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Full length article

## Cracked and shucked: GC-APCI-IMS-HRMS facilitates identification of unknown halogenated organic chemicals in French marine bivalves

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### ABSTRACT

High resolution mass spectrometry (HRMS)-based non-target analysis coupled with ion mobility spectrometry (IMS) is gaining momentum due to its ability to provide complementary information which can be useful in the identification of unknown organic chemicals in support of efforts in unraveling the complexity of the chemical exposome. The chemical exposome in the marine environment, though not as well studied as its freshwater counterparts, is not foreign to chemical diversity specially when it comes to potentially bioaccumulative and bioactive polyhalogenated organic contaminants and natural products. In this work we present in detail how we utilized IMS-HRMS coupled with gas chromatographic separation and atmospheric pressure chemical ionization (APCI) to annotate polyhalogenated organic chemicals in French bivalves collected from 25 sites along the French coasts. We describe how we used open cheminformatic tools to exploit isotopologue patterns, isotope ratios, Kendrick mass defect (Cl scale), and collisional cross section (CCS), in order to annotate 157 halogenated features (level 1: 54, level 2: 47, level 3: 50, and level 4: 6). Grouping the features into 11 compound classes was facilitated by a KMD vs CCS plot which showed co-clustering of potentially structurally-related compounds. The features were semi-quantified to gain insight into the distribution of these halogenated features along the French coast, ultimately allowing us to differentiate between sites that are more anthropologically impacted versus sites that are potentially biodiverse.

### 1. Introduction

Persistent Organic Pollutants (POPs) are of particular global concern primarily due to their poor degradability and also for their potential to accumulate in marine organisms. POPs have been implicated in the rise in marine mammal stranding, immunosuppression, reproductive impairment and population decline, and even mortality. (Pierce et al., 2008; Murphy et al., 2010; Bourillon et al., 2022) While action has been taken to regulate legacy POPs, new alternative chemicals are continuously introduced into the global market leading to their detection in different environmental matrices and urging the need to develop methods able to identify previously-unreported (or unidentified) contaminants. This new wave of chemicals gives rise to emerging POPs, chemicals which may have POP-like properties but are not yet regulated internationally as implementation of global regulations is a long process. (Wang et al., 2022).

To identify emerging POPs, VeillePOP (VEILLE POP, 2010) (Veille

sur les nouveaux polluants organiques persistants dans les mollusques marins, Prospective monitoring of persistent organic pollutants of emerging concern in marine mollusks) an interannual study is coordinated and conducted; funded by the French Office of Biodiversity (OFB). VeillePOP documents the levels and trends of contaminants of emerging concern (CEC) not routinely followed in monitoring programs, and for which limited (or no) data for the marine environment are available at national level. Started in 2010, intertidal mollusks are collected at different coastal and estuarine sites along the French coast, including those under the influence of French major watersheds. The sought contaminants have constantly evolved including brominated and chlorinated flame retardants (FRs) (Munsch et al., 2015), per- and poly-fluoroalkyl substances (PFASs) (Munsch et al., 2019), synthetic musks (Aminot et al., 2021), and organophosphate esters (Aminot et al., 2023) (flame retardants and plasticizers – OPEs). VeillePOP, which this work is a part of, aims to contribute to the improvement of knowledge on CEC, by providing essential spatial and temporal data on their presence in the

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marine environment and following the impact of regulations.

Interestingly, many legacy and emerging POPs are extensively halogenated, which for the case of chlorine and bromine-containing compounds, the presence of their stable isotopes makes them easy to notice in a mass spectrum. Due to the presence of isotopologues, chemicals that are structurally the same but contains atoms with different number of neutrons, the mass spectrum of polychlorinated or polybrominated compounds form specific patterns. This pattern can be exploited to infer the type and number of halogens present in a molecule using the relative ratios of the isotopologues and thus serve as additional confirmatory data. However, halogenation is not a characteristic exclusive to anthropogenic compounds as halogenated natural products (HNPs) possess similar features and structural scaffolds. (Vetter, 2006) Among the 30,000 marine natural products within the Comprehensive Marine Natural Products Database (CMNPD, <https://www.cmnpd.org/>) (Lyu et al., 2021), 2800+ are halogenated. The presence of HNPs in marine samples have been reported, sometimes at even higher concentrations than halogenated organic contaminants (HOCs). (Wu et al., 2021; Fernando et al., 2018) *How do we then unravel this chemical space, wherein many chemical features remain unknown?*

Non-targeted analysis (NTA) using high resolution mass spectrometry (HRMS), one of the most effective tools for comprehensively assessing chemical space, has recently revolutionized the ability of scientists to identify chemical contaminants. Instrumental innovations over the last decade alongside the increasing availability of open science tools and databases, has enabled the development of techniques that allow scientists to characterize chemical space to an extent that was previously onerous. Improvements in the mass accuracy, mass spectral acquisition speed, mass resolving power, sensitivity of HRMS instruments, and resolution of different chromatographic techniques enabled the detection of bioaccumulative chemicals in bivalves (Goto et al., 2020), fish and reptiles (Teehan et al., 2022; Renaguli et al., 2021), and marine mammals. (Hoh et al., 2012; Alonso et al., 2017; Cossaboon et al., 2019; Cariou et al., 2021) Using these capabilities, the mass spectrometry community have improved our ability to translate mass-to-charge data into chemical information including unambiguous chemical formula assignments and structural annotation elucidation.

Typically, GC-HRMS equipped with electron ionization (EI) is used for the measurement of semivolatile and volatile compounds like POPs. However, EI as a strong ionization technique suffers from considerable in-source fragmentation. While the fragmentation of the molecule is informative, it is only efficiently utilized if the compound is present in a database like NIST. Unfortunately, high resolution EI databases are currently limited to a few thousand compounds and is insufficient for NTA and does not provide coverage for HNPs. Moreover, the intensity of the precursor ion when measured in EI mode is relatively low if not present. It is then challenging to perform a database search to look for potential molecules that match the exact mass of the unknown feature. Electrospray ionization (ESI) is a soft ionization technique that has found many applications for the analysis of polar to semi-nonpolar organic contaminants. (Singh et al., 2021; Krier et al., 2022; Ulrich et al., 2019; Luo et al., 2020) However, many of the compounds of interest that are usually separated by gas chromatography, do not ionize well in ESI. To overcome this, we pursued the use of APCI as an ionization source for GC-based exposome analysis. APCI has been demonstrated to efficiently ionize EI amenable compounds with less in-source fragmentation which translates to improved sensitivity. (Strehmel et al., 2014; Zheng et al., 2018; Li et al., 2015) In a preliminary analysis of PCBs, PBDEs, and organochlorine pesticides, we observed better sensitivity using APCI in positive mode (APCI+) compared to EI. This is in agreement with several works that have demonstrated the utility of APCI+ for the analysis of POPs and emerging contaminants (Izquierdo-Sandoval et al., 2022; Megson et al., 2016; Zacs et al., 2019; Aalizadeh et al., 2022; Mesihää et al., 2017) specially because it forms molecular ions ( $[M]^+$  or  $[M + H]^+$ ) which translates to unambiguous formula prediction. On the other hand, in negative mode (APCI-),

