The role of analytical chemistry in exposure science: focus on the aquatic environment

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† In Memoriam

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Summary

Exposure science, in its broadest sense, studies the interactions between stressors (chemical, biological, and physical agents) and receptors (e.g. humans and other living organisms, and non-living items like buildings), together with the associated pathways and processes potentially leading to negative effects on human health and the environment. The aquatic environment may contain thousands of compounds, many of them still unknown, that can pose a risk to ecosystems and human health. Due to the unquestionable importance of the aquatic environment, one of the main challenges in the field of exposure science is the comprehensive characterization and evaluation of complex environmental mixtures beyond the classical/priority contaminants to new emerging contaminants.

The role of advanced analytical chemistry to identify and quantify potential chemical risks that might cause adverse effects to the aquatic environment, is essential. In this paper, we present the strategies and tools that analytical chemistry has nowadays, focused on chromatography hyphenated to (high-resolution) mass spectrometry because of its relevance in this field. Key issues, such as the application of effect direct analysis to reduce the complexity of the sample, the investigation of the huge number of transformation/degradation products that may be present in the aquatic environment, the analysis of urban wastewater as a source of valuable information on our lifestyle and substances we consumed and/or are exposed to, or the monitoring of drinking water, are discussed in this article. The trends and perspectives for the next few years are also highlighted, when it is expected that new developments and tools will allow a better knowledge of chemical composition in the aquatic environment. This will help regulatory authorities to protect water bodies and to advance towards improved regulations that enable practical and efficient abatements for environmental and public health protection.

Keywords: environmental analytical chemistry, water, exposure science, high resolution mass spectrometry, chromatography, emerging contaminants

1. Introduction

The production and use of chemicals is an indispensable aspect of the current worldwide economy and modern life. A key driver for the increasing use of chemicals is the growth of the global population. This, combined with rapid, albeit uneven, economic and technological development, has led to a considerable increase in global production, consumption of goods and mobility, together with increased demand for food and energy (EEA, 2013). In addition, demographic changes such as the ageing population and the tendency to move from rural areas to urban areas will lead to changes and possible increase in the use and emission patterns of, for instance, pharmaceuticals (Boecking et al., 2012; Tränckner and Koegst, 2010). Worldwide, over 125 million organic compounds are registered in the Chemical Abstract Service (CAS) database. Today, there are more than 100,000 chemicals in the inventory of the European Chemicals Agency (ECHA, 2017). The release of these compounds and resulting risks for human health, the environment and the water cycle, have raised the concern of scientists and policy makers.

The increasing awareness of potential risks of organic contaminants for aquatic ecosystems and human health has encouraged scientific and public discussion and political action to introduce measures to improve water quality. As minimization of sources is difficult to achieve, often end-of-pipe solutions such as advanced technologies to remove harmful compounds are implemented (e.g. additional processes in wastewater and drinking water treatment). The conventional processes applied in wastewater treatment plants (WWTPs) are designed to remove the bulk of organic load, measured as biochemical oxygen demand (BOD) or total organic carbon (TOC). However, many organic micropollutants (OMs) are not efficiently removed, and wastewater effluents usually contain amounts of pharmaceuticals, personal care products (PCPs), or illicit drugs, among others, that end up in the aquatic environment (aus der Beek et al., 2016; Bijlsma et al., 2014; Gracia-Lor et al., 2012; Gros et al., 2010; Jelic et al., 2011; J. Liu et al., 2015; Loos et al., 2013; Schymanski et al., 2014b). Additional treatments, such as advanced oxidation or activated carbon, to reduce the input of these contaminants into the aquatic environment are being implemented progressively on certain plants (Eggen et al., 2014). Drinking water treatments, such as nanofiltration or reversed osmosis, can also contribute to the removal of OMs.

Chemical pollution has been identified as one of the nine planetary or regional boundaries for which anthropogenic impact needs to be reduced (Rockström et al., 2009b, 2009a; Steffen et al., 2015). Despite improvements in regulations and the efforts to reduce the production and use of the most hazardous chemicals, chemical pollution still poses a significant risk to nearly half of the water bodies monitored in Europe (Malaj et al., 2014). Only

a few contaminants have been included in the list of priority substances (PS) to be monitored according to the Water Framework Directive (WFD) of the European Commission (EC, 2000). The amended directive for PS (EC, 2013) introduced a Watch List of emerging pollutants or other chemicals for which the available monitoring data are insufficient to assess the environmental risk. Environmental Quality Standards (EQS) have been established for PS (EC, 2008) to protect the aquatic environment from adverse effects of chemical substances. The 1st Watch List, launched in 2015, has been recently updated (EC, 2018), and with these measures it is expected that pollution from PS will be progressively reduced. Nevertheless, the number of PS and river basin specific pollutants will still remain very small compared with the number of chemicals released into the environment.

