower (Figure 6). However, the differences in the absolute amounts obtained did not represent significant deviations from the true values. As discussed above, CPs with varying chlorine contents exhibited various response patterns related to different instrumental conditions, which mainly resulted from the varying degrees of chlorination.

**Figure 4.** Elimination of matrix effects in samples by accurate mass extraction, presented by EIC comparison. A) Total ion chromatogram (TIC) of an air sample and the corresponding EIC extraction (C_{13}Cl_{10}) at different mass tolerances (50 ppm and 0.5 amu); B) TIC of a food sample and the corresponding EIC extraction (C_{13}Cl_{9}) at different mass tolerances (50 ppm and 0.5 amu).
Figure 5. Comparison of calculated chlorination and content of SCCPs obtained with the NCI-TOF-HRMS method (blue bars) and the NCI-LRMS method (green bars) for (A) calculated chlorination comparison in food samples, (B) content comparison in food samples, (C) calculated chlorination comparison in industrial CP products, (D) content comparison in industrial CPs products, (E) calculated chlorination comparison in XAD-based air samples, and (F) content comparison in XAD-based air samples.

Figure 6. Comparison of SCCP individual congener contents obtained using the NCI-TOF-HRMS method (green bars) and the NCI-LRMS method (red bars) for (A) congener group distribution of SCCPs in industrial products, and (B) congener group distribution of SCCPs in XAD-based air samples.
Conclusions

The novel GC-Q-TOF-MS method offers a number of benefits over established GC/NCI-LRMS methods for the analysis of CPs in environmental samples. This method was especially efficient in the simultaneous analysis of SCCPs and MCCPs in complex environmental samples, and was efficient in eliminating CP self-interference by accurate mass extraction. The results obtained for different environmental samples showed that the high-resolution TOF-MS method was capable of reducing interferences from different matrices. In addition, the GC-Q-TOF-MS method shows a comparable linear dynamic range and detection limits to previous methods, along with improved accuracy. Moreover, this method is suitable for high-throughput analyses of large sets of samples due to its efficiency in both analysis time and quantification processes. Further application of this GC-Q-TOF-MS method should be considered to achieve more accurate analyses of CPs in different matrices.

Time Efficiency and Suitability for Routine Analysis

Unlike the earlier LRMS method\textsuperscript{11,12} that required four separate runs to acquire all necessary SIM ions for identification and quantification, the new HRMS approach only required one injection. The higher selectivity afforded by the HRMS approach allowed effective use of automatic peak integration instead of the time-consuming manual integration required for LRMS data. This combination reduced turnaround time on samples from a few months to a few days.

The calculated chlorine content obtained using the NCI-TOF-HRMS method were generally higher than the degrees of chlorination calculated using the NCI-LRMS method, with the exception of industrial CP products and two food samples (potato 2 and razor 1). This variation could be accounted for the low content of CPs bearing fewer chlorine atoms (CPs that generate ions with \( m/z \sim 300 \)), as determined under a high resolution (in the SIM of the LRMS, interference occurred at \( m/z \sim 300 \)).

In this study, analyses of MCCPs were conducted using only the NCI-Q-TOF-HRMS system. Due to a shortage of available data in the literature, no inter-lab comparison results were available for MCCPs. Results from this study showed that the MCCP concentration in air was lower compared to that in other matrices, with the contents ranging from 0.04 to 0.89 ng/m\(^3\) obtained for the XAD-based samples. In the food samples, the MCCP levels were between 603 ng/g and 7,478 ng/g.

For the industrial products, the concentration of LCPs (SCCPs + MCCPs) were in the range of 3,796–6,235 ng in six CP-52 products (CP2, CP3, CP4, CP5, CP7, and CP8) of 10 ng/µL (in which the total amount of LCPs should be 2,000 ng), indicating that the results were overestimated. It is possible that the calculated degree of chlorination of the industrial products were at the low end of the calibration curve of chlorine content versus MS response. The degree of chlorination was inversely correlated with the quantification results, and the lower chlorine content of the industrial products relative to the environmental matrices might result in the overestimation of CP concentrations. The results implied that more specific reference standards with a wider chlorination range should be synthetized to build more accurate quantified and qualified CP methods for different matrices.

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