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Wide-scope screening of polar contaminants of concern in water: A critical review of liquid chromatography-high resolution mass spectrometry-based strategies

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ABSTRACT

The number of chemicals with potential to reach the environment is still largely unknown, which poses great challenges for both environmental scientists and analytical chemists. Liquid chromatography coupled to high-resolution mass spectrometry (LC-HRMS) is currently the instrumentation of choice for identification of wide-scope polar chemicals of concern (CECs) in water. This review critically evaluates all steps involved in screening for polar CECs in water, including sampling and extraction, analysis by LC-HRMS, data (pre-)treatment, evaluation and reporting. Passive samplers and direct injection, in combination with LC-HRMS, provide new opportunities compared with conventional grab water sampling, as do instrumental advances such as ion-mobility spectrometry coupled to HRMS (IM-HRMS). In this paper, we argue that target, suspect and non-target screening should not be viewed as three separate principles, but rather as conceptual approaches to general data treatment strategies that can be linked together. Due to the large amount of data generated, smart prioritisation strategies are needed, in particular for non-target screening, to reduce complexity and focus on data of high interest. We critically evaluate existing strategies and consider that each prioritisation step will result in data loss (as any other step in a screening study), requiring compromises depending on the research question to be tackled. Many different data treatment strategies have been developed in recent years, but structure elucidation remains a challenging and time-consuming task. We discuss current and potential future trends, e.g. effect-based methods that can be used as future prioritisation tools, technological advances like IM-HRMS and improved software solutions that can enable new data treatment strategies.

1. Introduction

With the development of high-resolution accurate mass spectrometry (HRMS), a whole new field opened up within analytical chemistry, providing new opportunities for analysis of organic substances [1,2]. The untargeted data acquisition modes of HRMS instruments make the chemical profile of a sample accessible, within instrument limitations, and have paved the

Abbreviations: ANNs, artificial neural networks; APCI, atmospheric pressure chemical ionisation; APPI, atmospheric pressure photoionisation; CCS, collision cross-section; CDA, chemistry-directed analysis; CECs, chemicals of concern; DDA, data-dependent acquisition; DIA, data-independent acquisition; DSFP, digital sample freezing platform; DWTP, drinking water treatment plant; EBTs, effect-based trigger values; EDA, effect-directed analysis; EI, electron impact; ESI, electron spray ionisation; FTICR, fourier-transform ion cyclotron resonance; FWHM, full width at half maximum; GC, gas chromatography; HCA, hierarchical cluster analysis; HILIC, hydrophilic interaction liquid chromatography; HLB, hydrophilic-lipophilic balance; HPLC, high performance liquid chromatography; HRMS, high resolution mass spectrometry; IM-HRMS, ion mobility spectrometry high-resolution mass spectrometry; IMS, ion mobility spectrometry; IR, infrared spectroscopy; LC, liquid chromatography; LC-HRMS, Liquid chromatography high-resolution mass spectrometry; log DOW, logarithmic octanol-water distribution ratio; LSER, linear solvation energy relationship; *m/z*, mass-to-charge; NMR, magnetic resonance spectroscopy; PFASs, poly- and perfluoroalkyl substances; PMOCs, persistent and mobile organic chemicals; PNECs, predicted no-effect concentrations; POCIS, polar organic chemical integrative samplers; QSRR, quantitative structure-retention relationship; QSTR, quantitative structure-toxicity relationship; Q-TOF, quadrupole time-of-flight; RT, retention time; S/N, signal-to-noise ratio; SDB-RPS, styrene-divinylbenzene reverse phase sulfonated; SPE, solid phase extraction; TIMFIE, time-integrating microflow in-line extraction; TOF, time-of-flight; UHPLC, ultra-high performance liquid chromatography; VEC, vacuum-assisted evaporative concentration; WAX, weak anion exchange; WWTP, wastewater treatment plant.

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way for screening approaches to investigate the extensive datasets created [3,4]. The term 'screening' refers in this context to a strategy aimed at deciphering HRMS data, *viz.* target screening, suspect screening and non-target screening [5], and not the practice of scanning for chemicals across a set of samples. Modern HRMS instruments routinely achieve mass accuracies below 5 ppm and mass resolution >10 000 at full width at half maximum (FWHM) [6]. The high resolving power and mass accuracy of HRMS instruments enable i) calculation of the elemental composition from any detected mass with high confidence and ii) structure elucidation, and iii) alleviate the *a priori* need for reference standards [1,7]. Further, structure elucidation is not limited to known chemical structures, with definite identification having been performed successfully for previously unknown structures [3,8]. At present, screenings for hundreds and even thousands of chemicals can be achieved using HRMS [9–12]. However, the vast array of possibilities that HRMS can offer also brings great challenges, such as very complex datasets, lack of software tools and reference libraries, a growing need for new synthetic reference standards for confirmation purposes [5,13], and a rapidly advancing field that becomes more complex and more difficult to keep up with by the day.

