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Chloride-attachment atmospheric pressure photoionisation for the determination of short-chain chlorinated paraffins by gas chromatography-high-resolution mass spectrometry

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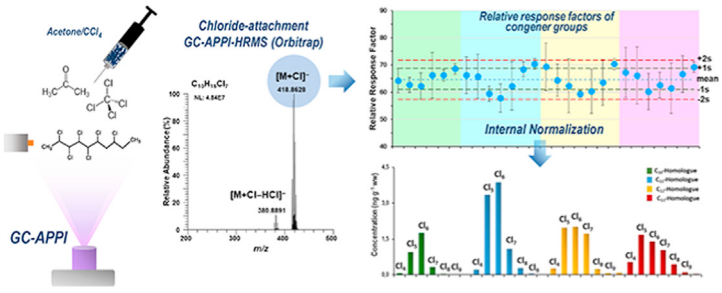
HIGHLIGHTS

- GC-APPI-HRMS was applied for the first time to determine SCCPs in fish samples.
- The use of acetone/CCl_4 mixture promote the selective formation of $[M+Cl]^-$ ions.
- Chloride-attachment GC-APPI response does not depend on the number of Cl atoms.
- This strategy allows to quantify SCCPs by an internal normalization approach.
- The new method allowed a sensitive and selective determination of SCCPs.

GRAPHICAL ABSTRACT



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ABSTRACT

In this work, a new gas chromatography-high-resolution mass spectrometry (GC-HRMS) method based on atmospheric pressure photoionisation (APPI) has been developed for the accurate determination of short-chain chlorinated paraffins (SCCPs) as a reliable alternative to the established methods. To the best of our knowledge, this is the first time these compounds has been analysed by GC-MS using atmospheric pressure photoionisation (APPI). Efficient ionisation of SCCPs was achieved using the new GC-APPI source by the formation of $[M+Cl]^-$ adduct ions in negative ion mode using dopant-assisted APPI with a mixture of acetone/CCl_4 (3:1, *v/v*). Operating at a resolution of 70,000 FWHM (full width at half maximum) and monitoring the $[M+Cl]^-$ adduct ions for each congener group, a selective determination of the SCCPs was achieved, avoiding isobaric interferences between homologue groups with different carbon chain length and chlorination degree. Moreover, the GC-APPI-HRMS response of each congener group was mainly influenced by its concentration and did not depend on the number of chlorine atoms in the molecule as occurs with the GC-MS methods based on the electron-capture negative ionisation (ECNI). Thus, the contribution of the different carbon and chlorine homologue groups in the SCCP mixtures was determined by the internal normalization method, and the quantification was performed independently of the chlorine content of the SCCP standard mixture employed. The developed GC-APPI-HRMS method offers some interesting advantages over the existing methods, particularly the possibility to quantify individual SCCP congener groups, the use of a simple calibration method for quantification, and an important time-saving in the data processing, especially over ECNI-based traditional methods. The GC-APPI-HRMS method allowed the determination of SCCPs at low concentration levels in fish samples with low

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method limits of detection (17–34 pg g^{-1} wet weight for total SCCPs), good precision (RSD < 7%) and trueness (relative error < 8%) and can be proposed as a reliable alternative of the established methods for the determination of these pollutants in environmental samples.

1. Introduction

Chlorinated paraffins (CPs) are complex mixtures of chlorinated *n*-alkanes containing thousands of isomers with carbon chain lengths, from C_{10} to C_{30}, and variable chlorine contents, between 30% and 70% by weight [1]. To cope with the great diversity of compounds, CPs are classified according to their carbon chain lengths as short-chain (SCCPs, from C_{10} to C_{13}), medium-chain (MCCPs, from C_{14} to C_{17}) and long-chain chlorinated paraffins (LCCPs, more than C_{17}) [2]. These compounds are used in a wide range of industrial applications, such as additives in metalworking fluids, as well as flame retardants and plasticizers. Moreover, their production has been estimated at around 13 million tons in the period 1935–2012 [3] and continues increasing by about 1 million tonnes per year. Even though CPs have been considered as high-volume chemical, data about their environmental fate is limited, mainly due to their challenging chemical analysis. Among CP mixtures, SCCPs are of particular concern since they are toxic and persistent in the environment, can be long-range transported, and have a high potential to bioaccumulate and biomagnify through the food chain [4–6]. Thereby, SCCPs have been listed by the Stockholm Convention as persistent organic pollutants (POPs) under annex A to eliminate their use and production [7]. Moreover, they have also been included in several international regulatory lists such as the European Water Framework Directive [8].

The analytical determination of SCCPs is challenging mainly due to the high complexity of the mixtures, the insufficient chromatographic resolution between congeners, and the difficulties to perform an accurate quantification [9,10]. SCCPs are currently analysed by gas chromatography (GC), although the complete separation of all CP congeners remains unachieved by a single-capillary GC column, resulting in chromatograms with a broad hump corresponding to the coelution of a large number of peaks that could be interfered with other CP mixtures (e.g., MCCPs) or related halogenated compounds with similar retention times (e.g., polychlorinated biphenyls and organochlorine pesticides). Comprehensive two-dimensional gas chromatography (GC×GC) has been used to improve the separation of SCCPs, but this technique only allowed a partial separation between congener groups with significant overlapping between homologues with different chlorination degrees [11]. Generally, the determination of SCCP mixtures has been performed by gas chromatography coupled to electron-capture negative ionisation low-resolution mass spectrometry (GC-ECNI-LRMS) [12–15] by monitoring the $[M-Cl]^-$ and $[M-HCl]^-$ ions for congener group-specific analysis. However, multiple GC runs for the analysis of standards and samples are required to monitor all the ions corresponding to the different homologue groups [15]. Moreover, mass interferences of these ions with longer chain CP congeners and different chlorination degrees strongly affect the quantitative results [16]. In addition, the ionisation efficiencies achieved with ECNI are highly dependent on the chlorination degree of CP congeners, and differences in the homologue composition between standards and samples often cause significant errors in the quantification (>300%) [17]. To decrease the strong dependency of ECNI with the chlorination degree, some approaches have been employed based on a linear relationship between the response factors of the CP homologue groups and their chlorine contents [15], and on the calibration by multiple linear regression selecting characteristic ions common to all homologous groups [18]. Nevertheless, it is necessary to use SCCP standards with homologue compositions similar to those found in the samples to achieve an accurate quantification [15,17,19]. GC-ECNI-HRMS has also been proposed to remove the isobaric CP interferences, but mass resolution higher than 20 000 [20] as well as multiple GC injections per sample for monitoring all selected ions are needed [19]. Recently, a GC-ECNI-Orbitrap/HRMS method working in full-scan mode has been proposed for the analysis of SCCPs and MCCPs in a single GC run, since it showed fewer interferences coming from other halogenated compounds, although responses of the CP congener groups were still dependent on their chlorination degree [10]. As an alternative to GC-ECNI-MS methods, direct injection coupled to atmospheric pressure chemical ionisation (APCI)-quadrupole time-of-flight high-resolution mass spectrometry (APCI-qTOF/HRMS) under chloride-attachment [9,21,22] or bromide-attachment [23] conditions have been recently proposed. Using those methods, the analysis of SCCPs has been performed by monitoring the chloride or bromide adduct ions generated by the addition to the mobile phase of halogenated reagents, such as dichloromethane, chloroform, or even bromoform. These methods are less affected by the congener chlorination degree, although, for the chloride-attachment strategy, a mathematical deconvolution method is required to resolve the separation of the individual CP congener groups since the mass resolution achieved was not high enough to reach a complete removal of the isobaric interferences [24].