polyhalogenated chemicals like PBDEs ionize by the simultaneous loss of a halogen and by gaining an oxygen atom or just the loss of a halogen. (Singh et al., 2020) While this won't be a problem for groups of molecules whose ionization mechanism is understood (which most likely means that standards are available), it can prove to be confusing for unknown molecules as we are not sure if what we are dealing with is the mass of an intact molecule or the mass of an adduct. Because of this, we decided to only pursue positive mode. By having access to the intact molecular ion information, workflows that have been demonstrated to work well for LC-HRMS, where database matching usually begins with a search for molecules that match the exact mass, can also be employed. In addition, accurately measured mass and isotopologue information translates to improved ability in chemical formula prediction and also structure elucidation using the fragmentation spectra. Thus far, the approaches mentioned above identify molecules on an individual basis, however, there is growing evidence on the presence of substances of unknown or variable composition, complex reaction products, or biological materials (UVCBs) in environmental matrices for which it may be helpful to use properties shared within a group of homologues to help elucidate their identity. (Lai et al., 2022).

Within the last five years, there have been several works that demonstrated the ability of IMS coupled with HRMS to help uncover the chemical exposome including, but not limited to, per- and polyfluoroalkyl substances (PFAS), polyaromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), and polybrominated diphenyl ethers (PBDEs). (Zheng et al., 2018; MacNeil et al., 2022; Celma et al., 2020; Foster et al., 2022) However, as the use of IMS in NTA is still at its infancy, there are still limited data on experimentally measured collisional cross section (CCS) values to allow database CCS matching. Moreover, the use of IMS in chemical exposome work has mostly been to complement mass measurements instead of being exploited for CCS as an indicator of chemical relatedness. In this context, we use relatedness to refer to the similarity in the structural backbone of the molecules being studied. Fundamentally, IMS is a measure of how an ionized molecule travels through a specific space under the influence of some force which varies depending on the type of ion mobility cell. The time it takes for a molecule to traverse this cell is a function of, but not limited to, its shape and size. It can then be imagined that molecules that contain the same molecular backbone or scaffold would travel the mobility cell at similar times with small differences due to the differences in functional groups present and how they are oriented in space. Another way scientists have identified structurally related compounds is by virtue of their Kendrick mass defect (KMD, equation (1) (Kendrick, 1963; Hughey et al., 2001). KMD is calculated from the difference of the Kendrick mass and the nominal Kendrick mass of an organic molecule. The Kendrick mass in this work was calculated by multiplying the measured  $m/z$  with the ratio related to a mass scale reflecting the substitution of  $^{35}\text{Cl}$  for H (Jobst et al., 2013), while the nominal Kendrick mass was obtained by rounding down the  $m/z$ . When plotted, structurally-related features align but spaced by the unit used for converting the measured  $m/z$  to the Kendrick mass, which can be custom-normalized depending on the sought after repeating unit (MacNeil et al., 2022; Koelmel et al., 2022).

$$\text{KMD} = \left( m/z \times \frac{34}{33.96012} \right) - \text{nominal Kendrick mass} \quad (1)$$

In this work, we take advantage of all these advances and demonstrate how IMS-HRMS was strategic in tentatively identifying polyhalogenated UVCBs in French marine bivalves using standards and existing annotations as a guide. We discuss in detail the strategies we used including: a) automatized identification of isotopologue series and their relative ratios using the open cheminformatic tool HaloSeeker (Léon et al., 2019); b) using Visualizer (Molecular formula from monoisotopic mass, 2022), an online resource for putative molecular formula calculation and automatic PubChem search; c) narrowing down list of predicted formulas using halogenation pattern; and d) KMD

(normalized to Cl) and CCS facilitated tentative identification of structurally-related polyhalogenated organic molecules. Ultimately, the workflow we developed enabled us to determine the distribution of the identified halogenated features along the French coast and to indirectly gain insight whether the halogenated chemicals we detected in bivalves are potentially of anthropogenic or of natural origins by comparing their geographical distribution. This paper, however, focuses mostly on the qualitative and semi-quantitative aspects of GC-HRMS NTA and should be interpreted as such.

## 2. Materials and methods

A brief description of the method used is presented below, with a detailed version available in the [supporting information](#) (SI). Each sample is made from whole soft tissue composite of either 50 mussels or 15 oysters (all depurated for 24 h) shelled and further shucked and freeze-dried.

**Sample Collection.** Bivalve samples were collected in 2019 or 2020 out of spawning season in different sampling sites along the French coast as part of VeillePOP. The sampling sites are marked in Figure S1 differentiating between sampling sites where mussels (*Mytilus*, blue spheres,  $n = 15$ ) or oysters (*Crassostrea*, yellow spheres,  $n = 10$ ) were collected. A total of 25 samples were processed.

### 2.1. Sample preparation

Samples were prepared following a method adapted from Sun *et al* (2012) (Sun *et al.*, 2012) (diagram available in Figure S2). The freeze-dried samples (1 g) were extracted in two steps with dichloromethane (DCM) after addition of surrogate standards (labeled with  $^{13}\text{C}$  or  $^2\text{H}$ , details in the SI) by pressurized liquid extraction (PLE, Dionex). The extract was purified twice: first by gel permeation chromatography (SX-3) then eluted using 50 mL of DCM / n-Hexane 3:97 (v/v) from a column of 5 g of deactivated silica at 5%  $\text{H}_2\text{O}$ . The extract was evaporated then spiked with 1,3,6,8-tetrachloro-9H-carbazole ( $^{13}\text{C}_{12}\text{H}_5\text{Cl}_4\text{N}$ , as internal standard, 50  $\mu\text{g}/\mu\text{L}$  in the final extract) before reconstituting with nonane to make a final volume of 50  $\mu\text{L}$ . All sample preparations were done in clean conditions (low-dust atmosphere and positive pressure). Prior to NTA, the extraction method was validated by calculating the recoveries of various halogenated chemicals including but not limited to legacy POPs, PCBs, and PBDEs. Briefly, the mean matrix-matched and blank corrected recoveries for polychlorinated pesticides were between 62.9 and 114.1%, except for beta and gamma hexachlorohexanes which were below 20%, 68.5 to 97.2 for PCBs, and 64.8 to 129.9 for PBDEs. A complete list of the chemicals used, their detected levels in the blanks and unspiked matrix-matched samples, and their individual recoveries are summarized in the excel sheet SI, under the 'List of standards + recoveries' tab. Two procedural blanks were prepared per sample batch (6 total) and analyzed together with the samples in addition to solvent blanks. Features were considered if the intensity is at least three times higher than the average in the blank levels. Peak areas were normalized using the peak area of the internal standard. Analytes were semi-quantified using the peak area of their corresponding isotopically labelled surrogate standard whenever available otherwise using their structural analogs. A complete list of isotopically-labelled surrogates are in the word SI.