Anthropogenic synthetic chemicals are an emerging issue, as they have been identified as contaminants of emerging concern (CECs) in different water environments, e.g. groundwater [14–16], surface water [17,18], drinking water [19–21] and marine water [22,23]. Wastewater treatment plants (WWTPs) have been identified as key point sources of CECs to the aquatic environment, as treatment processes have been found to be insufficient for removal of many CECs [9,18,24,25]. In recent years, HRMS has become a valuable new tool in identifying CECs and their presence in water, and efforts have been made to optimise HRMS-based workflows and to develop new prioritisation and identification strategies [26–28]. In order to obtain a comprehensive picture of the presence of CECs, a combination of HRMS with gas chromatography and liquid chromatography (GC and LC) is necessary [29,30]. For GC-electron impact (EI) ionisation, hundreds of thousands of reference spectra are available in spectral libraries, which is an important advantage over LC analysis. However, GC as a separation technique is limited to nonpolar, semi-volatile or volatile compounds, or requires derivatisation. LC separation, on the other hand, allows for screening of a much wider range of compounds, including polar and very polar compounds. Thus, LC coupled to HRMS is the technique of choice for wide-scope screening in water [31].

This paper presents a critical review of reported screening approaches using LC-HRMS to analyse polar and semi-polar organic contaminants in water, including marine and fresh water (lake, river), groundwater, drinking water, stormwater, landfill leachate, and WWTP influent and effluent. It covers i) sampling and sample treatment, ii) instrumental methods using LC-HRMS, iii) data preprocessing, iv) conceptual approaches, v) prioritisation strategies and vi) structure elucidation and validation. It comprehensively compiles and critically questions available instrumentation, tools and strategies at every stage of a water screening study aimed at CECs using LC-HRMS. It thereby complements review articles for specific CEC groups, not always addressing the full analytical chain, or more technically focused reviews found elsewhere [12,29,32,33]. Thus, this paper provides an overview of existing technology and knowledge, challenges and how to address them, and crucial knowledge gaps and needs for future development.

2. Sampling and sample treatment

The optimal strategy for sampling and sample treatment depends on the research question and can only be designed when the objective and the methodology for a study have been well defined. Water samples can be collected as i) grab samples, i.e. a fixed volume at a fixed point of time, ii) composite samples, i.e. time- or flow-proportional active samples and iii) time-integrated passive samples. Grab water sampling is the most commonly used method, since it is simple and cheap and environmental concentrations can easily be determined. However, a grab sample only reflects the chemical profile at the time point when the sample was collected and its representativity is therefore limited [34]. In cases where fluctuating concentrations or episodic pollution events are expected (e.g. WWTP effluent, rain events, flooding), numerous grab samples are needed in order to obtain a representative chemical profile [34]. Composite samples provide a representative chemical profile for a period of interest (typically 24 h or a few days) and average concentrations can readily be determined [35,27,36]. However, reactive compounds may degrade during the collection period depending on current environmental conditions (temperature, radiation) and storage options [37]. To avoid compound degradation, extractions can be carried out *on-site*, e.g. using the time-integrating, microflow, in-line extraction (TIMFIE) samplers developed recently for pesticide monitoring [38].

Passive sampling is a good option for obtaining average chemical profiles over a period of time (typically several days up to several months) [16,34]. For passive sampling, a collection medium is used to accumulate chemicals. For relatively hydrophilic contaminants (such as CECs), polar organic chemical integrative samplers (POCIS) are commonly used to determine chemical profiles over a period of days to several weeks [34,39]. While grab sampling in principle is non-discriminative, passive sampling is selective depending on the collection medium. However, POCIS media for relatively broad chemical enrichment are available [16,22], which improves the representativity. Another common sampler for polar analytes in water is Chemcatcher, which uses styrene-divinylbenzene reverse phase sulfonated (SDB-RPS) Empore™ extraction discs [40,41]. In order to calculate water concentrations from passive sampler data, uptake rates and partitioning coefficients to the passive sampler are needed [34] and, if not available, a calibration study may be necessary. For some sorbents, readily prepared passive samplers are commercially available, e.g. POCIS packed with Oasis hydrophilic-lipophilic balance (HLB) or Chemcatchers equipped with different sorbent media.

A vast number of extraction methods have been developed for target analysis of polar organic micropollutants using LC-low resolution mass spectrometry, e.g. [42]. These methods are normally optimised for a limited number of well-defined chemicals, often requiring discriminating clean-up procedures, which may not be optimal for HRMS screening of a wide range of CECs. The high mass accuracy and high mass resolution of HRMS instruments compared with low-resolution instruments significantly improve differentiation between ions of interest and background signals, and therefore clean-up becomes less critical [12]. Extraction methods for LC-HRMS are commonly based on solid phase extraction (SPE) and use different sorbents, depending on the physicochemical properties of the target compounds [12]. Some studies have used specific SPE sorbents like weak anion exchange (WAX) [43], while HLB is commonly used as a sorbent for broad chemical enrichment [12,44–46]. Mixed-bed multi-layered SPE using a cartridge with four different sorbents, i.e. HLB, anion and cation exchange resins (Strata XAW and Strata XCW) and a nonpolar sorbent (Isolute ENV+) [28], has been developed to enrich neutral, cationic and anionic CECs of a broad range and has become a popular alternative to HLB for wide-scope screening [7,10,47–49]. SPE cartridges stacked in series [50] is another attractive alternative for wide-scope screening. Few studies have developed

online SPE methods for HRMS-based screening of water samples, and most have focused on quantitative target screening [51–53], rather than identification of unknown CECs [54]. Online SPE has the advantage of a higher degree of automation compared with off-line SPE, which leads to higher sample throughput once the method has been set up, but at the expense of reduced flexibility [55]. Other extraction strategies besides SPE include active charcoal filtration followed by Soxhlet extraction [19] and liquid-liquid extraction [56]. Direct injection and large-volume injection are promising alternatives to SPE, because sample handling is reduced to a minimum and virtually no chemicals are lost, which makes direct injection especially interesting for wide-scope screening [57–59]. Although the applicability of direct injection is limited (as the analytes are not pre-concentrated and the matrix is not removed by a clean-up step), recent advances in the sensitivity of HRMS instruments and the availability of large-volume injection have made these strategies attractive for present and future applications. To avoid the limitation of no pre-concentration in direct injection approaches, a recent study suggested and demonstrated great potential in using vacuum-assisted evaporative concentration (VEC) in combination with direct injection for HRMS applications [60].

