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The relevant role of ion mobility separation in LC-HRMS based screening strategies for contaminants of emerging concern in the aquatic environment

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ABSTRACT

Ion mobility separation (IMS) coupled to high resolution mass spectrometry (IMS-HRMS) is a promising technique for (non-)target/suspect analysis of micropollutants in complex matrices. IMS separates ionized compounds based on their charge, shape and size facilitating the removal of co-eluting isomeric/isobaric species. Additionally, IMS data can be translated into collision cross-section (CCS) values, which can be used to increase the identification reliability. However, IMS-HRMS for the screening of contaminants of emerging concern (CECs) have been scarcely explored. In this study, the role of IMS-HRMS for the identification of CECs in complex matrices is highlighted, with emphasis on when and with which purpose is of use. The utilization of IMS can result in much cleaner mass spectra, which considerably facilitates data interpretation and the obtaining of reliable identifications. Furthermore, the robustness of IMS measurements across matrices permits the use of CCS as an additional relevant parameter during the identification step even when reference standards are not available. Moreover, an effect on the number of true and false identifications could be demonstrated by including IMS restrictions within the identification workflow. Data shown in this work is of special interest for environmental researchers dealing with the detection of CECs with state-of-the-art IMS-HRMS instruments.

1. Introduction

High-resolution mass spectrometry (HRMS) has demonstrated an outstanding potential for target, suspect and non-target screening of contaminants of emerging concern (CECs) in environmental analyses (Gago-Ferrero et al., 2015; Hernández et al., 2019; Hollender et al., 2017; Schymanski et al., 2015). HRMS instruments provide accurate-mass full-spectrum acquisition data that enable to screen for a virtually unlimited number of substances (Hernández et al., 2019; Schymanski et al., 2015). However, mining the large amounts of data generated in MS or MS/MS mode (with information of retention time (RT), mass-to-charge ratio (*m*/z) and peak intensities) is time-consuming, and there is a risk of reporting false positive/negative identifications in complex matrices (Regueiro et al., 2016). Therefore, efforts have been devoted to the development of more sophisticated processing algorithms (Alygizakis et al., 2019; Bade et al., 2016; Hohrenk et al., 2020; Samanipour et al, 2018, 2019), as well as RT or fragmentation predictions tools (Aalizadeh et al., 2019; Bade et al, 2015a, 2015b, 2015a; Barron and McEneff, 2016; Kaufmann et al., 2017a, 2017b, 2017b; Ruttkies et al., 2016; Stanstrup et al., 2015; Wolf et al., 2010; Yang et al., 2020; Yeung et al., 2020), and the incorporation of other techniques to smooth feature identification (Bijlsma et al., 2019; Brack et al., 2016; Brunner et al., 2020; Gago-Ferrero et al., 2018; Krauss et al., 2019).

Ion mobility separation (IMS) coupled to HRMS (IMS-HRMS) is a promising and powerful tool for the (non-)target and suspect analysis of small organic molecules in complex matrices (Bijlsma et al., 2019; Mlynek et al., 2020; Regueiro et al, 2016, 2017). In brief, IMS separates ionized compounds based on their mobility through a gas (usually N_2 or He) in the presence of an electric field. Such ion mobility mainly depends

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on the charge, shape and size of the molecule (Gabelica et al., 2019; Lee, 2017). Consequently, IMS theoretically permits the filtering of interfering species such as isomeric or isobaric compounds (D'Atri et al., 2018; Lee, 2017; Regueiro et al., 2016; Shvartsburg and Smith, 2008).

In addition, IMS can provide an extra identification parameter for the confirmation of CECs (Bijlsma et al., 2019; Regueiro et al., 2016). The drift time (DT), *i.e.* the time it takes for an ionized species to travel through the mobility device, can be converted into a Collision Cross Section (CCS) value based on the measurement of a series of calibrants. CCS values are instrument independent values that are not affected by matrix composition or chromatographic separation (Gabelica et al., 2019; Gabelica and Marklund, 2018; Lee, 2017). As a consequence, CCS can be implemented as parameter into the criteria applied for the confirmation of candidate structures (Celma et al., 2020; Monge et al., 2019; Nuñez et al., 2019).

Some studies have assessed the precision of empirical CCS measurements in real samples compared to CCS values from reference standards or databases, and reported that CCS deviations were commonly <2% (Dodds et al., 2020; France et al., 2020; Gabelica et al., 2019; Paglia and Astarita, 2017; Stephan et al., 2016; Stow et al., 2017; Tejada-Casado et al., 2018), We recently proposed to include CCS into screening criteria for the identification of small molecules in environmental analyses and suggested that the maximum deviation between empirical and expected CCS value should be 2% (Celma et al., 2020).