A working group headed by the NORMAN network identified that risks and impacts of complex mixtures of chemicals on water quality (Brack et al., 2017) will challenge monitoring, prioritization, assessment and management within the WFD, and an integrated strategy accounting for knowledge gaps is recommended. One of the major challenges is to improve the monitoring and strengthen comprehensive prioritization and risk assessment of complex mixtures. Integrative effect-based tools (EBTs), such as bioassays and biomarkers, are recommended in monitoring water quality. EBTs are particularly useful to bridge the gap between chemical contamination and ecological status; they can cover a broad range of exposure and toxicity mechanisms in diverse organisms, and include effects of non-studied compounds and mixtures, as well as the combined effect of mixtures of compounds (whether or not identified) (Brack et al., 2012).

Prioritization, monitoring and assessment under the WFD tend to emphasize regulated, well-known substances, while emerging substances are not adequately addressed (Heiss and Küster, 2015). The present evaluation in European water bodies is mostly based on information on occurrence of target substances versus EQS values. Although some substance classes, such as pesticides, have been widely covered (Moschet et al., 2014), only a small percentage is currently considered in environmental risk assessment (de Zwart et al., 2018). Identifying potential chemical risks in the aquatic environment requires extensive information on the occurrence of a large number of contaminants.

Besides the difficulties to identify what to measure and where in the aquatic scenario, the additional challenge is to understand which concentration of an individual substance or combination of substances (mixtures) raises concern in terms of potential risk. To evaluate the potential harmful effects, both hazard and exposure information is needed. The current EU Regulation on chemicals management (Registration, Evaluation, Authorization and restriction of Chemicals (REACH)), created a mandate to deliver adequate exposure information to enable

appropriate safety assessments, and foster the safe use and management of chemicals. Exposure information is also required in other European regulatory frameworks, including regulations on plant protection products, biocidal products, construction products, general product safety, classification, labelling and packaging, control of air quality and major-accident hazards. Furthermore, EU strategies promoting moving to a non-toxic environment by 2050, striving towards a circular and bio-based economy, and encouraging green and sustainable chemistry, add additional challenges requiring adequate exposure information. Proper measurement and analyses strategies need to be developed to fulfill the regulatory requirements and to facilitate informed decision-making supporting the EU 2050 goals. To generate and analyze adequate exposure information, the application of excellent exposure science is crucial.

Exposure science, in its broadest sense, studies the interaction between stressors (primarily chemical, biological, and physical agents) and receptors (e.g. molecules, cells, organs, humans, other living organisms, and non-living items like buildings), and the associated pathways and processes potentially leading to negative effects on human health and the natural and built environment (Bruinen de Bruin et al., 2018). Therefore, the need for Programs to promote increased generation of exposure information and fit-for-purpose exposure assessment tools, followed by independent assessments and use by risk managers and policy makers, is increasingly important. Analytical chemistry is one of the indispensable disciplines in this field (**Figure 1**). The application of appropriate analytical strategies and tools is essential for a comprehensive characterization of the environment and to understand and evaluate the exposure of the population to emerging chemical risks.

Insert Figure 1

Environmental analytical chemistry has several challenges, such as:

- A huge number of compounds can be present in the environment, and many of them are still unknown. The great diversity in chemical composition of organic contaminants, from non-polar to highly polar compounds, and from low to high volatility, makes the detection and identification of potentially hazardous compounds an analytical challenge. No universal analytical method can be applied to detect and identify all contaminants that may be present in environmental samples. Despite the analytical efforts, a notable number of compounds still requires specific methods and experimental conditions for their determination (e.g. highly volatile compounds, highly polar/ionic compounds, or

compounds with distinct polar and apolar functionalities (surfactants)), hampering their inclusion in multi-residue multiclass methods.

- Most organic contaminants are present at very low concentrations in complex/unknown, ever-changing matrices, and the analytical methodology for their detection, identification and quantification is far from being routinely applicable. It is highly specialized and expensive, and requires the use of sophisticated instrumentation and experienced analysts, particularly when applying wide-scope screening methodologies for suspect and non-target analysis (see later in the manuscript). In addition, valuable techniques commonly used for elucidation of the identity of organic compounds, such as infrared spectroscopy (IR), nuclear magnetic resonance (NMR) and X-Ray, cannot be applied (or have very limited applicability) in the field of environmental analytical chemistry because of their limited sensitivity, making (HR)MS the almost sole analytical technique able to provide information for identification of these compounds.
- Transformation via biotic or abiotic processes in the environment becomes an additional difficulty, as this multiplies the number of compounds of potential interest, many of which are still unknown. The almost infinite number of transformation products (TPs) in the aqueous environment makes it extraordinary difficult to perform a comprehensive evaluation of their presence and effects on the environment. The lack of occurrence data for TPs imposes a notable limitation in the evaluation of exposure risks.