3. Instrumental methods using LC-HRMS

While high performance LC (HPLC) is still a common separation system, the use of ultra-high performance LC (UHPLC) has been strongly increasing in recent years [61]. Compared with HPLC, UHPLC offers shorter run times and more sufficient chromatographic resolution to minimise co-elution and improved sensitivity, but is sensitive to blockage by particles and requires improved acquisition rates of the detector [32,61]. Currently, LC separation for HRMS-based screenings is mostly achieved using reverse-phase LC (RPLC) conditions, e.g. using a C18-column and a gradient of an aqueous phase and methanol or acetonitrile [5,62]. RPLC works well for a wide range of compounds, including chemicals with logarithmic octanol-water distribution ratio (log D_{OW}) values typically between -2 and 4 [63]. RPLC has been applied in wide-scope screening [5] and in screenings aimed at specific chemical classes of interest, e.g. pesticide transformation products [11] or poly- and perfluoroalkyl substances (PFASs) [50]. Highly polar substances, i.e. substances with negative log D_{OW}, are not well retained in RPLC and are therefore not well separated [63]. This analytical gap for very polar and therefore very mobile chemicals should be considered, especially for persistent and mobile organic chemicals (PMOCs) which are CECs for water quality due to their high mobility in the aquatic environment and their persistence through drinking water treatment plants (DWTPs) [63]. Other separation techniques, like hydrophilic interaction liquid chromatography (HILIC), mixed-mode LC (MMLC) and supercritical fluid chromatography (SFC) have been developed specifically to separate mixtures of polar and very polar chemicals [64–67] and might therefore be better solutions for analysis of PMOCs. HILIC is becoming a popular complementary tool for HRMS screening of water samples, with an increasing number of studies employing HILIC in their workflow [8,68–70].

Hybrid mass analysers of the time-of-flight (TOF) family, e.g. interfaced with a quadrupole (Q-TOF), and of the Orbitrap family, e.g. interfaced with a linear ion trap (LTQ Orbitrap family) or a quadrupole (Q Exactive family), equipped with electron spray ionisation (ESI) are today the most common detectors interfaced with LC for HRMS data acquisition [12,62]. Other ionisation techniques, e.g. atmospheric pressure chemical ionisation (APCI) or atmospheric pressure photoionisation (APPI), can complement the substance spectrum. These ionisation techniques cover less polar compounds commonly not ionised by ESI [71], but APCI and APPI are rarely used in water screening studies [71]. TOF and Orbitrap mass analysers are both suitable for wide-scope screening, and ESI in negative and positive ionisation mode is commonly (but not always) run in separate injections for complementary analysis [5]. Fourier-transform ion cyclotron resonance (FTICR) mass spectrometry provides the greatest resolving power available today. However, because of its complexity and high cost, FTICR is rarely used for analysis of CECs, but rather to characterise organic matter [6,62]. Orbitrap instruments provide higher mass resolution than TOF instruments [2,5,12]. Recent years have seen continual and rapid development of new generations of detectors with significantly improved performance. According to vendor information, at the time of writing Orbitrap and TOF systems can reach mass resolution of up to 1 000 000 (Orbitrap Fusion Lumos, Thermo Fisher Scientific) and 80 000 (e.g. Q-TOF maXis II, Bruker). However, the resolving power of Orbitrap instruments is acquisition rate-dependent, so use of its peak resolution can be limited when high scan rates are desired [6], e.g. when interfaced with UHPLC.

TOF analysers offer high data acquisition rates, which makes them more compatible with modern UHPLC and facilitates work in data-independent acquisition (DIA) modes, i.e. simultaneous fragmentation of all ions [62]. Orbitrap analysers, on the other hand, were in the past mostly interfaced with HPLC and operated in data-dependent acquisition (DDA) modes, i.e. sequential MS2 scans of defined masses, often the most intense ions in a survey scan [12]. Modern Orbitraps can now be interfaced with UPLC and operated in DIA [72], thanks to improved scan rates, but this has so far rarely been used for water screening [73]. DIA fragments all ionisable compounds within a given m/z range, which creates highly complex fragment ion spectra with no direct relation between precursor and fragment ions. In contrast, DDA performs MS2 scans for defined masses only, which provides fragment ion spectra directly linked to the respective precursor ions. However, DDA is mostly inherently biased towards the most abundant signals, so its applicability can be significantly limited for trace analysis [73]. An exclusion list can help to reduce fragmentation of unwanted masses during DDA, e.g. to avoid selection and fragmentation of system contamination through exclusion of signals present in system blanks [74]. An inclusion list can be used to trigger fragmentation of masses of interest, which would otherwise not be fragmented due to too low signal intensity [11]. An alternative approach for generating interference-free MS2 spectra, while including masses with small signals, is to initially scan all ions to prioritise masses of interest, followed by DDA using the prioritised masses in an inclusion list [23,75,76]. However, this approach can be rather time-intensive, as it depends on re-injection of the samples. Generally speaking, DDA data is better suited to structural elucidation, whereas DIA data is more comprehensive and therefore better suited to data archiving and screening of well-known chemicals (target and suspect screening).