One of the most common problems when applying wide-scope suspect and non-target screening strategies for the identification of CECs is the lack of standards for the final confirmation step. Therefore, key information for identification is often absent, such as RT or CCS (Hernández et al., 2019; Schymanski et al., 2015). Although there has been an increase in the number of online available databases of CCS values (Celma et al., 2020; Picache et al., 2019; Ross et al., 2020; Zhou et al., 2020), the number of entries in those databases is still limited and the available information is biased to common and well-known substances. In this sense, *in-silico* prediction tools of CCS represent a step forward into a more comprehensive incorporation of IMS into the screening workflow (Colby et al., 2019; Ewing et al., 2017; Lee et al., 2018; Zanotto et al., 2018). Hence, there has been an increase in the number of data-driven machine-learning models with predictive accurateness in the window of ± 3–6% for CCS using Travelling Wave-IMS and Drift Tube-IMS (Bijlsma et al., 2017; Gonzales et al., 2016; Mollerup et al., 2018; Plante et al., 2019; Ross et al., 2020; Zhou et al, 2016, 2017). Subsequently, several studies have been recently published using prediction of mobility data to gather more confidence in tentative identification when reference standards were unavailable (Bijlsma et al, 2017, 2019; Celma et al., 2020; Zhou et al., 2016).

In this work, an updated workflow with the inclusion of IMS is applied with emphasis on the advantages observed when mobility data is used during data processing and/or for feature identification. Additionally, the benefits of implementing IMS-HRMS for wide-scope screening of CECs in environmental samples are highlighted by means of illustrative examples collected over the experience gathered in different studies considering different scenarios, from target screening (with reference standards), to suspect screening (large list of compounds to be searched) where reference standards are not available.

2. Materials and methods

2.1. Samples selected as case study

This study shows different examples of the benefits of IMS-HRMS by means of real samples gathered through different research projects. Samples included herein cover the environmental aquatic system *i.e.* influent and effluent wastewater (IWW and EWW, respectively), river water (RW) and lake water (LW) from water bodies in the Mediterranean central littoral of Spain. The extraction methodology followed was adapted from previous studies (Bijlsma et al., 2014; Fonseca et al., 2020; Pitarch et al., 2016). Briefly, water samples were processed by means of solid-phase extraction (SPE) using generic stationary phases (Oasis HLB, Waters Corporation) with different preconcentration factors (×25 for IWW, ×100 for EWW and ×2500 for RW and LW). All extracts were afterwards reconstituted in 10% MeOH solutions and 1 μL of the final extracts were injected in the UHPLC-IMS-HRMS system.

2.2. Instrumentation

Samples were analysed using a Waters Acquity I-Class UPLC system (Waters, Milford, MA, USA) connected to a VION IMS-QTOF mass spectrometer, using electrospray ionization (ESI) interface operating in both positive and negative ionization mode. Briefly, chromatographic separation was performed using a CORTECS® C18 2.1 × 100 mm, 2.7 μm fused core column (Waters) at a flow rate of 300 μL min^{-1} over a gradient of 18 min using H_2O (A) and MeOH (B) as mobile phases, both with 0.01% formic acid. MS data were acquired using the VION in HDMSe mode, over the range *m/z* 50–1000. All data were examined using an in-house built accurate mass screening workflow within the UNIFI platform (version 1.9.4) from Waters Corporation. More details about the instrumentation can be found in Supporting **Information**.

2.3. Target and suspect screening

Targeted screening was performed using an in-house database with 970 entries with information about retention time, mass spectrometric data and CCS values for different adduct species of 556 reference standards in both positive and negative ionization mode. The database is online available for consultation at the *Zenodo* repository (Celma et al., 2019), and contains compounds with different physicochemical properties and uses including pesticides, pharmaceuticals, illicit drugs, hormones, mycotoxins and new psychoactive substances. Detailed information about the development and curation of the database can be found elsewhere (Celma et al., 2020). Additionally, an in-house database with 972 substances, for which reference standards were not available at our laboratory, was used for the suspect screening of samples covering parent compounds, metabolites and environmental transformation products of pesticides, pharmaceuticals, hormones and illicit drugs.

The criteria recently proposed for the identification of CECs in environmental analyses by IMS-HRMS (Celma et al., 2020) was followed in the present work, considering different confidence levels. Briefly, for confirmation purposes at level 1, mass accuracy of both precursor and fragment ions should be < 3 ppm, RT deviation <0.1 min and CCS deviation <2% from the reference standard value. For levels 2 and 3, *i.e.* where no reference standard is available, mass accuracy of precursor and fragments ions should be below 3 ppm from the potential molecular formula. For the prediction of ion mobility data, the model developed by Bijlsma et al. (2017) with an accuracy threshold for predicted CCS values of 6% was followed.