### 2.2. Instrumental parameters

Analyte separation was accomplished using a Scion 456-GC equipped with an Rxi-5Sil MS column (40 m  $\times$  0.18 mm, 0.18  $\mu\text{m}$ , Restek, Bellefonte, PA, USA, with helium as carrier gas (flow rate 3.0 mL/min). The injection (2  $\mu\text{L}$ ) was carried out at 280  $^\circ\text{C}$  in "splitless" mode. Atmospheric pressure chemical ionization (GC-APCI II) ion source (Bruker, Billerica, MA, USA) operating in positive mode was used followed by mass detection via a Bruker Daltonics timsTOF (trapped ion mobility

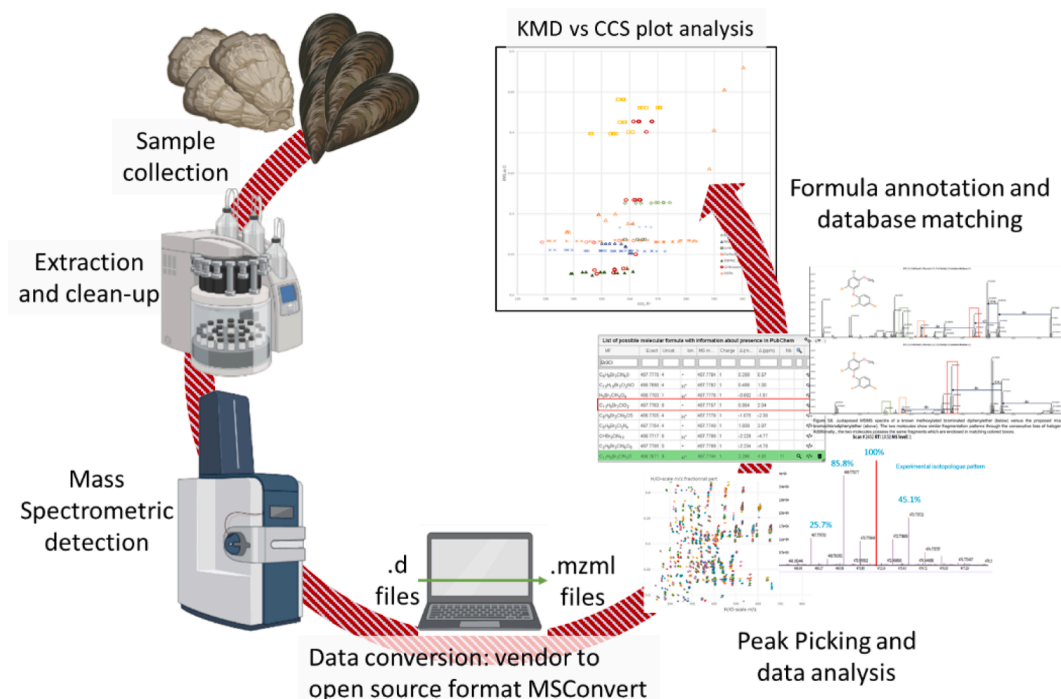
spectrometry coupled with time-of-flight high resolution mass spectrometry) in IMS (or TOF)-full scan and data-dependent MSMS (ddMS2) modes, respectively. HRMS data was acquired in positive mode, over a range of  $m/z$  from 100 to 1000 at a resolving power of  $> 40,000$  at  $m/z$  622 (at 3.5 Hz acquisition rate). The GC oven is programmed from 120 to 300  $^\circ\text{C}$ , over a total time of 25 min. One limitation of this work is that it only allows elution of small to intermediate molecules; modifications are needed to cater to higher molecular weight compounds. The GC-APCI source (heated by transfer line) and the transfer line are operated at 300  $^\circ\text{C}$  (capillary transfer is at 250  $^\circ\text{C}$ ) with a corona current of 1.8  $\mu\text{A}$  and ultra-pure nitrogen (99.999%) as the sheath and auxiliary gas. The final workflow developed for the identification of halogenated organic compounds in marine bivalves is shown in Fig. 1. Standard mixtures of organochlorine pesticides (OCPs), PCBs, PBDEs, emerging brominated and chlorinated chemicals, and HNPs, were analyzed together with the sample extracts forming our in-house database ( $n = 152$  compounds), and an alkane mix was run for determination of Kovats retention indices. The mass and mobility calibration was done in ESI mode, every two days, by a direct infusion of the ESI-LTuning Mix from Agilent Technologies (Part number: G1969-85000), as prescribed by the instrument manufacturer. The front end was then switched to a GC-APCI source for sample analysis.

### 2.3. Data analysis workflow

Identification of halogenated features in bivalve samples was performed in two phases. The first phase entailed target screening the data for the features that we have standards for while the second phase involved the use of several open software for identifying and annotating potentially halogenated features. Raw Bruker files (.d format) were converted to the standard open format (.mzML) using MSConvert (a feature of the open tool Proteowizard (version: 3.0.21045-7732b6429). (Adusumilli and Mallick, 2017) HaloSeeker 2.0, an open tool written in the R-language, was used for automatized peak picking, feature alignment, and identification of potentially chlorinated and brominated features ( $\text{F}_2 +$ ); complete software parameters are outlined in the SI. (Léon *et al.*, 2019) Molecular formula were predicted for the unknown features using Visualizer ([cheminfo.org](https://cheminfo.org)) (Molecular formula from monoisotopic mass, 2022) using the following elements:  $\text{C}_{0-100}$   $\text{H}_{0-200}$   $\text{N}_{0-20}$   $\text{O}_{0-20}$   $\text{Cl}_{0-10}$   $\text{Br}_{0-10}$   $\text{I}_{0-4}$   $\text{F}_{0-20}$ , considering both  $[\text{M}]^+$  and  $[\text{M} + \text{H}]^+$  formation at 10 ppm mass accuracy. [Cheminfo.org](https://cheminfo.org) houses various freely available chemistry tools including formula prediction which function from the internet browser. The proposed formulas were narrowed down using the halogenation profile. Identification confidence levels were assigned using a GC-HRMS specific scoring system (Koelmel *et al.*, 2022). The open tool El-Maven (Agrawal *et al.*, 2019), allowed us to query our data without relying on vendor software. The list of masses identified through HaloSeeker was used to manually inspect the extracted ion chromatograms accessed through El-Maven. El-Maven facilitated the processing of ddMS2 data in the.mzML format, manual grouping of samples, visualization of the extracted ion chromatogram within a user-specified mass error (in ppm), inspection and comparison of experimental isotopologue relative ratios against the predicted theoretical isotopologue distribution of the formulas provided by EnviPat, and also visualization of the corresponding fragmentation spectra, if present. (Loos *et al.*, 2015) An example is provided in the SI (Figure S3-S7) to walk the reader through the steps required to go from unknown mass to putative identifications using the unknown  $m/z$  467.7767. Note that we used the monoisotopic mass for formula predictions as most tools use this information as input, however, for semi-quantitation we used the peak area of the exact mass (also referred to as intensoid mass which is the mass of the most abundant isotopologue) for extracting ion chromatograms as it provides better sensitivity.