Ion mobility spectrometry (IMS) coupled to HRMS (IM-HRMS) has recently been introduced on the market and promises significantly improved instrumental performance by adding one additional dimension of separation to the analytical system, i.e. separation in an electric field based on the shape-dependent velocity of the molecule [77]. This additional separation dimension leads to an improved selectivity due to an increased separation capability and is particularly useful for the separation of isobars, isomers and even enantiomers [43,77,78]. IM-HRMS instruments provide four-dimensional data, comprising chromatographic retention time (RT), mass-to-charge (m/z), ion abundance and drift time, the latter a physicochemical property measured by IMS [78]. Drift time can be used to derive the collision cross-section (CCS) of an ion, a value consistent between instruments and across experimental conditions [79–81]. This makes prediction tools and

databases for CCS values attractive and feasible [80–82]. Drift-time alignment can be used to produce relatively clean product ion spectra from data acquired in DIA, which benefits identification approaches especially in complex sample matrices [82], and can be especially valuable for data archiving and retrospective screening. IM-HRMS has only rarely been used for water analysis to date (e.g [58].).

Most studies use generic settings for their LC system (e.g. analytical column, mobile phases, gradient, column temperature) and for their mass analyser (e.g. mass range, scan rate, collision energy) [5,83]. Part of the HRMS community is advocating, and devoting efforts towards, harmonising acquisition parameters to improve inter-laboratory comparability [84], but chemicals outside the observable space of these harmonised protocols will be systematically discriminated against (Fig. 1).

4. Data preprocessing

The quantity and complexity of the raw data need to be reduced by data preprocessing before data of relevance for specific research questions can be extracted and evaluated [3]. Data preprocessing typically includes RT alignment, mass correction, peak picking and componentisation, i.e. grouping of signals (e.g. isotopes, adducts, multicharged ions) belonging to the same unique molecular structure [3], eventually resulting in a component list (Fig. 2). Preprocessing parameters are crucial for the performance of a screening workflow. For example, the peak picking algorithm determines which signals are integrated. Non-integrated signals will be missed, while too many integrations will create a 'noisy' (many background signals) component list. Vendor software predefines most data preprocessing parameters or permits only minor adjustments [85], which limits the possibilities for optimisation. Several open-source options exist for data preprocessing outside vendor software, e.g. RMassBank [86], enviMass [87], XCMS [88] and mzMine 2 [89]. Open-source options for data preprocessing have been used in a number of studies (e.g [36,48,90,91].), but they require advanced knowledge of programming and raw data handling. The NORMAN digital sample freezing platform (DSFP), a data repository for "digitally frozen" samples used for retrospective screening, has recently been introduced

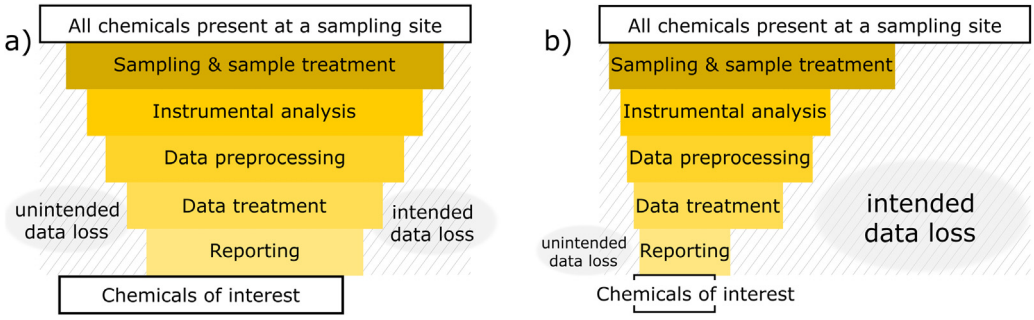

Fig. 1. Visualisation of sequential focus on a cluster of chemicals of interest in a) wide-scope screening and b) specialised screening, i.e. aimed at a specific chemical family of interest.