3. Results and discussion

3.1. IMS-HRMS screening workflow

Screening workflows using HRMS are well established and applied in several studies covering a wide range of aquatic matrices and analytes of interest (Hernández et al., 2019; Hollender et al., 2017; Menger et al., 2020; Schymanski et al., 2015) with liquid chromatography (LC) being nowadays the separation technique of choice, as most CECs are LC-amenable due to their medium-to-high polarity (Hernández et al., 2019; Menger et al., 2020). Nevertheless, large datasets generated in data independent acquisition (DIA) modes make the data processing and final identification of CECs challenging when performing these types of analyses. In this acquisition mode, all ions generated in the ion source are sent to the collision cell for fragmentation without precursor ion

selection. This alternation between full-scan and untargeted MS/MS events at different collision energies allows obtaining information on the accurate masses of the (de)protonated molecules as well as their fragment ions. However, DIA data is more complex and, therefore, strategies that curate these convoluted datasets are of high interest to facilitate environmental analysis. Although screening strategies have been improved, IMS was not hitherto included in screening workflows, and the coupling of LC to IMS-HRMS opens new possibilities to monitor CECs in the environment.

Fig. 1 outlines a screening workflow from data-acquisition to feature identification in environmental analyses using the 4-dimensional datasets (RT, DT, accurate mass and intensity) generated by LC-IMS-HRMS instruments. In this work we propose to consider the role of IMS at two different stages of the process:

(i) *Peak picking, alignment and componentization.* As previously mentioned, IMS theoretically allows the resolution of coeluting substances. Therefore, all ions deconvoluted within a single component of the feature list are required to have the same RT and DT as the precursor ion. These ions include the (de)protonated molecule, commonly predominant in low collision energy (LE) spectra, and ion fragments, commonly observed in the high collision energy (HE) spectra. In this sense, interfering ions coming from other substances different from the analyte of interest are removed due to their different ion mobility, resulting in much cleaner mass spectra.

(ii) *Feature identification.* A remarkable benefit of IMS is the provision of an additional identification parameter. Thus, CCS values can be used for feature identification as an extra point into the confidence gathered for a positive identification. In *target screening*, the empirical CCS should match with that previously measured from a reference standard with a maximum deviation of 2% (Celma et al., 2020). For cases where no reference standard is available, *i.e. suspect* and *non-target screening*, prediction of CCS is pivotal to benefit from that additional identification point. Although predicted CCS values are approximations to the real CCS values and cannot be strictly considered (in contrast to real-measured values), the application of CCS prediction can help discarding candidate structures that do not clearly match with the empirical mobility observed. Hence, the identification process of unknown compounds is smoothed and accelerated by the reduction of the number of candidate structures to investigate.

3.2. The application of IMS-HRMS

3.2.1. Drift time alignment – spectral cleaning

During the 4-D peak picking, alignment and componentization process, ions corresponding to the same mass spectrometric feature in both LE (either (de)protonated molecule or adduct ion) and HE (fragment ions) functions should share the same RT and DT as the parent compound. In this way, the automatic processing filters out ionized species that are different from the compound investigated, since all ions exiting