During the last decades, the use of atmospheric pressure chemical ionisation (GC-APCI) and atmospheric pressure photoionisation (GC-APPI) as ionisation sources for GC-MS applications has been extensively explored since they provide a soft ionisation that preserves the integrity of the molecular ion and reaches high sensitivity for a wide range of compounds [25]. Thus, the recently developed GC-APPI interface [26] has been successfully applied for the GC-HRMS determination of several families of pollutants, such as PCBs [27], polycyclic aromatic hydrocarbons [28,29], phthalates [29], neutral fluorinated compounds [30], and polychlorinated naphthalenes [31], among others.

The present work aimed to develop a new sensitive and selective GC-APPI-HRMS method for a reliable determination of SCCPs in environmental samples based on chloride-attachment atmospheric pressure photoionisation and quantification of the individual SCCP congener group. To this end, the GC-APPI operational parameters, as well as the use of chlorinated solvents and dopants that may affect the ionisation of the target compounds, were optimised to avoid isobaric interferences between CP congeners. Several mathematical approaches were also tested to ensure accurate quantification of SCCPs. The developed GC-APPI-HRMS method was validated and applied to the analysis of selected fish samples.

2. Materials and methods

2.1. Chemical and standards

A standard solution of CP congener mixture (Mix 2), containing 1,2,5,6,9-pentachlorodecane (CP-3), 1,2,4,5,9,10-hexachlorodecane (CP-6), 1,2,4,5,6,9,10-heptachlorodecane (CP-7), 2,3,4,5,6,7,8,9-octachlorodecane (CP-9) and 1,2,3,4,5,6,7,8,9-nonachlorodecane (CP-10), at concentrations ranging from 0.5 to 19 μg mL^{-1} was purchased from Dr. Ehrenstofer GmbH (Ausburg, Germany). Standard solutions of SCCP mixtures (100 μg mL^{-1}) with a total chlorine content of 51.5%, 55.5%, and 63%, and standard solutions of $^{13}C_6$-hexachlorobenzene ($^{13}C_6$-HCB, 100 μg mL^{-1}) and δ-hexachlorocyclohexane (δ-HCH, 100 μg mL^{-1}), used respectively as injection and surrogate internal standard, were also supplied by Dr Ehrenstofer GmbH. Working standard solutions at concentrations lower than 10 μg mL^{-1} were prepared by appropriate dilution of the stock solutions in isooctane and stored at 4 °C until their analysis. To study the effect of potentially interfering compounds on the determination of SCCPs, two standard solutions, containing a mixture of seven polychlorinated biphenyls (PCB-Mix 1, CB-28, CB-52, CB-101, CB-118, CB-138, CB-153 and CB-180) at a concentration of 10 μg mL^{-1} in isooctane and twenty-two organochlorine pesticides (Pesticide-Mix 1037) at a concentration of 10 μg mL^{-1} in cyclohexane, were purchased from Dr Ehrenstorfer (LGC Standards, Teddington, UK).

Isooctane, dichloromethane, and *n*-hexane (for gas chromatography SupraSolv®, purity ≥ 99.8%) were obtained from Merck (Darmstadt, Germany). Besides, acetone (LiChrosolv®, purity ≥99.8%) supplied by Merck, tetrahydrofuran (Photrex™ reagent, purity at 99%) from J. T. Baker (Deventer, Holland), and anisole (analytical standard, purity ≥ 99,9%), chlorobenzene and toluene (Chromasolv™ Plus, for HPLC analysis, purity ≥ 99%) supplied by Sigma-Aldrich (St Louis, MO, USA), were used as dopants for the optimization of APPI of the SCCPs. Helium Alphagaz™ 1 (purity ≥ 99.999%), used as GC carrier gas, was supplied by Air Liquide (Madrid, Spain), while nitrogen (purity > 99.995%), from Linde (Barcelona, Spain), was employed as make-up gas for GC-APPI source. Sulphuric acid (95–97%) and anhydrous sodium sulphate (purity > 99%) of residue analysis grade were obtained from Merck. Florisil (0.15–0.25 mm) of residue analysis grade and silica gel (Gel 60) of chromatographic analysis quality were also obtained from Merck. Before use, the Florisil and silica gel were baked overnight at 550 °C and kept in an oven at 180 °C. Silica gel modified with sulphuric acid (44%, *w/w*) was prepared by slowly adding an appropriate amount of sulphuric acid to the activated silica at room temperature. All glassware was cleaned using chromosulphuric acid, rinsed consecutively with Milli-Q water, methanol, and acetone, and dried overnight at 180 °C before use.

2.2. Samples and sample treatment

Fish samples (salmon and tuna) were purchased from a local supermarket and were selected for the analysis of SCCPs since they are among the most frequently fish products found in the Spanish diet [32]. Salmon was of aquaculture origin, while tuna was caught in the Mediterranean Sea. Once fish was washed, the non-edible parts were removed to obtain the muscle clean tissue and it was triturated, homogenized, and lyophilized for three days. Then, the dried tissue was ground in a glass mortar to a fine powder and stored in glass vials in the dark at 4 °C before analysis.

The extraction of the lyophilized fish samples was performed on an ASE 100 Accelerated Solvent Extractor System (Dionex, Sunnyvale, CA). Before pressurized liquid extraction (PLE), an adequate amount of the δ-HCH was added to 1 g of the freeze-dried fish sample, which was left overnight at room temperature to equilibrate. The sample was then mixed with sodium sulphate at a fish/Na_2SO_4 ratio of 1:2 (*w/w*) in a mortar until a homogenous mixture was obtained. The extraction cell (34 mL) was loaded by inserting a glass fibre filter into the cell outlets, followed by 20 g of acidified silica (44% sulphuric acid) as the fat retainer and the sample. Fish samples were extracted at 100 °C with a solvent mixture of n-hexane/CH_2Cl_2 (1:1, *v/v*) using 3 cycles of 5 min each and working at 1500 psi, a flush volume of 60% and a purge time of 90 s. For fractionation, the extract was then concentrated to ca. 2 ml using a rotary evaporator at room temperature and carefully transferred to the top of a glass column (200 mm × 15 mm I.D.) filled with 15 g of activated Florisil, previously rinsed with 50 mL of n-hexane. Two fractions were collected: (F1) with 30 mL of n-hexane followed by 80 ml of a solvent mixture of n-hexane/CH_2Cl_2 (95:5, *v/v*), that contained the PCBs and PBDEs, and (F2) with 30 mL of a mixture of n-hexane/CH_2Cl_2 (1:1, *v/v*) where the SCCPs were eluted. The extracts were then rotary evaporated to approximately 2 mL adding 100 μL of isooctane as a keeper. Afterwards, the extract was carefully concentrated under a gentle nitrogen stream up to 50 μL and 1 μL was injected into the GC-APPI-HRMS system after adding an adequate amount of $^{13}C_6$-HCB as injection internal standard to obtain a final concentration of 5 ng mL^{-1} in the final extract.