The ion mobilities were extracted then converted to CCS from the raw files using Data Analysis software 5.3 (Bruker Daltonics, Bremen Germany). For visualization, we plotted KMD (Cl scale) versus CCS.





**Fig. 1.** Non-target analysis workflow (counter clockwise) starting from sample collection and preparation (includes shelling, pooling, freeze drying, and homogenization) of marine bivalves, sample extraction and clean-up, mass and ion-mobility spectrometry detection, data conversion (ProteoWizard), peak picking (HaloSeeker) and analysis (EL-Maven), and annotation using various open and online resources. A more detailed version is available (Fig. S2B).

Where applicable, predicted CCS were calculated freely using dmCCS within CCSBase ([https://ccsbase.net/dmccs\\_predictions](https://ccsbase.net/dmccs_predictions)) (Ross et al., 2020) using the SMILE strings of the putative structures. The SMILE strings were obtained through ChemSketch (free from ACD labs) (Free Chemical Drawing Software for Students | ChemSketch. ACD/Labs, 2023). The annotated features were semi-quantified using surrogate standards where applicable or using the peak area of the closest structural analog (details in the SI). The differences in the spatial distribution of the contaminants and natural products found in this work are then described to gain insight into which areas are more anthropologically impacted and which areas are potentially biodiverse.

### 3. Results and discussions

#### 3.1. KMD vs CCS plot facilitates grouping of structurally-related compounds

Using our workflow, we were able to ultimately annotate 157 compounds in French bivalves composed of HOCs and HNPs. The list of HOCs were predominantly composed of 49 PCB congeners ( $Cl_{2-9}$ , confidence level 1: 29 compounds, confidence level 2: 20 compounds) with 6 PBDEs (confidence level 1: 3 compounds, confidence level 2: 3 compounds) and 9 DDT-related compounds (confidence level 1: 3 compounds, confidence level 4: 6 compounds). On the other hand, we also found 19 halogenated anisole containing features (confidence level 1: 4 compounds, confidence level 2: 13 compounds), 21 halogenated 1-ethoxy-2-methylbenzene (EMB) derivatives (all confidence level 3), 30 brominated hexahydroanthene derivatives (BHDS, confidence level 1: 4 compounds, confidence level 3: 26 compounds), and 25 halogenated N-heterocycles (confidence level 1: 12 compounds, confidence level 2: 11 compounds, confidence level 3: 2 compounds) many of which are putative HNPs. While several Diels-Alder OCPs (e.g. dechloranes) and legacy POPs were analyzed as part of this work, we only detected them in standard mixtures but not in our samples, and thus will not be discussed further. A summary of the features found (together with their

compound class, predicted formula,  $m/z$ , mass error in ppm, retention time, retention index, mobility, CCS, and annotation confidence level) and their semi-quantified concentrations in each sampling point are summarized in the spreadsheet SI under ‘Feature Analytical Information’ and ‘Analyte Concentration Summary’ tabs, respectively.

Annotation of unknown features that matched chemicals present in the in-house database was straightforward, however, many of the unknown features were identified by virtue of a KMD (CI scale) against CCS plot (Fig. 2). Note that this was a deliberate departure from the more commonly used  $m/z$  vs CCS (Zheng et al., 2018) and  $m/z$  vs KMD (MacNeil et al., 2022) plots. For better comparison, the halogenated features found in this work were plotted and a juxtaposition of the three different plots are presented in the SI (Figure S8). One advantage of the KMD vs CCS plot is that it allows inference of potentially structurally related chemicals which forms easily distinguishable clusters or form a straight line. The identified groups were color and marker coded to aid visualization. Compared to the  $m/z$  vs CCS plot (Figure S8 B), where it is challenging to identify chemicals belonging to the same class, there is better separation of different compound classes in a KMD vs CCS plot even before the point markers were modified to discriminate between different compound classes. While this feat can be partially achieved using an  $m/z$  vs KMD plot (Figure S8 C), the use of CCS with KMD allows the visualization of different isomers present which would normally overlap in an  $m/z$  vs KMD plot. Isomers overlap in Figure S8 C resulting in the false simplicity of the plot.

The use of CCS has already been described for the measurement of PAHs, PBDEs and PCBs using drift tube and travelling wave ion mobility technologies. (Zheng et al., 2018; Izquierdo-Sandoval et al., 2022; Foster et al., 2022) To see how well our CCS measurements compare to published data, we calculated the percent difference between some representative PCBs (CB 28, 52, 105, 118, 153, 180, and 189) and PBDEs (47 and 99) measured in this work using the data provided by Izquierdo et al (Izquierdo-Sandoval et al., 2022) as reference. For these compounds, the difference was found to be between 2.6 and 5.2%, which is minimal considering that different instruments were used for measuring CCS.



**Fig. 2.** Kendrick mass defect (Cl scale) vs CCS ( $\text{\AA}^2$ ) of the halogenated organic contaminants and natural products, standards and unknowns, used (standards) or found (samples) in this study. Structures of some chemicals representative of the different compound classes are included inside squares whose color match their respective class together with the symbol on the upper left corner. BDE: brominated diphenyl ether; DDTs: dichlorodiphenyltrichloroethane related compounds; OCP: organochlorine pesticide; HNP: halogenated natural product; HOC: other halogenated organic contaminant; PBDE: polybrominated diphenylether; EMB: 1-ethoxy-2-methylbenzene.

However, we recommend a comparison of a bigger number of chemicals to properly establish the interplatform comparability of CCS measurements.

### 3.2. DDT-related chemical, PCBs, and PBDEs

Nine potentially DDT-related compounds were found using the extracted ion chromatogram for the in-source fragment of DDT ( $m/z = 235.0081$ ) which for the features found in this work had very similar CCS values (range:136.1–138.3  $\text{\AA}^2$ ). Unlike other chemical groups found in this work, DDT-related compounds suffered from in-source fragmentation that prevented observation of the molecular ion. Nevertheless, using reference standards, we were able to confidently annotate *p,p'*-DDD, *p,p'*-DDE, and *p,p'*-DDT. The other peaks were annotated, with the exception of two peaks, using information obtained from the work of Mackintosh et al and DDT-related reference standards analyzed in this work and expert knowledge on DDT-related compounds in marine bivalves. (Mackintosh et al., 2016) The highest levels of the DDT-related compounds were found in the Bay of Biscay and Mediterranean Sea sampling locations specifically Hérault Bay (HéB) and Prévost lagoon (PrL), and also the sampling sites along and near the Seine estuary. The three most abundant DDT-related chemicals were *p,p'*-DDE, *p,p'*-DDD, and *p,p'*-DDT. DDT-related chemicals are widespread POPs and were also detected in blue mussel from the Baltic Sea and Jakarta Bay via a non-target approach. (Rebryk and Haglund, 2021; Dwiytino et al., 2016).