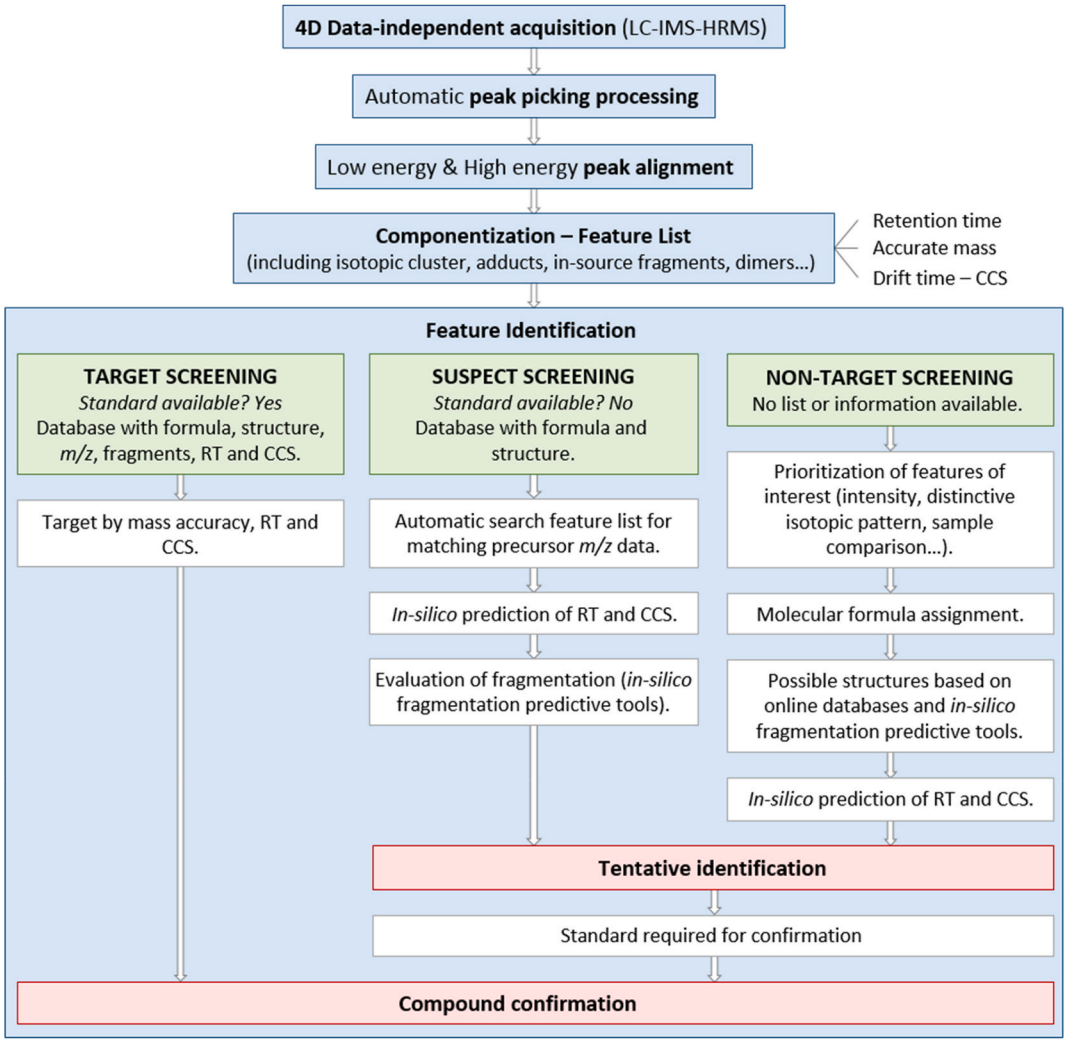

Fig. 1. Data-independent acquisition, processing and feature identification workflow for LC-IMS-HRMS target, suspect and non-target screening approaches.

the chromatography at a certain time are also separated depending on their mobility. At this point, the location of the mobility device plays an important role for the DT alignment. The mobility device is located after the ionization source and before the collision cell in the majority of IMS-HRMS instruments. Thus, (de)protonated molecules and their corresponding fragment ions have the same DT value in conventional IMS instrument setups. Although less frequent, there are other instrumental configurations where the mobility device is located after the collision cell and in those cases, the benefits of DT alignment may not apply.

Fig. 2 is an illustrative example highlighting the spectral cleaning provided by DT alignment of LC-IMS-HRMS data. A positive hit for the pesticide tricyclazole was found at a RT 5.74 min in the 4-D raw data of an analysis of a surface water sample (Fig. 2a). The conventional HRMS spectra (Fig. 2b) showed the precursor ion of tricyclazole (*m/z* 194.04310) in the LE spectra (Fig. 2b top), which is highlighted with a blue arrow. The most abundant peak, i.e. base peak with *m/z* 242.28388, corresponds, however, to another compound present in the sample. In addition, several ions that were present in the HE spectra (Fig. 2b bottom), but non-related to tricyclazole hinder the interpretation of the fragmentation pattern of tricyclazole. However, when applying IMS, all ions eluting at 5.74 min could also be separated based on their ion mobility resulting in different values of DT as highlighted by the red or black dots in Fig. 2c. The DT of tricyclazole (3.82 ± 0.2 ms) and the corresponding fragment ions in this range, represented by the blue highlighted areas, can be aligned. By means of this drift time alignment, all ions with DT different than those coming from tricyclazole (i.e. outside this blue area) are filtered out from the spectra. Thus, in this case, where IMS takes place before the mass fragmentation occurs, all fragments and their associated DT should be the same as the corresponding protonated molecule. Visually, all ionized species out of the blue bands are removed from the spectra, resulting in a drift time aligned MS spectra (only showing ions within RT 5.74 ± 0.03 min and DT 3.82 ± 0.2 ms) as shown in Fig. 2d. The drift time aligned MS spectra facilitates interpretation based on the tricyclazole structure, and do match with that observed for the reference standard. Although IMS is known for the extra identification parameter provided by the CCS value (Regueiro et al., 2016), the spectral cleaning associated with the drift time alignment is in many cases pivotal for the improvement of screening strategies performance. As shown in this example, the information gathered can be more easily interpreted and, therefore, the data mining of large datasets is notably accelerated, especially in complex-matrix samples.