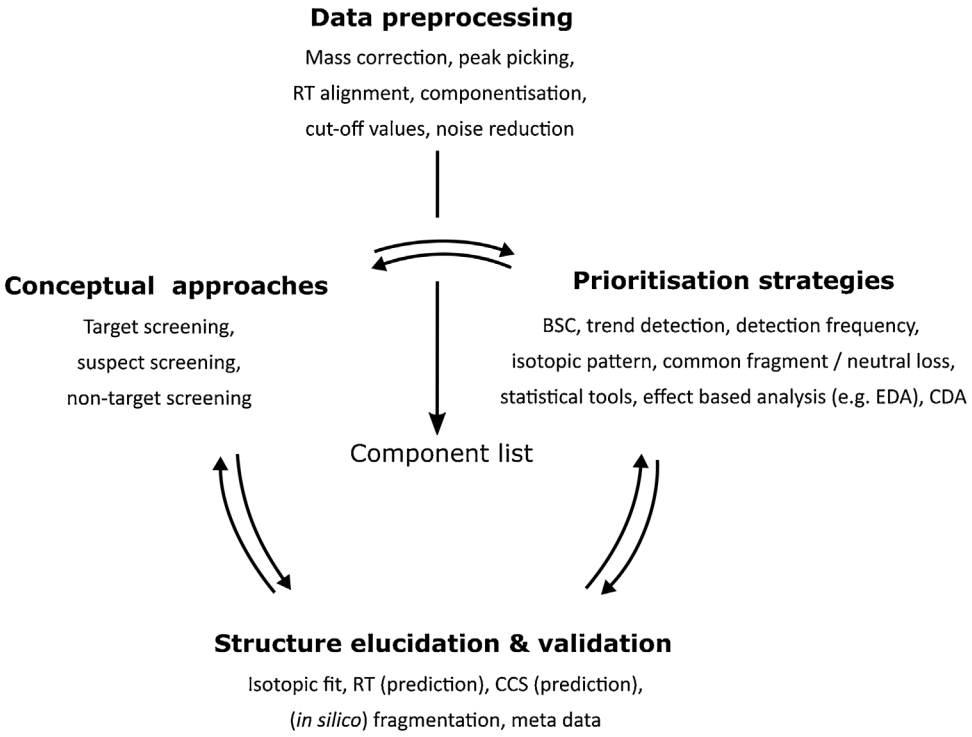

Fig. 2. Overview of options for data preprocessing and treatment in high-resolution mass spectrometry (HRMS) screening applications. RT = retention time, BSC = binary sample comparison, EDA = effect-directed analysis, CDA = chemistry-directed analysis, CCS = collision cross-section.

[26]. DSFP performs automatic preprocessing of raw data using the peak picking algorithm from XCMS and performs componentisation using the non-target R package [92]. A recent study showed that differences in algorithms between different software packages significantly influence the outcome of data preprocessing [93]. Therefore, data preprocessing is a crucial step that determines the quality of the data used for further studies.

Cut-off values for signal intensity or signal-to-noise ratio (S/N) are commonly used to reduce the general complexity of component lists and have been applied during data preprocessing and during component prioritisation steps [5,12]. Other cut-off values, e.g. for RT or *m/z*, are conceivable, but to our knowledge have not been used in water screening applications. Some strategies have been developed to reduce background noise, e.g. through automatic exclusion of compounds detected in blank samples [19,94] or mandatory detection in several replicate samples [23,59,75].

5. Conceptual approaches

Water samples may contain tens of thousands of individual compounds of both natural and anthropogenic origin. Therefore, LC-HRMS analysis of these samples leads to a great number of signals, even after data preprocessing, most of which correspond to previously unidentified substances and substances of no concern. At present, the number of components that can be evaluated within evaluation workflows is still limited by computational power and by time-intensive manual steps [31]. Therefore, depending on the specific objectives of each study, directed data treatment strategies need to be elaborated, balancing the workload with the number of false negatives caused by too strict procedures, while retaining components of interest in the data pool.

Three main conceptual approaches for data treatment of LC-HRMS data are described in the literature, namely target screening, suspect screening and non-target screening (Fig. 2). Target screening refers to the easiest and most straightforward approach, by which samples are screened for a list of predefined target compounds, i.e. compounds with reference standard information available from the same instrument (expected mass, RT, diagnostic fragments and, for some instruments, CCS) [5,75]. 'Target analysis' is occasionally used as an alternative term for target screening [2,95]. The term 'target screening' should be used when referring to the conceptual HRMS-data treatment approach, to avoid confusion with conventional target analysis, which can be performed using low-resolution mass spectrometry and where the internal standard method (preferably using isotopically-enriched forms of the analytes) is applied for quantitative chemical analysis. Target screening often requires little to no prioritisation and can be performed in a relatively automated way for many compounds in a timely manner, e.g. Gago-Ferrero et al. [10] screened for >2 000 compounds using a wide-scope target screening approach.

Suspect screening describes the strategy of screening for known or predicted compounds in HRMS data, therefore requiring prior knowledge about the compounds of interest. This type of screening is based on comparison of ionised masses of chemicals suspected to be present in the samples (suspects) with measured masses in the component list. Suspect screening does not require reference standards from the start, as the exact monoisotopic mass of an ionised suspect can easily be calculated, which is a great advantage over conventional analysis using low-resolution MS [7]. Many strategies have been developed to create suspect lists and include compilations of known toxic chemicals [19,45], predicted transformation products of chemicals of concern [69,96], predicted ozonation transformation products [54] and use of data from regulatory databases, e.g. market data [27,97]. Common mass error thresholds used for suspect screening lie between 2–3 mDa or 3–5 ppm, depending on the mass resolution of the instrument and the ionisation mode [11,12,50]. Toxicity indicators such as predicted no-effect concentrations (PNECs), predicted through e.g. quantitative structure-toxicity relationship (QSTR) models [98] or read-across models [99], have been used for risk assessment of newly identified and (semi-)quantified compounds [9,23,46], but have not been used for component prioritisation. It is challenging to use toxicity indicator values as a prioritisation tool for specific components, because accurate quantification without reference standard is currently not possible, but it can potentially be used in the future to guide attention towards compounds of concern. In 2015, the NORMAN network established the NORMAN Suspect List Exchange, a collection of suspect lists relevant for environmental monitoring questions, to facilitate exchange and use of highly curated suspect lists among researchers [100]. Suspect screening has great potential for retrospective screening, i.e. screening of archived HRMS data, which facilitates its use as an early warning system for occurrence of newly identified contaminants of concern [83]. The recently introduced NORMAN DSFP, a platform created for retrospective suspect screening [26], will help to further facilitate and advance the use of retrospective suspect screening, especially in an international context.