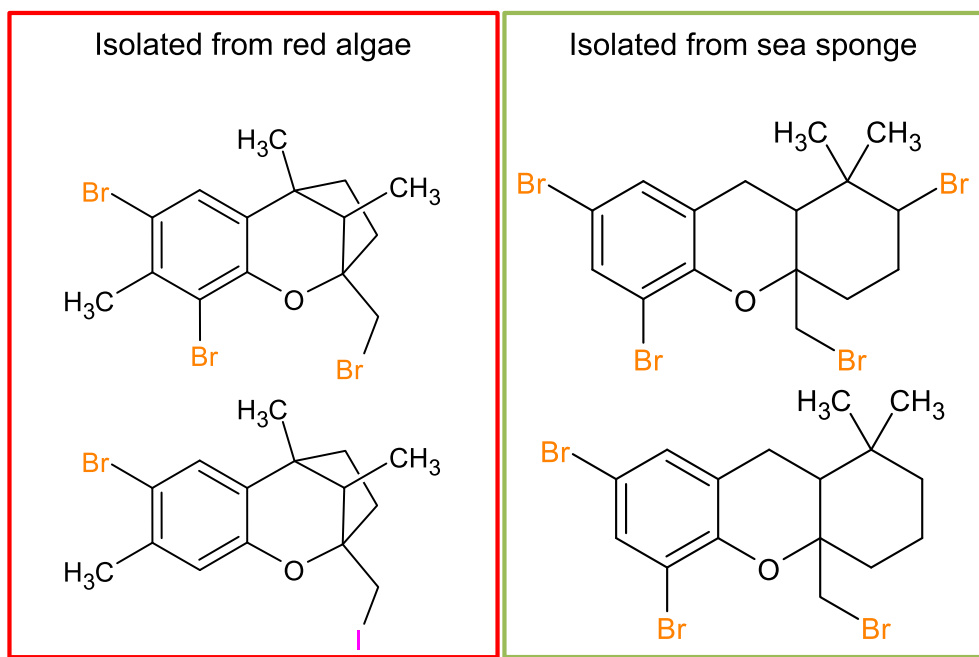
The highest levels of PCBs and PBDEs, on the other hand, were detected in the sampling points along and near the Seine estuary, the South Bay of Biscay, and the Loire estuary. A total of 49 PCB congeners were found, 19 of which we did not have standards for (four octachloro-, three heptachloro-, four hexachloro-, five pentachloro-, two tetrachloro-, and one dichlorobiphenyl) but were confirmed based on the co-clustering of their CCS with known PCBs, exact mass, isotope pattern, and fragmentation spectra. The five most abundant PCBs detected were CB 153, CB 138, CB 183, CB 149, and CB 174. BDE-47 and BDE 99 were

highest in the Bidassoa estuary. It is encouraging to see that certain locations have relatively lower levels of known organic contaminants including the Western English Channel, Seudre estuary, and Arcachon bay.

### 3.3. Polybrominated hexahydroxanthene derivatives (BHDs)

BHDs are polyhalogenated compounds of natural origin (Covaci et al., 2007; Hiebl et al., 2006; Vetter et al., 2007) that have been reported in various marine biota. (Covaci et al., 2008) Using a standard mixture provided by Professor Walter Vetter (University of Hohenheim, details regarding the synthesis of this standard mixture is described in Vetter et al) (Vetter et al., 2018) we were able to identify (level 1) one tetrabromo- and one tri-bromo-BHD. In addition, we were also able to observe three tetrabromo and two tribromo- BHD components that have not been described previously. Furthermore, 23 additional BHD-related compounds were identified by screening CMNPD for structurally-related chemicals. (Lyu et al., 2021) This includes 1  $C_{15}H_{16}Br_4O$ , 2 isomers of  $C_{15}H_{17}Br_3O$ , 5 isomers of  $C_{15}H_{18}Br_2O$  (CMNPD691) (CMNPD691, 2022), 3 isomers of  $C_{16}H_{18}Br_2O$  (CMNPD4344) (CMNPD4344, 2022), 3 isomers of  $C_{15}H_{19}BrO$  (CMNPD6648) (CMNPD6648, 2022), 4 isomers of  $C_{15}H_{18}Br_2O$  (CMNPD699) (CMNPD699, 2022), and 5 isomers of  $C_{16}H_{17}Br_3O$  two pairs of which were co-eluting but were distinguishable by IMS (Figure S9). These features form several clusters in Fig. 2, presented as yellow squares (KMD range: 0.39 to 0.44), suggesting molecular scaffold similarity, including 6 other features ( $C_{15}H_{16}Br_4O$  and 5 isomers of  $C_{16}H_{17}Br_3O$ ) with formula assignments but for which evidence of previous reports are not currently available. A zoomed-in version of the BHD cluster including the proposed structures are available in Figure S10. Some representative structures are presented in Fig. 3. BHDs were found to be highest, and almost exclusively, in sampling sites along the Mediterranean coast, especially in Hérault Bay (HéB), Prévost lagoon (PrL), and Thau Lagoon (ThL).

While this group of compounds were mostly reported to be isolated from sea sponge (CMNPD3828, 2022; CMNPD3829, 2022), the three



**Fig. 3.** Proposed structures of a few BHD-related compounds found to be most abundant in bivalve samples collected from the Mediterranean Sea. Inside the red box are those originally reported to be isolated from red algae (*Laurencia microcladia*, *Laurencia caraibica*) while those in the green box were reported in sea sponge (*Cacospongia* sp.). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

tetrabrominated (CMNPD16760, 2022) and five monobromoiodinated (CMNPD691, 2022) features that were found in this work were originally reported to be isolated from red algae, and are highest in Thau lagoon (ThL). This suggests that the organisms responsible for the biosynthesis of these chemicals thrive in this potentially biodiverse region, however, the same region is also impacted by historical contaminants as highlighted in the previous section.