2.3. GC-APPI-HRMS instrumentation

SCCP determination was achieved on a Trace 1300 gas chromatograph coupled to a Q-Exactive Orbitrap mass spectrometer (Thermo Fisher Scientific, San Jose, CA, USA), employing an atmospheric pressure photoionisation source (GC-APPI) (MasCom Technologies GmbH, Bremen, Germany). The chromatographic separation was carried out using a TG-5MS (15 m × 0.25 mm I.D., 0.25 μm film thickness) fused-silica capillary column (Thermo Fisher Scientific). Helium was used as carrier gas at a constant flow rate of 1.0 mL min^{-1}. The injector was operated at 270 °C in splitless injection mode (1 min) and the injection volume was 1 μL. The oven temperature was set as follows: 90 °C (held for 1 min) to 200 °C at 20 °C min^{-1} and then to 300 °C at 15 °C min^{-1} (held for 5 min). The transfer line, source and capillary temperatures were set at 280 °C, 200 °C and 180 °C, respectively. The GC-APPI source was equipped with a 10.6 eV krypton lamp (Syagen, Santa Ana, CA, USA) and operated in the negative ion mode due to the high electronegativity of the target compounds. For the photoionisation of SCCPs, vapours of acetone/carbon tetrachloride (3:1 *v/v*, 70 μL min^{-1}) were used as optimal dopant/reagent mixture, and nitrogen was employed as make-up gas (gas pressure of 5 a.u.). Moreover, S-Lens RF was set at 20% to improve the ion transmission to the mass analyser. Data were acquired in full-scan mode from *m/z* 60 to *m/z* 700 at a mass resolution of 70,000 FWHM (full width at half maximum at *m/z* 200). Besides, to achieve the highest sensitivity with a well-defined peak shape (at least 12 points per peak), the automatic gain control (AGC) and maximum injection time were set at $1 \cdot 10^6$ and 50 ms, respectively. The extracted ion chromatograms (XICs) were obtained using mass extraction windows with a tolerance of ±5 ppm to guarantee a high selectivity and quality of the results. Xcalibur υ 3.1 software was employed to control the instrument setup and process the data acquisition.

2.4. Quality control criteria

Specific tests to check the GC separation, the sensitivity of the GC-APPI-HRMS and the validity of the calibration were carried out daily. Procedural blanks covering both instrumental and sample preparation procedures were routinely performed during the analysis, and a quality control material consisted of a salmon

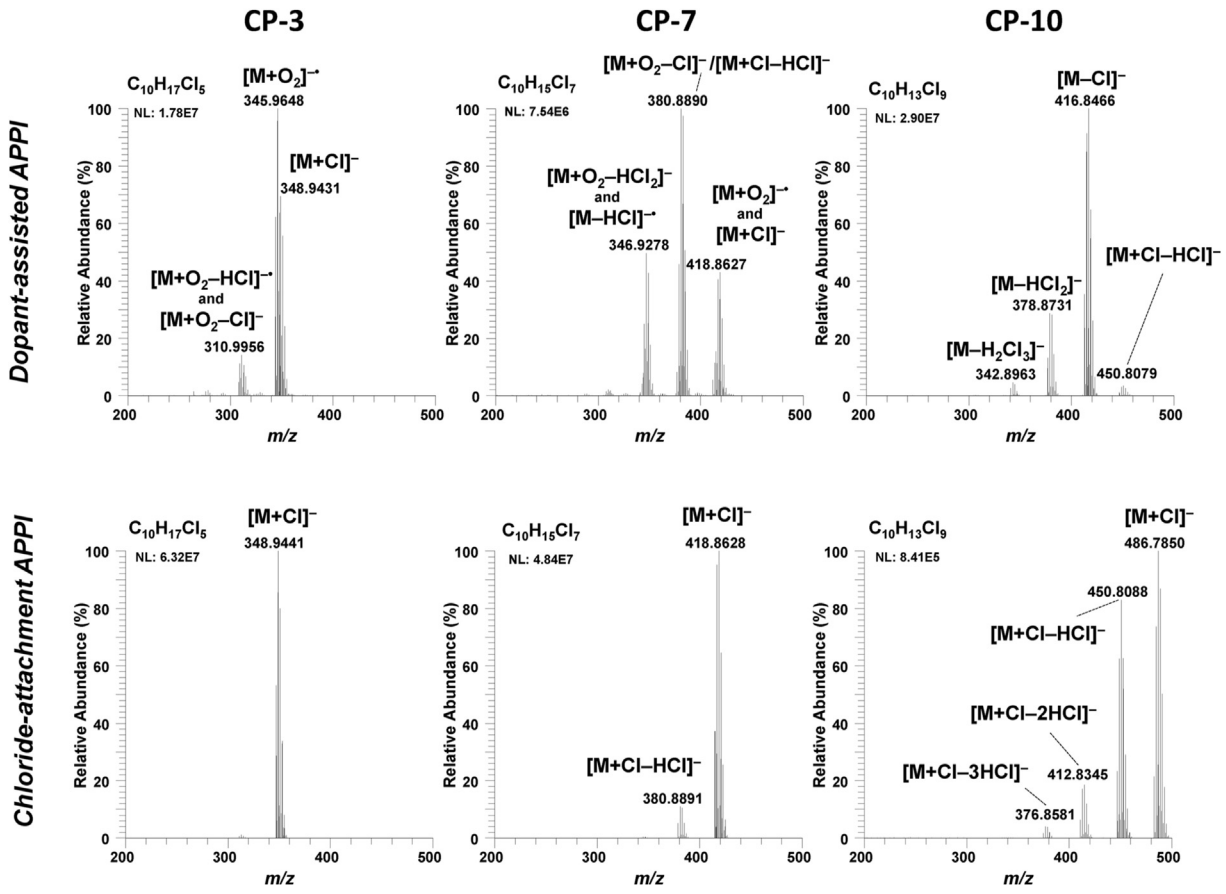

Fig. 1. GC-APPI-HRMS mass spectra of 1,2,5,6,9-pentachlorodecane (CP-3) (*left*), 1,2,4,5,6,9,10-heptachlorodecane (CP-7) (*middle*), and 1,2,3,4,5,6,7,8,9-nonachlorodecane (CP-10) (*right*) obtained by dopant-assisted APPI with acetone (*up*) and chloride-attachment APPI with acetone/CCl_4 (3:1, *v/v*) (*down*).

sample with non-detectable amounts of the SCCPs spiked at 0.5 ng g^{-1} wet weight (ww), was periodically analysed to ensure that the whole analytical method was maintained under control. Recoveries of target compounds were routinely checked and ranged between 91 and 96% for the total SCCP content. Moreover, the Orbitrap mass analyser was calibrated every 72 h using an electrospray source with a calibration solution containing caffeine, MRFA peptide, Ultramark 1621 and butylamine in acetonitrile/methanol/water (2:1:1, *v/v*) with 1% (*v/v*) formic acid, to ensure the accuracy on the mass calibration and resolution. Instrumental (iLOQs) and method limits of quantification (mLOQs) were experimentally established by analysing SCCP standards and a blank salmon spiked at low concentration levels. Intra-day precision was routinely tested by analysing (n = 3) a quality control material (blank salmon spiked at 0.5 ng g^{-1} ww).