While target and suspect screening are based on previous knowledge about the expected chemicals, non-target screening as a conceptual approach is based on component prioritisation and does not consider a (tentative) structure from the start. In non-target screening, masses of high interest are first prioritised from component lists using tools from a range of prioritisation approaches. The prioritised masses then need to undergo structure elucidation before tools developed for suspect screening become available for further data evaluation. Structure elucidation is still a very time-consuming task, since it relies on critical evaluation by experts and is often performed manually. This makes efficient and smart prioritisation critical for non-target screening. The term 'non-target screening' (or 'non-targeted screening') is also used in the literature in a different way, namely to describe all studies based on HRMS data except target screening, i.e. suspect and non-target screening [19,43,101]. Similarly, the term 'non-target analysis' has been used to describe studies investigating HRMS data acquired in untargeted data acquisition modes (e.g. DDA and DIA) [31], and for investigations of unknown compounds [59]. We propose standardised use of these terms, to avoid misunderstanding and improve clarity, with the term 'non-target screening' referring only to conceptual data treatment approaches that do not consider structural information from the start (thus excluding target and suspect screening), and alternative terms like 'non-target analysis', 'untargeted screening' or 'untargeted analysis' being used for studies generally based on HRMS data acquired by untargeted data acquisition methods (e.g. DDA and DIA).

6. Prioritisation strategies

Prioritisation is an overarching term for strategies designed for the purpose of reducing complexity by focusing on data of high interest while removing irrelevant data (Fig. 2). While prioritisation is essential in non-target screening, as it is the first step in a non-target screening data treatment workflow, it can also be very helpful in suspect screening. One common and potent prioritisation principle is binary sample comparison, i.e. comparison of presence/absence or of signal areas of compounds between two samples. Binary sample comparison has been used e.g. to detect CECs formed within WWTPs [54,69], persisting after drinking water treatment [102] or present in an event but absent in baseline chemical composition (case *vs.* control) [103]. It should be noted, however, that the two samples included in binary comparisons should ideally be closely related, to avoid introduction of false

positives and false negatives caused by e.g. matrix effects or differences in sample handling. Replicate analysis can help to overcome false results caused by the background or other variation [59]. Binary sample comparison across different sample matrices is challenging because of differences in sampling and extraction procedures, and to date has rarely been used in water screening studies. One exception is a study focusing on prioritisation of bioavailable compounds through comparison of road runoff and runoff-exposed fish [75]. Trend analysis is another powerful prioritisation approach and is based on detection of intensity trends across a series of samples. Detection of time trends has led e.g. to identification of the new micropollutant class of quaternary triphenylphosphonium compounds [104], detection of industrial discharge events [3], and detection of spills of unknown substances [48]. Other trends that have been detected include spatial trends, e.g. [105], and trends across treatment steps, e.g. [106,107]. Detection frequency has been used to prioritise frequently occurring compounds [11,23,108], and intensity has been used to prioritise compounds presumably present at high concentrations (assuming good ionisation efficiency) and more likely to produce high-quality fragment ion spectra [31,93,109].

The characteristic isotopic patterns of chlorine and bromine can be used to prioritise chlorinated and brominated CECs [106,110], and mass defect calculations can help to identify homologous components, e.g. homologue series of PFASs using the Kendrick mass defect [56,94]. Searches for common fragments and common neutral losses can be used to prioritise components that are structurally related to other compounds of interest, e.g. biotransformation products of pharmaceuticals [69] and synthetic cannabinoids [111]. Clustering components using statistical tools, e.g. principal component analysis (PCA) [16,19,54] or hierarchical cluster analysis (HCA) [44,54], can also help to identify specific groups of interest.

Effect-directed analysis (EDA), i.e. prioritisation of toxic fractions of complex mixtures by combining testing for adverse biological responses and progressive fractionation to reduce chemical complexity [112], is a powerful tool for filtering biologically active chemicals. EDA has gained momentum in recent years and has been used e.g. for prioritisation of compounds inducing anti-androgenic responses [113], mutagenicity [71,114], and endocrine disrupting responses [114,115]. Effect-based assays, e.g. bioassays or fish embryo toxicity tests, have been used to prioritise whole samples with proven toxicity [116], and effect-based trigger values (EBTs) have been developed to categorise samples based on their measured toxicity [9]. Both EDA and effect-based assays as prioritisation tools are interdisciplinary, and therefore challenging, approaches that require additional competence and instrumentation besides LC-HRMS.

Similarly to prioritisation of samples or fractions for their biological activity, chemical characterisation of samples or fractions could be used. This could be achieved e.g. by prioritising datasets with high numbers of components with isotope patterns of halogens, environmental samples with chemical profiles similar to WWTP effluents or simply samples with relatively many suspect or target hits. Such prioritisation could be referred to as chemistry-directed analysis (CDA) (Fig. 2), analogously to the EDA concept. However, to our knowledge chemistry-directed analysis has not yet been used for prioritisation in water screening.

7. Structure elucidation and validation

Following prioritisation in a classical non-target screening workflow, the structure of candidate compounds needs to be elucidated. This is commonly accomplished by first assigning a probable molecular formula and then suggesting a tentative structure [3,13]. Both these steps rely on knowing the exact mass of the component and its fragments, which highlights the importance of high instrumental resolution and high quality of the fragment spectrum for structural elucidation. In particular, assignment of a tentative structure is still a great challenge and is generally approached by searching a database of chemical structures (e.g. Chemspider or PubChem) for promising candidates, which in most cases are candidates matching a predicted fragment pattern [5,117]. However, this approach limits possible candidates to those listed in the chemical database, which are all known structures, which will cause problems if the true compound is not known. Compounds with unknown structure that are not listed in chemical databases, e.g. most transformation products, have been referred to as “unknown unknowns” or “true unknowns” [3,106,109,118]. This highlights the need for software tools capable of elucidating true unknowns based solely on experimental data. Orthogonal approaches, including analytical techniques like nuclear magnetic resonance spectroscopy (NMR) and infrared spectroscopy (IR), are powerful tools for improvement of identification performance of true unknowns, which, however, have limited application possibilities in water screening studies, as both techniques require comparatively high substance amounts and purity grades that can only be reached using e.g. preparative LC [119,120]. Candidates which cannot easily be assigned a tentative structure are today commonly discarded and not reported, which poses a risk of losing candidates of interest (Fig. 1).