3.2.2. *CCS measurement robustness – additional identification value*

Complex matrices can strongly influence the screening outcome by interfering the chromatography and/or the mass spectrometric measurement, even resulting in the reporting of false negative results (Celma et al., 2018; Hernández et al., 2019; Menger et al., 2020). However, as IMS occurs in the gas phase and ionized species do not interact with other substances rather than the gas in the mobility device, matrix does not affect DT measurement and CCS-values are matrix independent. In this section, we aim to highlight how the implementation of IMS-HRMS helped in the identification of imazalil in 6 different surface waters affected by strong alteration of the chromatographic retention along the same sequence of analysis.

Table 1 shows the significant variation in the measured RT, while the mass error for the protonated molecule measurement as well as the deviation of CCS remained almost negligible. In this particular case, the RT deviation ranged from 0.14 min up to 0.30 min, while CCS deviation was consistently <2% from standards. Additionally, repeatability of CCS measurements was evaluated across samples showing RSD values < 0.3%. In cases where the RT notably deviates from the standard, European guidelines recommend to spike the sample with the candidate standard to confirm the identity of the compound (European Commission. Directorate General for Health and Food Safety., 2019). However, the additional confidence obtained by the CCS measurement in a

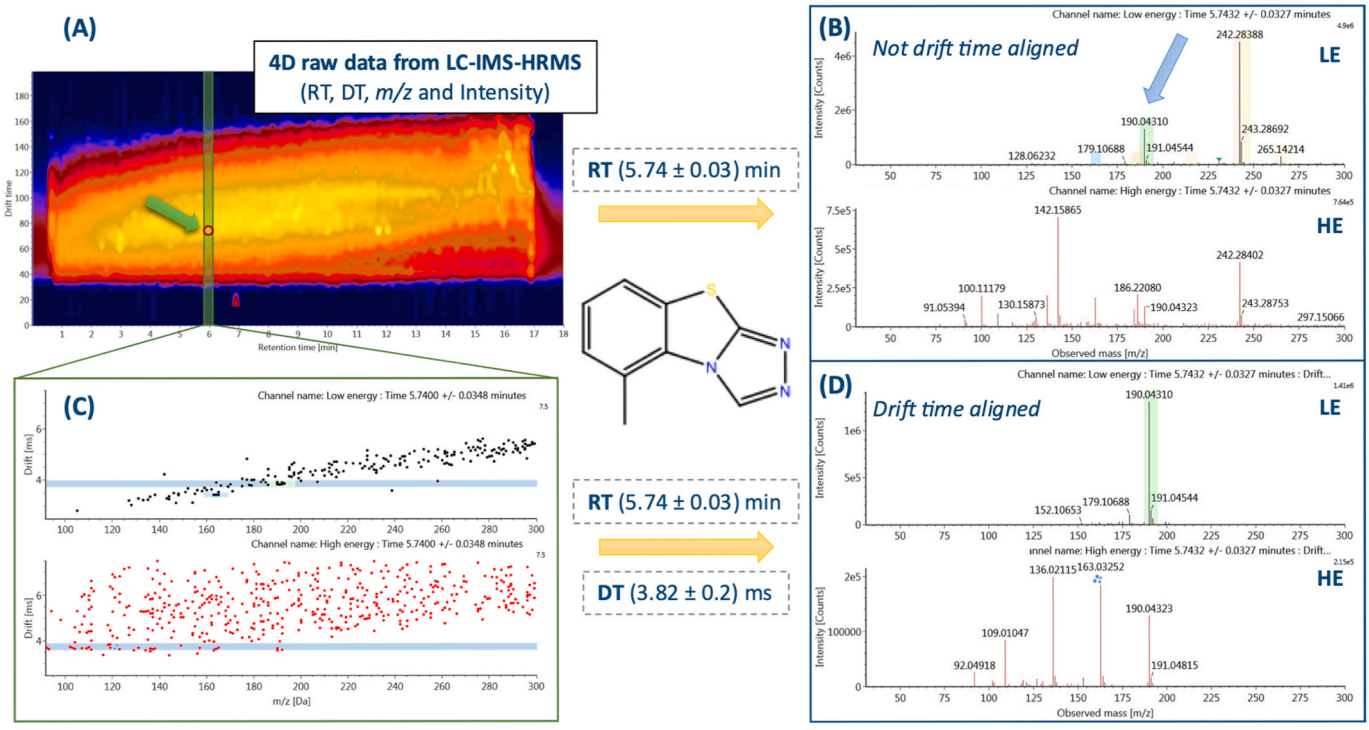

Fig. 2. Identification of tricyclazole in surface water. (A) Feature detection of *m/z* 190.04310 at RT 5.74 min and DT 3.82 ms (green arrow); (B) conventional LE (top) and HE (bottom) mass spectra without IMS drift time alignment corresponding to the RT window 5.74 ± 0.03 min; (C) ion mobility separation of co-eluting ions illustrated as red or black dots at the RT window 5.74 ± 0.03 min. Blue highlighted areas are the drift time ranges of 3.82 ± 0.20 ms at LE and HE; (D) LE (top) and HE (bottom) mass spectra with IMS drift time alignment showing only ions within the RT window 5.74 ± 0.03 min and DT window 3.82 ± 0.20 ms. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Variation between the observed *m/z*, detected retention time (RT) and collision cross-section (CCS) values for *imazalil* in six different surface water samples and the reference standard.

Sample	Obs. *M/z*	Mass error (ppm)	RT (min)	RT error (min)	CCS (Å^2)	ΔCCS (%)
Standard	297.0556[a]	–	7.45	–	166.56	–
Water #1	297.0550	−2.0	7.70	0.25	164.86	−1.02
Water #2	297.0555	−0.2	7.60	0.15	164.88	−1.01
Water #3	297.0562	1.9	7.59	0.14	165.20	−0.82
Water #4	297.0563	2.5	7.63	0.18	165.38	−0.71
Water #5	297.0554	−0.7	7.73	0.28	166.15	−0.25
Water #6	297.0562	1.9	7.75	0.30	165.46	−0.66

[a] Exact mass calculated from the molecular formula ($C_{14}H_{14}Cl_2N_2O$).

single-injection reduces time and costs of spiking and re-injecting the sample, as two separate evidences already exist (MS and CCS). This compound could be confirmed at level 1 including a note on that RT is deviated, but avoiding the need of re-injecting the sample or further investigation.