3. Results and discussion

3.1. Ionisation of SCCPs by GC-APPI

The ionisation of SCCPs by GC-APPI was focused on the formation of characteristic ions of each homologue group that avoids potential isobaric interferences between CP congeners with different carbon chain lengths and chlorination degrees. The ionisation must be assisted by a dopant since direct photoionisation does not take place in negative ion mode. Thus, vapours of several organic solvents, such as toluene, acetone, chlorobenzene, anisole, and tetrahydrofuran, were evaluated as possible dopant using a mixture of individual CP congeners (Mix 2). For all evaluated dopants, similar behaviour was observed in the mass spectra for all the compounds. For instance, the 1,2,4,5,6,9,10-heptachlorodecane ($C_{10}H_{15}Cl_7$) mass spectrum using toluene as dopant showed two abundant cluster ions corresponding to the superoxide $[M+O_2]^{-\bullet}$ and chloride $[M+Cl]^-$ adduct ions (see Fig. S1). In addition, some intense in-source CID fragments corresponding to the losses of Cl and HCl from the two adduct ions were generated, increasing the number of potential isobaric interferences with other CP congeners. Under these conditions, differences in the abundances of these characteristic ions were observed in the mass spectra of CP congeners depending on the chlorination degree. For instance, Fig. 1 (*up mass spectra*) shows the GC-APPI-HRMS mass spectra using acetone as a dopant of a penta-, hepta- and nonachlorodecane, respectively. Generally, the mass spectra for CPs with less than six chlorine atoms were characterised by a $[M+O_2]^{-\bullet}$ adduct ion as peak base and an intense $[M+Cl]^-$ adduct ion as can be seen in Fig. 1 for 1,2,5,6,9-pentachlorodecane (CP-3 congener). Meanwhile, the $[M+O_2-Cl]^-$ and $[M+Cl-HCl]^-$ in-source CID fragments were the most abundant cluster ions for heptachlor-substituted congeners (Fig. 1, CP-7 congener). Finally, the mass spectra for SCCPs with eight or more chlorine atoms only showed in-source CID fragments corresponding to successive losses of HCl or Cl units from the molecular ion and the formation of the superoxide adduct ion was not observed (Fig. 1, CP-10 congener). These different ionisation behaviours could lead to isobaric mass interferences due to the overlap of ions coming from the coeluting CP congeners. Considering the last advances on the anion-attachment APCI as an alternative technique for the ionisation of short-chain chlorinated paraffins [9,22–24,33], the formation of a chloride adduct ion in a

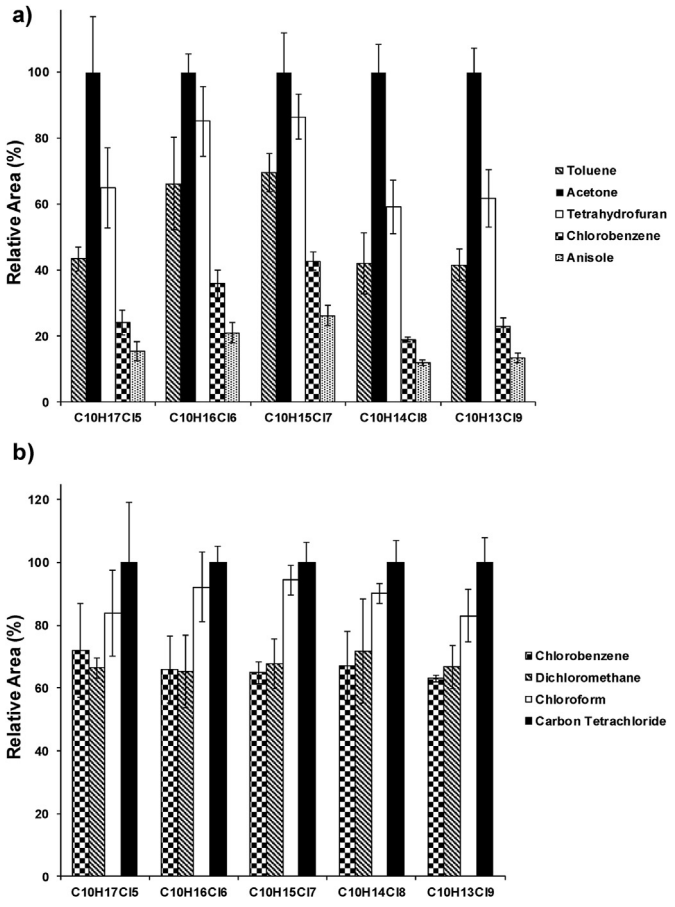

Fig. 2. Effect of dopant mixtures a) solvent/CCl_4 (3:1 *v/v*) and b) acetone/chlorinated agent (3:1 *v/v*) on the abundance of chloride adduct ion for individual chlorinated C_{10}-paraffins.

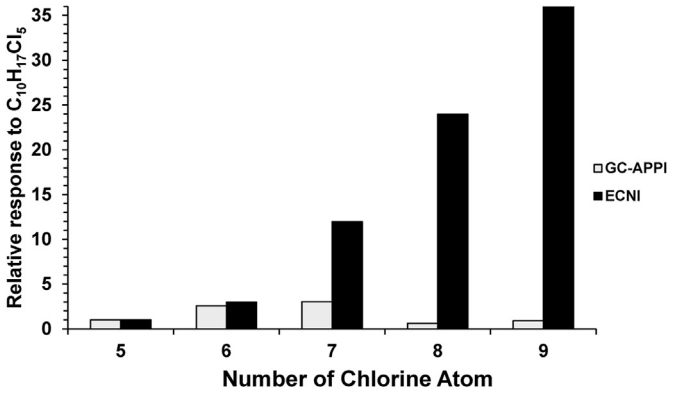

Fig. 3. Effect of the number of chlorine atoms on the response of the $[M+Cl]^-$ and $[M-Cl]^-$ ions obtained by GC-APPI-HRMS and GC-ECNI-MS, respectively.

GC-APPI source could be an excellent way to achieve an efficient ionisation of these compounds. Thus, the addition of a chlorinated solvent to the dopant for favouring the formation of chloride adduct ions was investigated. To do this, dopant (toluene, acetone, chlorobenzene, anisole, and tetrahydrofuran) and chlorinated solvent (chlorobenzene, dichloromethane, chloroform and carbon tetrachloride) vapour mixtures were introduced into the GC-APPI source in a 3:1 (*v/v*) ratio for optimising the response of the $[M+Cl]^-$ adduct ions. Fig. 2 (a) shows the effect on the response of individual CP congeners of solvent mixtures of dopants and carbon tetrachloride as a gas-phase reagent. Among them, acetone provided the best results for all the compounds. This may be due to the high vapour pressure of the acetone that increases the number of electrons released at the source during the photoionisation process and, consequently, improves the ionisation efficiency of the analytes. Therefore, acetone was chosen as the best dopant solvent for the optimal ionisation of the target compounds. To select the most appropriate chlorinated solvent to promote the formation of chloride adduct ions, mixtures of acetone with chlorobenzene, dichloromethane, chloroform, and carbon tetrachloride (3:1, *v/v*) were also tested (Fig. 2(b)). Under these conditions, the highest abundance of $[M+Cl]^-$ adduct ions were obtained with CCl_4 as a reagent solvent. This could be attributed to the lower dissociation energy of the C—Cl bond for CCl_4 (70 kcal/mol) compared to that required by the other chlorinated solvents (77—81 kcal/mol) which may favour the presence of a greater number of chlorine atoms in the gas phase [34]. The use of this dopant/chlorinated solvent mixture hindered the formation of $[M+O_2]^{-\bullet}$ due to the displacement of oxygen present in the APPI source by a chloride-enriched cloud. In addition, the abundance of the in-source CID fragmentation decreased and only ions from successive losses of HCl from the chloride adduct ion were observed in the mass spectra (Fig. 1, *down mass spectra*). Moreover, for SCCPs with more than seven chlorine atoms, the base peak of the mass spectrum depended on the reagent solvent used to release chlorine atoms. For instance, the 2,3,4,5,6,7,8,9-octachlorodecane (CP-9, $C_{10}H_{14}Cl_8$) generated a chloride adduct ion as base peak when chloroform or carbon tetrachloride was used, whereas $[M+Cl-2HCl]^-$ was the most intense ion using dichloromethane or chlorobenzene (Fig. S2). The amount of dopant/reagent ratio was also optimised from 10:1 (*v/v*) to 1:10 (*v/v*) at a fixed flow rate of 70 μL min^{-1}, obtaining the maximum $[M+Cl]^-$ response for all the compounds at a 3:1 (*v/v*) ratio of acetone/carbon tetrachloride.