Several approaches have been developed to validate tentatively assigned candidate structures, and high confidence in tentative identifications is nowadays possible [5]. However, lists of tentatively identified compounds likely include false positive findings [12], and their identity can only be confirmed when authentic reference standards are available and when chromatographic and spectral details measured on the same instrument show good matches [121]. Reference spectra from mass spectral libraries or from the literature are an obvious and reliable tool for validating tentatively assigned candidate structures, and the need for more publicly available LC-HRMS reference spectra has long been highlighted [13]. While reference spectra for LC-HRMS still do not exist to the same extent as for GC-EI, several publicly and commercially available spectral libraries now include LC-HRMS, e.g. MassBank, MoNA, mzCloud, NIST and METLIN [122,123]. However, the reference data available today are of varying quality, have been acquired on a limited number of instruments, covering a limited number of acquisition parameters, and still only cover a minor fraction of the chemicals potentially present in a sample.

Different *in silico* prediction tools have been developed to validate tentatively assigned candidate structures, e.g. suspect screening hits. A good isotopic fit, i.e. close similarity between measured data and an isotopic pattern predicted from the molecular formula of the candidate, is commonly included as an additional criterion during suspect screening [28,31]. Retention time prediction tools have been designed to automatically assess the plausibility of the measured RT of a candidate and are based e.g. on quantitative structure-retention relationship (QSRR) models [68,124], artificial neural networks (ANNs) [125], or linear solvation energy relationship (LSER) models [126]. Many studies have used RT prediction in their workflows [5,12]. Apart from RT prediction, CCS prediction tools have been developed since ion mobility-HRMS became available, and can be used to validate candidates measured on IM-HRMS instruments [79,80,82]. *In silico* fragmentation tools, many originating from the field of metabolomics, predict fragmentation patterns from existing structures and are powerful alternatives when candidate fragment spectra cannot be validated using reference spectra [118]. Predicted fragments are commonly used to remove unlikely candidates, e.g. by considering only candidates that produce at least one

predicted fragment [12,80,125]. *In silico* fragmentation tools are often already integrated in vendor software, but several open-source solutions also exist, e.g. MetFrag [127], CFM-ID [128] and CSI:FingerID integrated with SIRIUS [129]. The software, especially the open-source solutions, have continually improved over the years and have become powerful multifunctional tools. Today, they are not only equipped for validation of suspect screening hits, but also facilitate structure elucidation in non-target screening. Some of the most notable improvements include implementation of RT prediction, use of metadata, e.g. patent count and scientific literature count, and links to mass spectral libraries [121–123].

Each validation step reduces the number of candidates by removing those that are unlikely, and also adds confidence in tentative identification of candidates passing the procedure. The increasing interest in HRMS-based screenings also creates a need to communicate the confidence in new identifications in a way that reflects the available evidence. The varying levels of confidence are difficult to communicate concisely and accurately [95], but a clear understanding of the available evidence, which indicates the reliability of the new identifications, is vital to avoid false conclusions and misunderstanding in the scientific community. Five levels of confidence have been defined [95], and are widely used to communicate the confidence in findings of suspect and non-target screenings. They are: confirmed structure (level 1), probable structure (level 2), e.g. reference spectra match, tentative candidate (level 3), unequivocal molecular formula (level 4) and exact mass (level 5). It is common practice in a suspect screening workflow to consider all evidence at hand, to reduce the number of tentative identifications and increase the confidence before purchasing reference standards for final confirmation, where possible [12]. Often only newly confirmed (level 1) and tentatively identified structures with high confidence levels are reported.