### 3.4. Methoxylated halogenated diphenylethers

10 methoxylated BDEs (4-tetrabrominated and 6-pentabrominated, confidence level 1: 2 compounds, confidence level 2: 8 compounds) (Fig. 2 green circles, KMD: 0.31) were found to be present in French bivalves. In addition, five of our unknowns demonstrate a halogenation profile consistent with a molecule possessing 3 bromines and 1 chlorine (Fig. 2, red circles, KMD: 0.32) for which the closest formula match was  $C_{13}H_8Br_3ClO_2$ . Among the predicted formula matches, only one had a PubChem match  $C_{11}H_5Br_3ClN_3O$  and has 11 positional isomers. The predicted CCS for this group of compounds is  $160.0 \text{ \AA}^2$  which is well within the range of CCS values for the 5 features in our dataset (range:  $158.6\text{--}163.7 \text{ \AA}^2$ ). Despite the seemingly good match, PubChem records suggest that this is a precursor for pharmaceutical manufacturing, which did not make sense for the Charente estuary as we are not aware of any such activity in the area. Moreover, the observed fragments of the unknown molecule were challenging to explain using the structure proposed by PubChem. Looking back at the KMD vs CCS plot, these unknown features cluster right above methoxylated BDEs (MeOBDEs), suggesting that the structural scaffold may be similar to BDEs which made us think that these are potentially methoxylated-bromochlorodiphenylethers (MeOBCDEs). Methoxylated-bromochlorodiphenylethers have been reported in mussels (Malmv rn et al., 2005) and dolphin blubber (Alonso et al., 2017), while Agarwal et al described chlorinated BDE analogs, which are hydroxylated and methoxylated at the same time, extracted from marine sponges. (Agarwal et al., 2015) On the other hand, chlorinated BDEs have been reported as byproducts of PBDE pyrolysis. (Rupp and Metzger, 2005; Tue et al., 2019; Liang et al., 2022) A comparison of the fragmentation

spectrum of a methoxylated tetrabromodiphenylether standard that elutes within 0.43 min of one of the peaks shows similar fragments (Figure S11, SI) which supports the hypothesized structural backbone suggested by the CCS of the unknown features. MSMS spectra (acquired by electron ionization) provided by Alonso et al (Alonso et al., 2017) are in agreement with the spectra we obtained from this work (acquired by APCI) despite using different ionization methods. The annotation process of this group of halogenated features highlighted for us the utility of the KMD vs CCS approach for grouping together structurally similar compounds. We also wish to emphasize the importance of verifying that the observed fragmentation spectrum is able to support the proposed structure acquired from database matching. The highest concentrations of MeOBDEs and MeOBCDEs were mostly detected on sampling sites along the Atlantic coast from the South Bay of Biscay all the way to the English Channel, and interestingly had lower concentrations in the general Seine estuary area and the open water Mediterranean sampling sites.

### 3.5. Halogenated N-heterocycles

Five types of halogenated N-heterocycles were found including methylindoles (confidence level 3: 2 compounds), carbazoles (confidence level 1: 5 compounds), N-methylpyrrole (confidence level 1: 1 compound), dimethylbipyrroles (confidence level 1: 4 compounds, confidence level 2: 3 compounds, DMPs, Fig. 2, purple rhombi, KMD range: 0.28 to 0.29), and monomethylbipyrroles (confidence level 1: 2 compounds, confidence level 2: 8 compounds, MMPs, Fig. 2, brown rhombi, KMD range: 0.25 to 0.26).

Among the MMPs is Q1 ( $Cl_7$ ) (Vetter et al., 2000) which has been previously reported. Despite being structurally related, the median concentrations of MMPs were generally higher than DMPs in addition to differences in the geographical locations where DMPs and MMPs were found to be most abundant. MMPs were highest in ABE, ChI, UoI, and WCo bivalves, all located in the English Channel and of low anthropogenic pressure. DMPs, on the other hand, are relatively higher in the Mediterranean with four congeners found highest in Marseille Bay. Differences in the levels of MMPs and DMPs have also been reported in

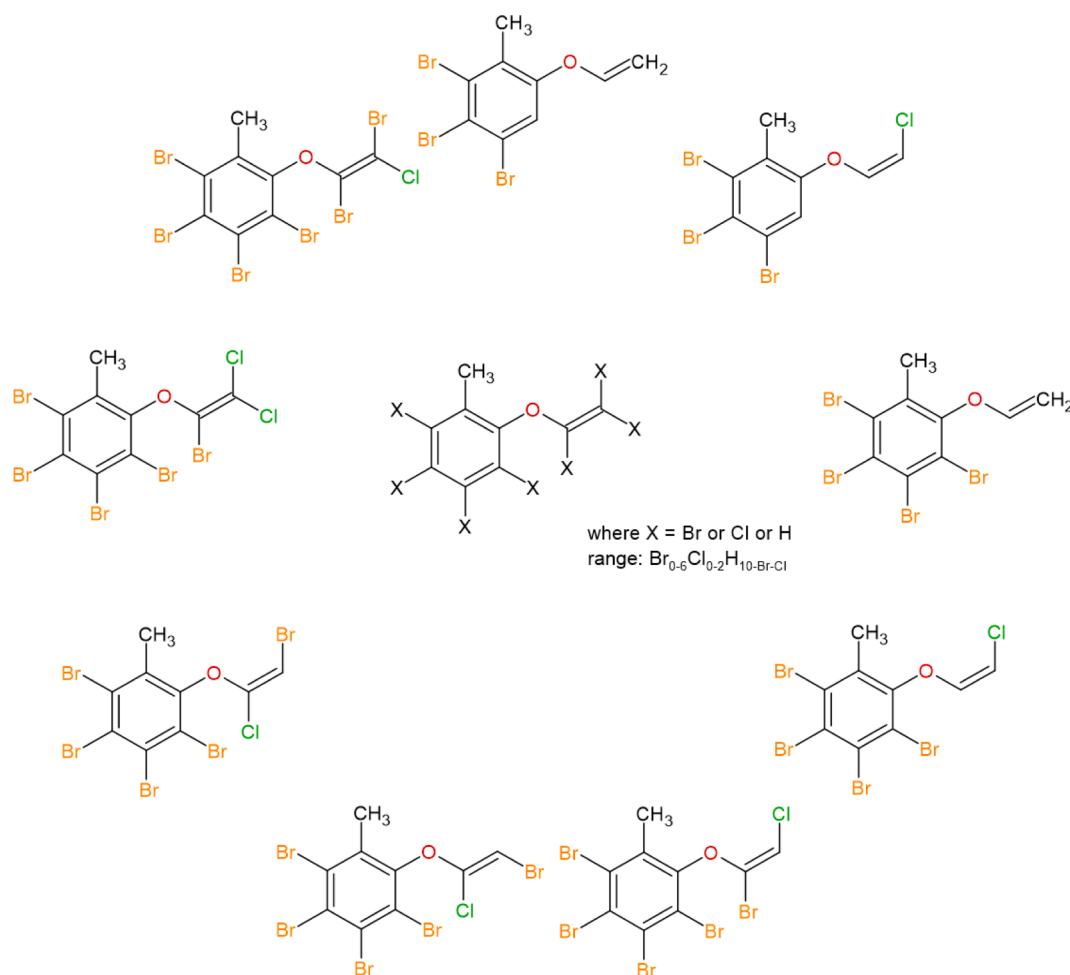
dolphins from different ecotypes (Shaul et al., 2015) suggesting that the presence of this group of compounds is influenced by environmental conditions. Kumar et al (Kumar et al., 2017) demonstrated how these chemicals can be produced through the action of ozone while Yang et al (Yang and Zhang, 2014) showed how halopyrroles can be produced as disinfection byproducts of chlorophyll. Using these works as guides, we hypothesize that these halogenated pyrroles are degradation byproducts/ transformation products that are formed in the marine environment as decaying organic matter that is rich in chlorophyll (precursor molecule, a natural polypyrrole compound) reacts with ozone and halides in seawater. (Kumar et al., 2017; Yang and Zhang, 2014) Compared to other sampling points in this study, the English Channel and the Mediterranean receive large inputs of water from the Loire and the Rhone estuaries, respectively. These estuaries receive water that had accumulated large amounts of decaying organic matter as their respective rivers go from source and empties to the sea. At the same time, the English Channel also receives nutrient rich water due to upwelling in the Bay of Biscay, which can then promote primary production. This rich supply of organic matter may be part of the reason why halogenated bipyrroles are observed to be higher in these locations. As for the difference in profiles between MMPs and DMPs, we think that an interplay between thermodynamics and kinetics may play a role, as the two locations have different climates with the English Channel being colder than the Mediterranean in addition to the difference in the abundance of starting material. Like other HNP, the exact origin of halogenated pyrroles is largely unknown despite being detected in many different studies. Bidleman et al (Bidleman et al., 2020) provides a more