This is of special interest in environmental screening strategies where ion mobility, in the authors' opinion, should be evaluated for its potential inclusion as an additional criterion for reliable identification in forthcoming guidelines applied to different fields of analytical research. The example shown in this section illustrates that deviations in RT observed in complex matrix samples may hamper the identification process in wide-scope screening, while the application of CCS provides the extra value needed for confirmation of the identity.

3.2.3. *Resolution of isomeric compounds – do they have different CCS values?*

Isomeric compounds share the same molecular formula but differ in the arrangement of the atoms, meaning that the overall chemical structure is different. Therefore, HRMS is not able to differentiate between isomeric substances if they share the same fragmentation patterns. In addition, if the polarity of the isomers is similar, the chromatographic separation may not be able to distinguish between isomers. Yet, isomers could theoretically show different CCS values.

The target database we have previously developed (Celma et al., 2019) contains information about several pairs of isomeric substances (even some groups of more than 2 isomeric compounds). Among these pairs of compounds, the most challenging ones are those with close RT values as they may pose an extra hurdle for their identification. An example is the pair consisting of ethiofencarb sulfoxide (*m/z* 242.08454 | 3.99 min | 146.54 Å^2) and methiocarb sulfoxide (*m/z* 242.08454 | 4.39 min | 156.88 Å^2). These pesticides have close RT values that can be easily affected in complex matrices and therefore complicate their identification in real samples. However, their CCS values are significantly different (*i.e.* Δ6.6%), which enables the application of CCS as a distinction tool. A similar example can be found in the group of steroid metabolites constituted by testosterone glucuronide (*m/z* 465.2483 | 8.93 min | 221.48 Å^2) and epitestosterone glucuronide (*m/z* 465.2483 | 10.18 min | 204.69 Å^2), which have significantly different CCS values (Δ7.6%). On the contrary, 17-α-boldenone (*m/z* 287.2006 | 9.54 min | 169.32 Å^2) and 17-β-boldenone (*m/z* 287.2006 | 9.86 min | 171.76 Å^2) have a slight difference in their chemical structure (the α/β orientation of the substituent in a carbon atom) and, as a consequence, they have very close CCS values (Δ1.4%) that do not permit proper differentiation between isomers. Yet, Tian et al. (2017) could resolve distinct configurations of chiral amino acids (either D- or L-) by IMS-HRMS by using their chiral ratio to discriminate sample origin (Tian et al., 2017). This study demonstrated that IMS can be also of additional value to separate chiral molecules. In these cases, a specific set up of the mobility cell and the use of a chiral gas (e.g. (S)-(+)-2-butanol) is often required (Zhang et al., 2019).