8. Challenges in HRMS analyses

Untargeted analysis has not only led to new data treatment possibilities, but has also brought new challenges for quality assurance and quality control. Traditional data quality control using predefined acceptance criteria cannot easily be performed since a vast number of potentially interesting compounds of a wide structural variety at a range of different concentrations can be expected [130]. In wide-scope target screening, method validation and quality assurance can be performed using a carefully selected subset of target analytes that represent the chemical space of the full target list [10]. However, this approach's feasibility is limited when the analytes of interest, and therefore the chemical space, are unknown (non-target screening) or reference standards are not available (suspect screening). Similar limitations occur when a limited number of stable isotope labelled internal standards are used for multiple (previously unknown) compounds to account for sample preparation and instrument analysis variations. The need to explore suitable internal standard mixtures for wide-scope screening studies that cover a large range of classes, ionisation efficiencies and polarities has recently been formulated [131], and is particularly important for (retrospective) semi-quantification of suspects or previously unknown compounds. Another possibility to correct for e.g. drifts in intensity or RT for a wide range of (unknown) compounds is to use quality control samples consisting of pooled aliquots of the studied samples throughout the analytical run, which has been established in the field of metabolomics [130]. This concept could proof useful for data correction, e.g. before prioritising peaks based on intensity trends. Peak finding algorithms have been identified as one key factor for the introduction of false positives and false negatives in HRMS-based studies, and the use of (technical) replicates with stringent filter criteria was suggested as an important measure to enhance data quality, as it improved repeatability and peak recognition [74]. Combining different peak finding algorithms has been suggested for reduction of false negatives, as it could potentially increase the component coverage [74], but when different software tools for peak finding were compared, low coherence was observed and the need for a better understanding of different algorithms was formulated [93]. This highlights the importance of data processing for the outcome of a screening study [93], and choice of data processing software on the outcome of a study. This will, e.g., affect how many false negatives are introduced by peak finding algorithms and how the operator's personal approach influences the outcome. The need for better quality criteria (e.g. reproducibility), specifically for untargeted analyses, has been stressed [132,133], and changes in publishing practices to include raw HRMS data and reporting of within-laboratory reproducibility have been suggested as measures to increase reproducibility of screening studies [133]. Reproducibility tests could also be implemented in retrospective screening studies (using e.g. publicly available raw data) to assure good quality of the selected data and to gain more insight into the reproducibility of HRMS-based screening studies. Quantification approaches using HRMS data have been developed for target screening (e.g [10].), but the question whether reliable (semi-)quantification without reference standards will be possible remains still unanswered. Authentic reference standards will, however, remain a necessity for unequivocal structure identification [133]. Quantification of newly identified compounds has been performed (e.g [11].), but semi-quantitative approaches, e.g. reporting of only concentration ranges, have also been developed to account for, and highlight, the uncertainties from e.g. unknown matrix effects and analysing samples at different time points (e.g [58].).

9. Conclusions and recommendations for future research

The most common sampling strategy today for LC-HRMS-based screening of water is grab water sampling. Alternative sampling approaches, e.g. composite samples or passive samplers, can provide a more representative chemical profile. For extraction of water samples, offline SPE is most commonly used. Due to improved instrument sensitivity, online SPE or direct injection methods are now being increasingly used, since they have the advantages of higher sample throughput and possibly less background contamination. Instrumental performance of LC and especially HRMS systems has increased in recent years and other tools, e.g. HILIC and IMS, have been identified as promising complements in analysis of challenging compounds. Data pre-processing is a rather generic step at the beginning of any data processing pipeline, but nevertheless defines the quality of the data to be further investigated. Data treatment cannot be displayed as a straightforward linear process (Fig. 2), but rather comprises a pool of different techniques and strategies, which can be applied depending on the data structure and the study objective. The three conceptual data treatment approaches (target, suspect and non-target screening) should therefore not be viewed as distinctly separate principles, but rather as general data treatment strategies with grey areas and links between them. Suspect screening for compounds with reference spectra available from a spectral library could arguably be perceived as lying closer to target screening, while wide-scope suspect screening for several thousand compounds with little background information available may be considered similar to non-target screening. False positive hits in suspect screening can re-enter the data pool as masses of interest and become part of non-target screening, while masses that pass prioritisation in non-target screening can be investigated in a similar way to suspects once a tentative structure has been

assigned. Many different data treatment strategies have been developed in recent years, but structure elucidation remains a challenging and time-consuming task.

In future work, time- and flow-proportional sampling approaches (e.g. passive sampling) and direct injection or online SPE need to be developed or optimised to improve the representativeness of the samples and make sample treatment more time-efficient. Instrumental performance will continue to improve and will be accompanied by other technological advances, such as IMS. Data treatment possibilities and software capacities will likely expand in the future, which will enable big data treatment approaches, e.g. studies including many (digitally archived) samples. It will also make prioritisation less critical, as great numbers of components can be investigated at once using more automated data treatment pipelines. Concerns about reproducibility and comparability of HRMS-based screening studies are already being discussed and will hopefully become an important topic in the future, as more automated workflows become more widely accepted and good, reproducible performance can be proven. Effect-based methods show great synergy with HRMS-based screenings and can become more popular as powerful tools for detecting issues of concern (e.g. through EBTs) and for prioritising toxic fractions (e.g. through EDA), especially in environmental monitoring and chemical management applications. Non-target screening as a conceptual approach is still very time-demanding, in particular since structure elucidation of unknown compounds based solely on instrumental HRMS information remains challenging. This step will need improved software solutions to become more time-efficient and reliable, and therefore more attractive, and collaborations with synthesis chemists and NMR or IR specialists are needed to advance the elucidation of true unknown compounds at the edge of our known chemical space. Prioritised components (in e.g. non-target screening) that could not be elucidated should be reported in future, to preserve their information until better structure elucidation tools become available. This information could also be used for novel suspect screening approaches using reference information instead of suspected structures (e.g. expected ionisation mode, expected mass, tentative fragments, tentative CCS value) and background knowledge on the specific research question they answer (e.g. matrix, occurrence, expected point source(s), treatment that forms the 'suspect'). Following current trends, it appears likely that suspect screening will come even more into focus as prediction tools (for e.g. transformation products, metabolites) become more widely used and data treatment workflows for suspect screening that result in high-confidence identifications in a timely manner become more broadly accessible. Ultimately, however, it is important to note that every step in LC-HRMS-based water screening discriminates compounds and that certain groups of interest (e.g. PMOCs) might require specifically optimised strategies.

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CRediT authorship contribution statement

Frank Menger: Conceptualization, Validation, Writing - original draft, Visualization. **Pablo Gago-Ferrero:** Conceptualization, Validation, Writing - review & editing, Supervision. **Karin Wiberg:** Writing - review & editing, Project administration, Funding acquisition. **Lutz Ahrens:** Conceptualization, Writing - review & editing, Project administration, Supervision.

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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