comprehensive recent description of the documented potential sources of DMPs and MMPs among many other HNPs. Further work is warranted to fully understand the source of these compounds.

Like DMPs, brominated methylindoles were detected to be highest in the general Mediterranean area (Thau Lagoon). Halogenated carbazoles on the other hand has an interesting profile as the highest levels of the Br<sub>3</sub>-carbazole was found in the South Bay of Biscay (Bidassoa Estuary) while the highest levels of chlorinated-carbazoles were detected in the Gironde estuary. Like other halogenated N-heterocycles, the specific source of halogenated carbazoles is unclear. However, a recent study found that the marine red alga *Corallina officinalis* naturally produce halogenated carbazoles. (Zhang et al., 2023).

### 3.6. Compounds tentatively identified as halogenated 1-ethenoxy-2-methylbenzene analogs

The biggest challenge in this work was encountered for the lower most cluster (Fig. 2, green triangles, KMD range: 0.22 to 0.23) which is composed of 21 features of diverse halogenation. Literature search led us to a study of marine mussels collected from Hiroshima Bay, Japan (Goto et al., 2020), which also referred to a study of fish oil from Norway. (Hoh et al., 2009) In both studies, unknown mixed halogenated compounds, with the following proposed molecular formulae were reported: C<sub>9</sub>H<sub>6</sub>Br<sub>3</sub>ClO (5 and 2 isomers, respectively), C<sub>9</sub>H<sub>5</sub>Br<sub>4</sub>ClO (3 and 1 isomers), and C<sub>9</sub>H<sub>4</sub>Br<sub>5</sub>ClO (1 isomer) in mussels (Goto et al., 2020), which match some of the unknown features in our unknown cluster. In this work, we were able to find C<sub>9</sub>H<sub>6</sub>Br<sub>3</sub>ClO (3 isomers), C<sub>9</sub>H<sub>5</sub>Br<sub>4</sub>ClO (4



**Fig. 4.** Tentatively identified halogenated 1-ethenoxy-2-methylbenzene compounds found in French bivalves. The middle structure shows the common structural backbone surrounded by the different mixed-halogenated congeners identified in this work. The position of the halogens are arbitrarily assigned.



isomers, 2 co-eluting), and  $C_9H_4Br_5ClO$  (3 isomers). Additionally, we also found  $C_9H_7Br_3O$  (2 isomers),  $C_9H_6Br_4O$  (3 isomers), and one peak each for  $C_9H_3Br_5Cl_2O$ ,  $C_9H_3Br_6ClO$ ,  $C_9H_3Br_3Cl_4O$ ,  $C_9H_3Br_4Cl_3O$ ,  $C_8H_7Br_5O$ ,  $C_8H_6Br_4O_2$  (Fig. 4) which to the best of our knowledge were previously unreported. Despite their resemblance with monomers used in flame-retardant products (Hanson et al., 2011), and like in the Japanese study, we want to argue that this group of compounds has a backbone that is of natural origin due to their presence in French sampling sites that are relatively less impacted by human activity like ABE, CHI, USI, and WCO. Like the case for bipyrrroles, we propose that their molecular scaffolds of natural origin subsequently get halogenated through a series of complex reactions occurring at the air-sea interface. However, unlike the Japanese study which approached their proposed structure from a contaminant point of view, we want to propose a natural product approach.

We thought that if it is an HNP, then the dehalogenated backbone of the compound group may be present in the marine natural product database. We queried CMNPD for  $C_9H_{10}O$  and indeed found two potential candidates: 1-ethenoxy-2-methylbenzene (CMNPD30237, 2022) and p-vinylbenzyl alcohol (CMNPD16144, 2022). It is interesting to see how the structure of 1-ethenoxy-2-methylbenzene closely resembles the backbone structure of Allyl 2,4,6-tribromophenyl ether (PubChem, 2022) (PubChem CID: 76767) only differing by the placement of one methyl group. Inspection of available fragmentation spectra of some of the features found in this work reveal a loss of  $-CH_3$  and  $-OC_2H_3$  (Figure S12). Furthermore, 1-ethenoxy-2-methylbenzene (EMB) has been reported to be extracted from *Coleofasciculus chthonoplastes*, a well-distributed cyanobacteria. (*Coleofasciculus chthonoplastes*, 2022) As enzymes facilitating incorporation of halogens in organic molecules are found in a broad range of organisms (Wagner et al., 2009), it is not surprising that a natural source for this cluster of HNPs exists. While we mention *C. chthonoplastes*, we are not saying that it is indeed the source of EMB-related HNPs, rather, organisms like or related to it may be the potential source. The widespread distribution of cyanobacteria may be able to explain its detection in Norwegian fish oil, Japanese mussels, and now this study. While p-vinylbenzyl alcohol is another potential option, the presence of a free alcohol group in its structure would render it to elute in a more polar fraction than the nonpolar binary solvent (DCM / nHex 3:97 (v/v) used in this work. Going back to the fragmentation spectra, only EMB has a structural scaffold that can explain the mass losses observed for the EMB-related compounds with MSMS (Figure S9). A summary of the proposed structures for features within this compound class is shown in Fig. 4.

Out of curiosity, we predicted the CCS of these proposed HNPs using CCSBase. (Ross et al., 2020) As we do not know the exact positioning of the halogens, we tried to predict CCS for different halogen positional isomers but the model predicts the same CCS irrespective of halogen placement. We also predicted CCS for the proposed structures by Goto et al (Goto et al., 2020) and obtained the same values. While the predicted CCS values were encouraging as they only varied between 0.5 and 6.0% when compared to the experimental CCS values, its predictive power is not yet enough to discriminate between positional isomers. EMB-derivatives with lower levels of chlorination (higher degree of bromination) are highest in the South Bay of Biscay while EMB-derivatives with higher chlorination level are highest in the Western English Channel sampling areas.