When dealing with illegal compounds identification, the differentiation between isomers is even more critical, as it may represent holding legal responsibilities associated with the presence of such banned substances. For example, methedrone (*m/z* 194.1176 | 2.34 min | 145.34 Å^2), 3,4-methylenedioxymethamphetamine (commonly known as MDMA or ecstasy) (*m/z* 194.1176 | 2.61 min | 145.77 Å^2) and 3-methoxymethcathinone (*m/z* 194.1176 | 2.39 min | 146.18 Å^2) have all similar fragmentation patterns and very close RT values, which complicates the identification process. Unfortunately, in this case IMS cannot provide additional insight since the CCS values are rather similar, with differences of maximum 0.6%. Contrarily, IMS can help to differentiate ketamine (*m/z* 238.0993 | 3.63 min | 148.84 Å^2) from 4-chloro-α-pyrrolidinopropiophenone (*m/z* 238.0993 | 4.02 min | 154.04 Å^2) since their CCS value differs with 3.6%.

Separation of protomers by means of IMS-HRMS has been evaluated elsewhere (McCullagh et al., 2019) highlighting the possibility of resolving different protomers for quinolone antibiotics. However, little is still known about the resolution needed to separate the protomers formed and the potential impact in screening approaches (signal reduction, false negatives/positives, etc.). This is a challenging issue and further studies need to be conducted towards the evaluation of protomers determination in complex matrices.

As shown, the potential of IMS for the resolution and unambiguous identification of isomeric substances and protomers is promising, but there are still some limitations mainly due to the low resolution power of commercial IMS instruments. Harvesting the extra benefits provided by IMS would require the implementation of higher resolution IMS systems (Kaufmann et al., 2020), and it is the hope of the authors that forthcoming developments in IMS instruments will accomplish pursue that objective.

3.3. *How does IMS affect the number of false positives in automated screening workflows?*

A common problematic issue in applying automated screening workflows is the possible reporting of misidentifications. In this section, the potential of IMS-HRMS to minimize the number of false positives in environmental water samples is explored and illustrated with some examples.

The collaborative project entitled "*Effect-directed analysis as a tool towards a non-toxic environment – identification of mixture effects and toxicity drivers in water (DANTE)*" aims to produce a robust strategy to assess environmental toxicity through the combination of toxicological and chemical analyses. Consequently, the screening strategy to be applied within this project needs to be carefully evaluated to produce reliable and intercomparable results. Four water samples (influent and effluent wastewater, river water and lake water) were spiked for quality control purposes, and are shown as a case study for the evaluation of the amount of false positive identifications using an automated screening workflow by LC-IMS-HRMS. Samples were spiked with a mixture of 59 compounds consisting of pesticides and pharmaceuticals prior to sample treatment (SPE). The whole list of standards that were used for spiking is available in Table S1 of the Supporting **Information (SI)**. After SPE, the samples were screened for these substances applying the following criteria: response >1000 counts; $[M+H]^+$ error <3 ppm; RT error <0.1 min; and CCS deviation <2%. Additionally, to assess the benefits of the prediction of CCS values, a suspect screening was applied for the same compounds but with predicted CCS (Bijlsma et al., 2017) as if no reference standards and, thus, experimental CCS were available. Briefly, this predictive model makes use of an artificial neural network (ANN) to predict CCS values from the input of 8 molecular descriptors. The threshold for the predicted CCS (CCS_{Pred}) data (Table S1 in SI) was established at < 6% (*i.e.* the prediction accuracy at the 95th percentile reported by Bijlsma et al. (2017)).

Fig. 3 shows the true identifications (solid color) and false positives (pale color) when applying different criteria. True identifications were