Other GC-APPI critical parameters, such as source and capillary temperatures, were also optimised. The source and capillary temperatures were evaluated between 200 °C and 250 °C and from 160 °C to 200 °C, respectively (Fig. S3). Since the source temperature strongly affected the fragmentation of chloride adduct ions, a source temperature of 200 °C was selected. Also, the best responses for all the compounds were obtained at a capillary temperature of 180 °C. Thus, it was possible to obtain a low fragmentation in mass spectra and, therefore, diminishing the risk of possible isobaric interferences between congeners. Under these conditions, a minimum resolution of 28,441 (FWHM) was required to overcome the internal interferences between homologue congener groups, avoiding the application of deconvolution or other mathematical procedures.

3.2. Quantification of SCCPs by GC-APPI-HRMS

Generally, an important disadvantage of the GC-ECNI-MS methods is the strong dependence of the response with the chlorination degree of the CP congeners, which increases with the number of chlorine atoms, making more difficult the quantitative determination of the analytes. To evaluate the behaviour of the GC-APPI source with the chlorination degree of SCCP congeners, several experiments were conducted to determine the response factor of each homologue group. Thus, a mixture of individual CP congeners (Mix 2) was analysed with the GC-APPI-HRMS method by monitoring the most abundant ions of the $[M+Cl]^-$ cluster (Table S1). Fig. 3 shows the relative responses obtained for the individual SCCP congeners using chloride-attachment APPI and ECNI. As can be observed, the relative responses of the SCCP congeners achieved using chloride-attachment APPI were more similar to

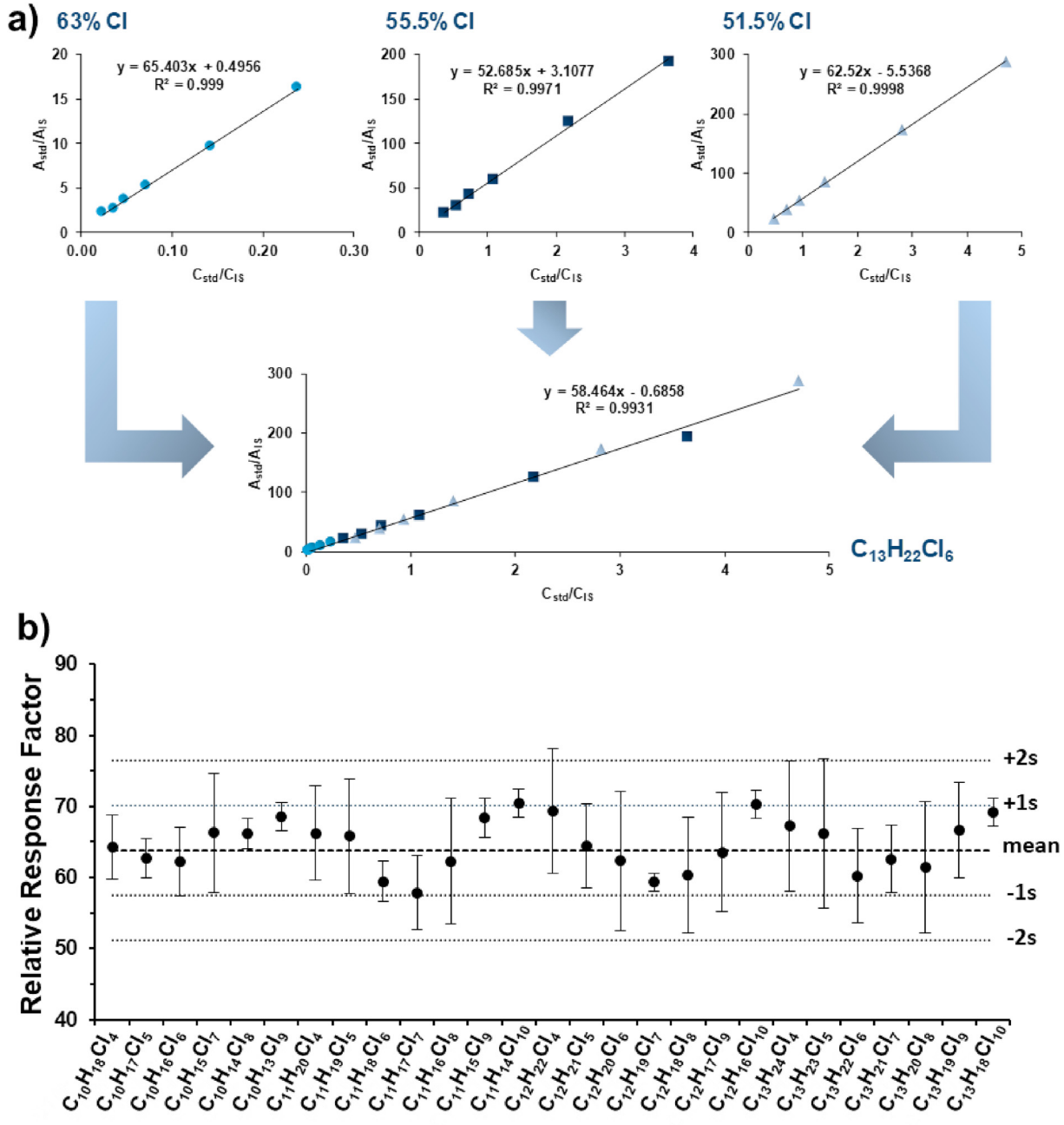

Fig. 4. a) Calibration curves of the homologue group $C_{13}H_{22}Cl_6$ using individual SCCP standard formulations (51.5%, 55.5% and 63% Cl) and a mixture of them and b) relative response factor plot of the homologue groups in the three SCCP standard formulations.