A more detailed summary of individual concentrations per sampling location is available in the SI under the “Analyte Concentrations Summary” tab. We arranged these features by compound class and rank-colored them. One challenge in this work is to be able to discriminate between anthropogenic and natural compounds. As a step towards this goal, we tested whether hierarchical cluster analysis (excel sheet SI, “Hierarchical Cluster Analysis” tab) would enable us to see how the different features would cluster considering that we are sure of the sources of some of our annotated features.

### 3.7. Hierarchical clustering analysis

There is a clear clustering of the halogenated features by sampling region (Excel sheet SI, Hierarchical Cluster Analysis tab). Samples that were collected from sites that are within proximity of each other generally cluster together including (color coded map together with HCA plot): the relatively pristine sites of the Western English Channel West Cotentin, Chausey island, Aber Benoit estuary, and Ushant island (red cluster), the Mediterranean Sea sites of Marseille bay, gulf of Fos, Hérault bay, Prévost lagoon, and Thau lagoon (orange cluster), the South Bay of Biscay sites of Adour, Bidassoa, and Nivelle estuaries (yellow cluster), the sites of the Eastern English Channel Somme bay, Seine bay, and Seine estuary including Elorn estuary (green cluster), the main macrotidal estuaries of the Bay of Biscay Loire and Gironde estuaries together with Charente and Vilaine estuaries, Pen Be, and Bourgneuf Bay (blue cluster), Etel estuary (purple cluster), and the Seudre estuary with Arcachon bay (light blue cluster, draining small catchments in the North part of the Bay of Biscay). The clustering of sampling sites within relative proximity of each other is not surprising considering that, in general, the bivalves may be exposed to the same types of regional organic contaminants and also that proximate ecosystems likely host the same marine organisms from which HNPs are produced.

Three general clusters, by compound, were observed for the features found in this work. The lowestmost cluster is composed of mostly PCBs, PBDEs, several DDT-related compounds and monochlorinatedcarbazoles. The middle cluster, compared to the first one, mostly consists of HNPs specially BHDs, EMB-derivatives, and DMPs. Lastly, the topmost cluster is made up of some EMB-derivatives, MMPs, and halogenated diphenylethers (HDEs). It can be said that the clustering is mostly driven by the types of chemicals and where they are found to be highest or lowest. Several regions of interest are highlighted using black boxes and will be described from top to bottom below.

The first and second boxes are mostly defined by MeOBDEs and MeOBCDEs in the general Bay of Biscay region, together with brominated carbazoles. The third box shows how some EMB-derivatives with higher chlorination level and MMPs are highest in the Western English Channel sampling areas while the fourth box highlights how EMB-derivatives with lower levels of chlorination are highest in the South Bay of Biscay. Compared to the previous group of compounds, the fifth box is completely composed of BHD-related compounds with a hotspot in the Mediterranean, suggesting that the organisms responsible for the biosynthesis of these chemicals thrive in this region. The sixth box, biggest group, is made up of mostly PCBs, varying levels of chlorination, with highest concentrations being reported from the Seine estuary and the other members of the green location cluster and some from the orange cluster (South Bay of Biscay). BDE-47 and BDE 99 were highest in the Bidassoa estuary. It is interesting to note how the monochlorocarbazoles clustered together with known HOCs while the brominated carbazoles clustered together with HNPs and while it is tempting to suggest that one group is anthropogenic and the other natural, it requires more specific analysis to be able to do so. It is also noticeable how there are relatively lower levels of known organic contaminants in the red (Western English Channel) and light blue (Seudre estuary and Arcachon bay) clusters. However, the last box on the left shows a local hotspot of DDT-related compounds in the Mediterranean sampling points accounting for 7 out of 9 features found, which earlier was where a hotspot for BHD-related compounds was described. While this approach has, in its current form, clear limitations we encourage the further expansion of this work to include other organic contaminants of known sources to be able to assess if it is a suitable step forward into discriminating between bioaccumulative HOCs and HNPs.

In this work, we have demonstrated how NTA data can complement target analysis by identifying new types of bioaccumulative halogenated chemicals with unknown bioactivities and toxicities. While many of the identified chemicals are considered as natural products, HNPs are deemed to be chemical of emerging Arctic Concern by the Arctic

Monitoring and Assessment Programme. (AMAP Assessment, 2016) Furthermore, the study design allowed for the simultaneous identification of areas that are more impacted by contaminants and areas which are potentially biodiverse as evidenced by the presence of HNPs. While currently limited to nonpolar halogenated compounds, the approach used in this work can be expanded to more polar biota extracts to enable the exploration of a wider chemical space which includes semipolar to polar components of the chemical exposome. From a method point of view, the KMD vs CCS space allowed the database-free grouping together of unknown halogenated chemicals using an intrinsic property that is shared among compounds possessing the same molecular scaffold. We believe that this approach can benefit work on the identification of UVCBs in environmental matrices as many of the chemicals found in this work may fall under this chemical category. (Lai et al., 2022) This work supports observations by MacNeil et al (MacNeil et al., 2022) suggesting that a data filter may be applied to capture polyhalogenated chemicals (compounds with > 5F atoms, >3Cl atoms, and > 2 Br atoms) in ion mobility paired HRMS data. Taking together the standards and unknowns, 231 of the 232 halogenated features had CCS values which are less than  $0.2 \times m/z + 100 \text{ \AA}^2$ , with the only monochlorocarbazole failing the filter which is not surprising considering that it is two chlorine atoms short of the recommended 3 chlorine atoms. These results are also consistent with the observations made by Mullin et al (Mullin et al., 2020) on detected xenobiotics in indoor dust. We believe a combination of both approaches will hasten screening of polyhalogenated chemicals in IMS-HRMS exposomics data. The method we described facilitates formula and compound group assignment for halogenated chemicals using ion mobility measurements. This work supports the benefits of using ion mobility in synergy with GC-APCI-HRMS described by earlier papers on the topic. (Izquierdo-Sandoval et al., 2022; MacNeil et al., 2022) Furthermore, this work sets up the baseline from which spatio-temporal monitoring of how HOCs and HNPs are going to change over time which can eventually pave the way for studying the interplay between climate change, chemical pollution, and biodiversity shifts.

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## CRedit authorship contribution statement

**Randolph R. Singh:** Conceptualization, Methodology, Formal analysis, Data curation, Visualization, Writing – original draft, Writing – review & editing. **Yann Aminot:** Conceptualization, Methodology, Validation, Writing – review & editing. **Karine Héas-Moisan:** Methodology, Validation. **Hugues Preud'homme:** Methodology, Resources, Writing – review & editing. **Catherine Munsch:** Conceptualization, Methodology, Validation, Writing – review & editing, Project administration, Funding acquisition.

## 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.

## Data availability

Data will be made available on request.

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## Appendix A. Supplementary data

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