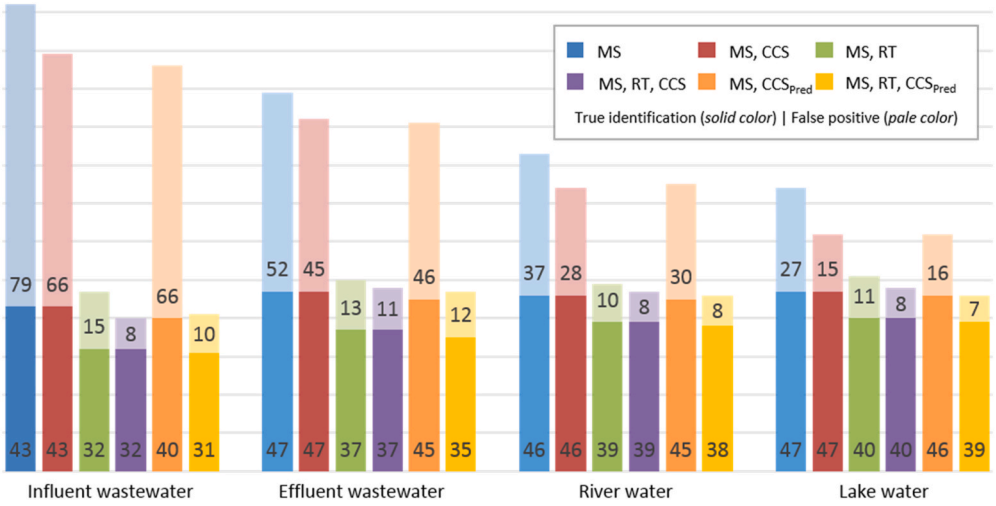

Fig. 3. Effect of identification criteria applied on the number of true and false identifications over a set of 59 standards spiked in real samples (*i.e.* influent and effluent wastewater, river and lake surface water). True identifications in solid color and false identifications in pale color. MS: accurate mass deviation <3 ppm, RT: empirical retention time <0.3 min from standard, CCS: empirical CCS <2% deviated from standard, CCS_{Pred}: empirical CCS value < 6% deviated from prediction. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

confirmed based on MS, RT and CCS; the same criteria was used to discard false positives. In general, the application of mass accuracy restrictions only (blue colored bar) was the criterion that rendered the maximum number of true identifications. However, the number of false positives (pale blue) and the time needed for data revision were also high. The inclusion of CCS into the criteria for identification (MS and CCS, red colored bar) did not result in a reduction in the number of true identifications (solid red), but it did reduce the number of false positives facilitating data revision.

The case is different when the conventional criteria in LC-HRMS for identification (MS and RT, green colored bar) is applied. In this case, a decrease in the number of true identifications was observed, mainly due to RT deviations. The inclusion of this parameter in the automated screening criterion strongly affected the identification performance. Yet, the number of false potential positives was also reduced by RT restrictions. As can be seen from Fig. 3 (blue, red and green bars), the reduction in false positive identifications when applying a RT filter is much higher than when considering CCS values. The latter could be somewhat correlated to the molecular mass, although CCS values for the same m/z sometimes ranged of more than 35 $Å^2$ (Bijlsma et al., 2017). When applying LC-IMS-HRMS criteria for the identification (MS, RT and CCS, purple colored bars), the effect of RT on the number of true/false positives is also limiting the performance of the screening in this case and, therefore, hindering the benefits of CCS. However, the inclusion of CCS permitted the removal of some false positives (pale purple) in comparison to only use MS and RT criteria (pale green). At this point, it is worth mentioning that less restrictive thresholds for RT compliance could be considered when analyzing complex matrices in order to avoid reporting false negative identifications. In this scenario of wider limits for RT, CCS can give an additional and complementary confidence in the identification.

When a suspect screening is applied using only predicted CCS values and no empirical data, the number of true identifications (MS, CCS_{Pred}, orange colored bar) was, in some cases, slightly reduced in comparison to experimental CCS values from standards (solid red). Again, when including RT with CCS_{Pred} as criteria, the effect of RT filtering dominates the screening performance and reduces the number of potential positives to be investigated. Despite the effect of RT filtering, predictive tools for ion mobility data are indeed helpful when no reference standard is available. Thus, predicted CCS values can be used as an additional value for the screening of CECs in complex matrices.

Most remarkably, the inclusion of CCS into the identification criteria for both target and suspect screening strategies was not detrimental for the screening performance, contributing to reduce the number of false positives without affecting the number of false negatives. Contrarily, RT notably affected the performance of the screening as the chromatography is much more affected by complex matrices components. These examples highlight the fact that automated screening workflows should be carefully applied and require the critical assessment of an experienced analyst in order to differentiate true identifications from false positives and to report curated and high quality results.

4. Conclusions

LC-IMS-HRMS is still scarcely used in the analysis of CECs in environmental samples, and therefore little is known about the benefits and drawbacks of the application of this technique in this specific field. In this study, an overview of the potential of LC-IMS-HRMS, with a discussion on the main pros and cons, is presented, making use of selected examples to illustrate its application to the screening of CECs in a wide range of water samples. The mass spectra cleaning provided by DT alignment, the value of CCS as additional identification parameter as well as the potential separation of isomeric and isobaric substances are some of the main benefits one can harvest from IMS-HRMS. Additionally, CCS prediction is a powerful strategy to improve the suspect and non-target screening approaches by reducing the number of candidates to investigate as well as providing extra evidence on tentative identifications. The effect of including CCS restrictions within the criteria for compound identification has been also assessed yielding a better performance than RT in large screenings. As shown, empirical CCS and predicted CCS values did not reduce the number of true identifications but the number of false positives to be investigated. Consequently, the data revision process is notably facilitated by eliminating candidates that do not match with the expected data, reducing the time consumed and increasing the throughput of the strategy.

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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

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