each other than those obtained with ECNI, in which the responses increased with the number of chlorine atoms in the molecule. In addition, the small differences observed in the APPI responses between congeners may be attributed to the length of the carbon chain or the effect of the position of the chlorine substituents in the molecule over the ionisation. Therefore, it can be deduced that the response of the chloride adduct ions by GC-APPI mainly depended on the concentration, considering negligible the effect of both the number and the position of chlorine atoms in the molecule. Therefore, it is possible to determine the concentration of each homologue group of congeners by an internal normalization. Thus, the contribution of each homologue group to the total SCCP area can be related to their concentrations in the SCCP mixture. Tables S2–S4 show the homologue group concentrations determined for the commercially available SCCP standard mixtures with a total chlorine content of 63%, 55.5%, and 51.5%. Using this approach, the profile concentrations found in the standard mixtures with different chlorine content were in agreement with those previously reported using direct injection-APCI-HRMS (TOF) method [22]. For quantitative purposes, calibration solutions of each SCCP standard mixtures were prepared at concentrations ranged from 0.5 to 5 mg L^{-1} (total concentration of SCCPs) and the calibration curves for each homologue group were determined using the internal standard method. As an example, Fig. 4(a) shows the calibration curves obtained for the $C_{13}H_{22}Cl_6$ homologue group in the three available SCCP mixtures. Generally, good linearity for all the homologue groups was achieved with determination coefficients (r^2) ranging from 0.991 to 0.999. Moreover, by combining

Table 1
Quality parameters of the GC-APPI-HRMS method using SCCP mixtures.

Homologue Group	Concentration found (mean ± sd, pg μL^{-1})		Precision (RSD %)		Trueness (RE %)	
	Low Level[a]	Medium Level[b]	Low Level[a]	Medium Level[b]	Low Level[a]	Medium Level[b]
$C_{10}H_{18}Cl_4$	0.49 ± 0.03	1.35 ± 0.06	6	4	1	−8
$C_{10}H_{17}Cl_5$	6.2 ± 0.2	16.8 ± 0.4	3	2	5	−5
$C_{10}H_{16}Cl_6$	10.6 ± 0.5	29 ± 1	4	4	5	−3
$C_{10}H_{15}Cl_7$	9.3 ± 0.4	27 ± 1	4	4	3	1
$C_{10}H_{14}Cl_8$	3.58 ± 0.04	10.5 ± 0.2	2	2	5	2
$C_{10}H_{13}Cl_9$	0.19 ± 0.01	0.56 ± 0.01	5	2	−4	−4
$C_{10}H_{12}Cl_{10}$	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]	n.d.[c]
$C_{11}H_{20}Cl_4$	4.0 ± 0.1	11.5 ± 0.6	3	5	8	3
$C_{11}H_{19}Cl_5$	34 ± 2	94 ± 5	6	5	4	−5
$C_{11}H_{18}Cl_6$	50 ± 2	135 ± 5	4	4	3	−7
$C_{11}H_{17}Cl_7$	49.9 ± 0.3	135 ± 3	1	2	4	−6
$C_{11}H_{16}Cl_8$	56 ± 2	154 ± 4	4	3	1	−8
$C_{11}H_{15}Cl_9$	6.7 ± 0.5	19.3 ± 0.8	7	4	−0.4	−5
$C_{11}H_{14}Cl_{10}$	0.35 ± 0.02	1.04 ± 0.02	6	2	−5	−6
$C_{12}H_{22}Cl_4$	3.7 ± 0.1	10.0 ± 0.4	3	4	7	−4
$C_{12}H_{21}Cl_5$	32 ± 1	87.9 ± 0.9	3	2	4	−5
$C_{12}H_{20}Cl_6$	47.5 ± 0.7	128 ± 4	2	3	5	−6
$C_{12}H_{19}Cl_7$	48 ± 3	141 ± 2	6	2	3	0.2
$C_{12}H_{18}Cl_8$	32 ± 1	91.8 ± 0.7	3	1	1	−5
$C_{12}H_{17}Cl_9$	13.3 ± 0.7	38 ± 1	5	3	1	−5
$C_{12}H_{16}Cl_{10}$	1.98 ± 0.09	5.4 ± 0.2	5	4	5	−4
$C_{13}H_{24}Cl_4$	1.62 ± 0.06	4.4 ± 0.1	4	2	4	−7
$C_{13}H_{23}Cl_5$	15.4 ± 0.4	42 ± 2	3	5	4	−5
$C_{13}H_{22}Cl_6$	26 ± 1	71 ± 1	4	2	2	−6
$C_{13}H_{21}Cl_7$	24 ± 1	69 ± 3	4	4	1	−4
$C_{13}H_{20}Cl_8$	20.3 ± 0.9	59 ± 2	4	3	−1	−5
$C_{13}H_{19}Cl_9$	12.1 ± 0.3	34.6 ± 0.7	3	2	1	−4
$C_{13}H_{18}Cl_{10}$	2.7 ± 0.1	8.0 ± 0.1	4	2	−2	−2
Total SCCPs	515 ± 16	1429 ± 80	3	6	3	−5

[a] Total SCCP concentration low level: 500 pg μL^{-1}
[b] Total SCCP concentration medium level: 1500 pg μL^{-1}
[c] n.d.: not detected.

Table 2
Quantification of the total SCCPs (ng g^{-1} wet weight) in selected fish samples using different approaches.

Sample	Concentration (mean ± s, n = 3)	
	SCCP standard mixture	Mix of three SCCP formulations[a]
Salmon #1	25.8 ± 1.2[b]	25.3 ± 1.2
Salmon #2	26.0 ± 0.3[b]	25.3 ± 0.2
Salmon #3	28.3 ± 0.9[b]	27.5 ± 0.9
Tuna #1	6.3 ± 0.4[c]	5.7 ± 0.4
Tuna #2	30.0 ± 1.0[c]	28.5 ± 1.3

[a] Standard mixture of SCCP formulations with 51.5%, 55.5%, and 63% Cl content.
[b] Quantified with a SCCP standard mixture with a 55.5% Cl content.
[c] Quantified with a SCCP standard mixture with a 63% Cl content.

the calibration data of the three SCCP mixtures in a single calibration curve, a good correlation between areas and concentrations was achieved ($r^2 > 0.993$), suggesting that the response of each homologue group did not depend on the total chlorine content of SCCP formulation used for quantification. Fig. 4(b) shows the mean of the relative response factors (RRF) obtained for each homologue group in the three SCCP formulations. As can be seen, a good agreement between all RRF values was achieved with a variability, expressed as a relative standard deviation, lower than 10%. In addition, all the results were within the range of (mean±2s), demonstrated that the responses were independent of the chlorination grade of the compounds. Therefore, it is not necessary to know the chlorine content of the samples before analysing for selecting the adequate standard for the quantification. Using this approach, a considerable reduction in the analysis and data processing time was achieved, especially over ECNI-based traditional methodologies.

3.3. Performance of the GC-APPI-HRMS method

To examine the feasibility of the developed GC-APPI-HRMS method for the determination of SCCPs instrumental and method quality parameters were established. Instrumental limit of detection (iLOD), defined as the lowest amount injected that is possible to detect on a well-defined broad hump of at least one congener group of SCCPs, was established for all the SCCP mixtures (51.5% Cl, 55.5% Cl and 63% Cl). iLODs ranged from 1 (SCCPs with 51.5% Cl) to 2 pg injected (SCCPs with 55.5% Cl and 63% Cl) of the total amount of SCCP formulation. Moreover, iLODs of each homologue group of congeners were also determined (Table S5) and ranged from 0.07 to 0.19 pg injected. These values were lower than those achieved by direct injection-APCI-qTOF (0.2–100 pg μL^{-1} for 5 μL injected) [22], and slightly lower than the values obtained by GC-ECNI-HRMS (0.03–2.02 pg injected) using an Orbitrap mass analyser [10]. Table 1 shows the quality parameters of the developed method calculated using the SCCP standard mixtures in a working range, expressed as the total amount of SCCP mixture, from 0.25 to 5 ng μL^{-1} at two different concentration levels (depending on the homologue group). Good precisions were achieved for each homologue group and the total SCCPs with relative standard deviation lower than 7%. The trueness of the developed method was also quite good with relative errors (RE, %) lower than 8%. Method limits of detection (mLODs) were determined by analysing a blank salmon sample spiked with the target compounds at low concentration levels (pg g^{-1} ww). Low mLODs were obtained for all the SCCPs mixtures and ranged from 17 to 35 pg g^{-1} ww. All these figures of merit demonstrated the good performance of the GC-APPI-HRMS method for the reliable quantification of SCCPs.

The selectivity of the GC-APPI-HRMS method for the

Table 3
SCCP concentrations (ng g^{-1} wet weight) of each homologue group in the selected fish samples.

	Concentration (ng g^{-1} wet weight)[a]				
Homologue	Salmon #1	Salmon #2	Salmon #3	Tuna #1	Tuna #2
$C_{10}H_{18}Cl_4$	0.0531 ± 0.0005	0.071 ± 0.006	0.050 ± 0.006	0.005 ± 0.001	<MLOQ[c]
$C_{10}H_{17}Cl_5$	0.96 ± 0.07	1.35 ± 0.02	1.06 ± 0.03	0.040 ± 0.003	0.0117 ± 0.0003
$C_{10}H_{16}Cl_6$	1.8 ± 0.1	2.56 ± 0.04	1.69 ± 0.04	6.4 ± 0.4	0.0032 ± 0.0004
$C_{10}H_{15}Cl_7$	0.31 ± 0.02	0.31 ± 0.01	0.231 ± 0.005	–	<mLOQ[c]
$C_{10}H_{14}Cl_8$	0.035 ± 0.002	0.025 ± 0.002	0.009 ± 0.001	–	–
$C_{10}H_{13}Cl_9$	<mLOQ[b]	–	–	–	–
$C_{10}H_{12}Cl_{10}$	–	–	–	–	–
$C_{11}H_{20}Cl_4$	0.21 ± 0.01	0.28 ± 0.01	0.23 ± 0.02	0.012 ± 0.001	1.00 ± 0.03
$C_{11}H_{19}Cl_5$	3.3 ± 0.2	4.46 ± 0.08	3.9 ± 0.2	0.035 ± 0.003	10.9 ± 0.1
$C_{11}H_{18}Cl_6$	3.9 ± 0.2	4.52 ± 0.03	4.1 ± 0.1	0.012 ± 0.001	10.2 ± 0.7
$C_{11}H_{17}Cl_7$	1.1 ± 0.1	1.01 ± 0.05	1.00 ± 0.04	0.0054 ± 0.0004	4.7 ± 0.4
$C_{11}H_{16}Cl_8$	0.28 ± 0.02	0.10 ± 0.01	0.125 ± 0.004	0.0032 ± 0.002	1.8 ± 0.1
$C_{11}H_{15}Cl_9$	0.046 ± 0.006	<mLOQ[b]	<mLOQ[b]	–	0.19 ± 0.01
$C_{11}H_{14}Cl_{10}$	0.017 ± 0.001	–	–	–	0.045 ± 0.004
$C_{12}H_{22}Cl_4$	0.27 ± 0.02	0.40 ± 0.01	0.36 ± 0.04	0.007 ± 0.001	<mLOQ[c]
$C_{12}H_{21}Cl_5$	1.98 ± 0.03	2.45 ± 0.04	2.5 ± 0.1	0.0032 ± 0.003	0.011 ± 0.001
$C_{12}H_{20}Cl_6$	2.03 ± 0.05	1.91 ± 0.05	2.21 ± 0.09	<mLOQ[c]	0.022 ± 0.002
$C_{12}H_{19}Cl_7$	1.7 ± 0.2	0.48 ± 0.03	1.94 ± 0.03	<mLOQ[c]	0.015 ± 0.002
$C_{12}H_{18}Cl_8$	0.24 ± 0.02	0.0162 ± 0.0003	0.180 ± 0.006	<mLOQ[c]	0.0047 ± 0.0009
$C_{12}H_{17}Cl_9$	0.059 ± 0.005	<mLOQ[b]	0.013 ± 0.001	–	<mLOQ[c]
$C_{12}H_{16}Cl_{10}$	0.079 ± 0.007	–	–	–	–
$C_{13}H_{24}Cl_4$	0.54 ± 0.04	0.69 ± 0.05	0.63 ± 0.06	0.0052 ± 0.0002	<mLOQ[c]
$C_{13}H_{23}Cl_5$	1.7 ± 0.1	1.66 ± 0.03	1.9 ± 0.1	0.0033 ± 0.0005	<mLOQ[c]
$C_{13}H_{22}Cl_6$	1.40 ± 0.06	1.10 ± 0.06	1.77 ± 0.06	<mLOQ[c]	<mLOQ[c]
$C_{13}H_{21}Cl_7$	1.04 ± 0.09	0.11 ± 0.01	1.22 ± 0.02	<mLOQ[c]	<mLOQ[c]
$C_{13}H_{20}Cl_8$	0.43 ± 0.04	0.13 ± 0.02	0.44 ± 0.02	<mLOQ[c]	<mLOQ[c]
$C_{13}H_{19}Cl_9$	0.098 ± 0.008	<mLOQ[b]	0.032 ± 0.002	–	<mLOQ[c]
$C_{13}H_{18}Cl_{10}$	0.024 ± 0.003	–	–	–	–

[a] Calculated as the mean (n = 3) ± standard deviation.
[b] mLOQ (Salmon): 0.002–0.008 ng g^{-1} ww.
[c] mLOQ (Tuna): 0.001–0.003 ng g^{-1} ww.

determination of SCCPs in the presence of some potential interfering compounds such as PCBs and organochlorine pesticides was investigated. Thus, two standard mixtures containing seven CB congeners (PCB-Mix 1) and twenty-two organochlorine pesticides (Pesticide-Mix 1037) (see section 2.2.) at a concentration of 1 ng μL^{-1}, were injected under the established GC-APPI-HRMS conditions. The ionisation efficiency achieved for most of these compounds was very poor even at these high concentration levels. PCBs yielded the $[M-Cl+O]^-$ ions while most of the studied pesticides generated the $[M+Cl]^-$ ion as the base peak of the mass spectra. The minimal resolution (R_{min}) required for avoiding possible interferences from polychlorinated biphenyls and organochlorine pesticides was estimated at 13,251 FWHM (Table S6). This minimal resolution was even lower than that required for avoiding the potential isobaric interferences between CP congeners (28,441, FWHM). Therefore, the use of the proposed GC-APPI-HRMS method, which operated at a resolution of 70,000 (FWHM, at *m/z* 200), provided a selectivity high enough to the determination of SCCPs with a negligible contribution of internal and external interferences.

3.4. Analysis of fish samples

To evaluate the real applicability of the developed GC-APPI-HRMS method for the determination of SCCPs in environmental samples, selected fish samples (three salmon and two tuna samples) were analysed in triplicate. Table 2 summarizes the results of the total SCCP concentrations obtained using a SCCP formulation which showed the most similar homologue composition to the analysed samples, and a standard mixture with similar amounts of the three SCCP formulations (51.5%, 55.5% and 63% Cl). Total SCCP concentrations ranged between 25.8 and 28.3 ng g^{-1} ww for salmon samples and from 6.3 to 30 ng g^{-1} ww for tune samples, with a precision, expressed as RSD%, lower than 7%. In addition, no significant differences were observed between the results obtained with the two calibration methods (p-value > 0.82), demonstrating the feasibility of the mixture of the three standard formulations for accurate quantification of SCCPs. Besides, the concentration profiles of the homologue groups showed that the C_{11}-chlorinated paraffins were the predominant congener group, especially for the $C_{11}H_{19}Cl_5$ and $C_{11}H_{18}Cl_6$ isomers (Table 3). Fig. 5 shows as an example the concentration profiles of the homologue groups found in a salmon sample and the SCCP standard mixtures with 63%, 55.5%, and 51.5% Cl content. As can be observed, the concentration profile of the salmon sample showed similarities with the homologue distribution of a SCCPs mixture with 55.5% and 51.5% chlorine content, although this last formulation contributed in a small proportion. So, a mixture of them should be used to avoid quantification errors when working with ECNI-based methods. However, this is not required when using the developed GC-APPI-HRMS method. Therefore, the use of the developed GC-APPI-HRMS method allowed the adequate quantification of both the total amount of SCCPs and the individual homologue groups of congeners using a mixture of commercially available SCCP standards with different chlorine content, which involves an important time reduction and a better selectivity than the traditional methods.

4. Conclusions

This work demonstrates, for the first time, the capabilities of the new GC-APPI source for the accurate determination of SCCP congeners in fish samples by GC-HRMS (Orbitrap). The use of chloride-

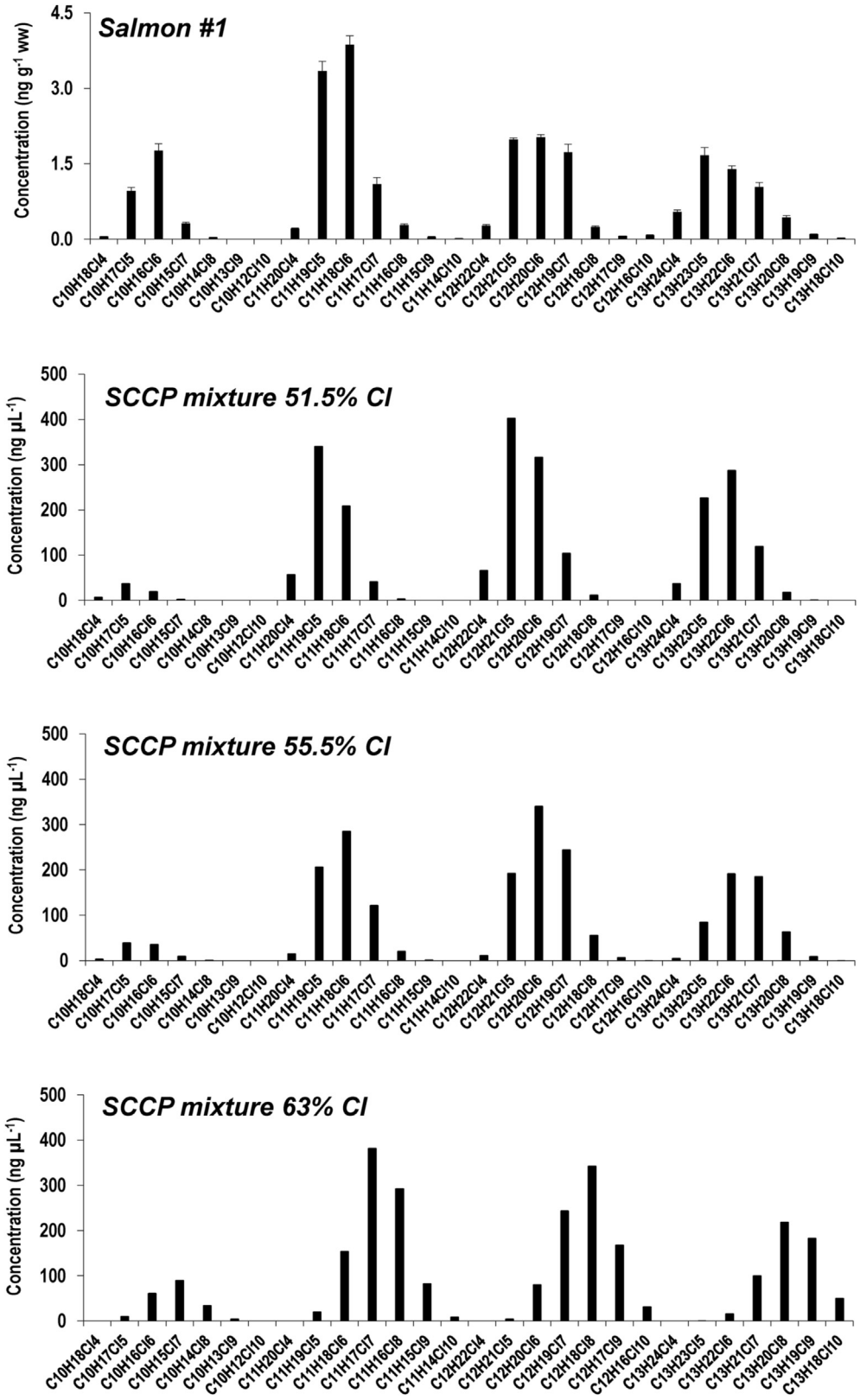

Fig. 5. Concentration profile of each homologue group of SCCPs obtained for sample #1 (salmon) and the standard formulations (51.5%, 55.5%, 63% Cl).

attachment approach combined with dopant-assisted GC-APPI-HRMS in the negative-ion mode with vapours of acetone/CCl_4, (3:1 *v/v*) allowed a high ionisation efficiency by the formation of intense $[M+Cl]^-$ adduct ions for all the homologue groups. In addition, monitoring of these adduct ions at high-resolution full-scan acquisition (70,000, FWHM) with an Orbitrap-HRMS instrument, the responses of the SCCP congeners were independent of the number of substituted chlorine atoms and were not affected by the possible interferences from other related halogenated compounds. The method allowed the accurate quantification of the specific CP-congener groups and total SCCPs by internal normalization method using mixtures of SCCP formulations with different chlorine contents (51.5%, 55.5%, and 63%) and provided valuable information on the homologue group composition and a significant reduction in the analysis time and data processing compared to established analytical methods. Therefore, chloride-attachment GC-APPI-HRMS can be proposed as a reliable alternative to the current methodologies for the analysis of SCCPs in complex environmental samples such as fish.

CRediT authorship contribution statement

J.F. Ayala-Cabrera: Conceptualization, Methodology, Investigation, Validation, Formal analysis, Writing – original draft. **M.T. Galceran:** Conceptualization, Methodology, Supervision. **E. Moyano:** Conceptualization, Methodology, Supervision, Project administration, Writing – review & editing. **F.J. Santos:** Conceptualization, Methodology, Supervision, Project administration, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aca.2021.338673.

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