Advanced analytical techniques are required for a comprehensive characterization of the aquatic environment, emphasizing the hyphenation of chromatography with low and high resolution MS, including multidimensional separations, recent chromatographic separation systems and new mass analyzers. High resolution MS (HRMS) presents strong potential for identification of a large number of organic contaminants and elucidation of unknowns derived from accurate-mass full-spectrum data acquired. Many papers have been published in the last years illustrating the excellent performance and tremendous possibilities of HRMS coupled to GC and/or LC to identify a great diversity of pollutants. A detailed review is out of the scope of the present manuscript, but some references can be given as illustrative examples (Andres-Costa et al., 2017; Aceña et al., 2015; Bade et al., 2015a; Bletsou et al., 2015; Díaz et al., 2012; Gosetti et al., 2016; Hernández et al., 2012, 2014, 2018; Hollender et al., 2017; Letzel et al., 2015; Lorenzo et al., 2018; Nurmi et al., 2012; Vergeynst et al., 2015; Wode et al., 2015).

People are exposed to many chemicals present in homes, the workplace, and other surroundings through multiple pathways via air, water, food and soil (Wambaugh et al., 2014). Risk assessment depends on two basic elements, exposure and hazardous effects, which are directly related to the presence and concentrations of hazardous compounds in the

environment. This is the key of the prioritization schemes that provide the scientific basis for regulatory procedures (Guillén et al., 2012).

A strategy based on the maximum environmental concentrations (MEC) has been used to prioritize 500 classical and emerging contaminants in four European river basins, using two indicators, the frequency of exceedance and the extent of exceedance of Predicted No-Effect Concentration (PNEC) (Von der Ohe et al., 2011). Toxicity estimation is an indispensable source for prioritization (e.g. DSSTox database, from EPA), along with exposure (e.g. ExpoCast) and bioactivity predictions (Tox21) (Rager et al., 2016; Tice et al., 2013). However, testing every chemical for every possible health and environmental effect is unrealistic and does not take into account the combined effect of complex mixtures, and therefore prioritization is again necessary.

Often, the lack of information, such as sufficient data on the occurrence or effects of a compound, may exclude it from current prioritization procedures (Dulio and Slobodnik, 2015). Thus, many compounds are ignored from the assessment, without any evidence of 'no harm'. The last review of the list of priority pollutants revealed that about 50% of the candidate substances were discarded because of the lack of data (Brack et al., 2017). This illustrates the growing need for monitoring programs to screen for a large number of contaminants including relevant TPs. Many efforts are being made at this challenging task, with substantial improvements in the last few years thanks to the impressive progress in analytical instrumentation and data processing techniques.

The **objective of this paper** is to present and discuss the main strategies and tools that modern analytical chemistry can apply in the field of exposure science, with the main focus on the identification of emerging chemical risks in the aquatic environment making use of chromatography hyphenated to (high resolution) mass spectrometry. This article is not conceived as a classical review, and it is directed to scientists from other disciplines related to exposure science. Thus, we do not pursue a detailed/in depth discussion on analytical methods, but to focus on upcoming trends and the tremendous possibilities that make analytical chemistry an indispensable science in this field. Although the work is European oriented, it is applicable on a global scale. We emphasize the relevance of advanced analytical chemistry to provide information on occurrence and behaviour of a huge number of organic contaminants and their TPs in the environment, which is essential in toxicology, environmental risk assessment, exposure science, and in updating regulation.

2. Emerging contaminants of recent concern in the aquatic environment

In the last years, many efforts have been made to provide reliable data on occurrence of emerging contaminants in the aquatic environment. A recent review on water analysis (Richardson and Kimura, 2016) mentioned several groups of concern, including artificial sweeteners, nanomaterials, hormones, disinfection by-products, benzotriazoles, siloxanes and microplastics. With the impressive improvement in analytical techniques and analytical strategies, the list of contaminants of emerging concern is notably increasing.

In addition to the above mentioned compounds of recent concern, some other families are, or will likely become, a priority in the near future due to its occurrence in the aquatic environment. Among these, can be emphasized pharmaceuticals and personal care products (PPCPs), per- and polyfluorinated alkyl substances (PFAS) and flame retardants (FRs). PPCPs are frequently found in urban wastewater and in receiving surface waters. Pharmaceuticals are often called pseudo persistent substances due to their continuous use and presence in waters. PCPs can contain preservatives, pigments, solvents/oils, nanoparticles, surfactants, pharmaceuticals, UV filters, fragrances, minerals and polymers, and their physico-chemical properties vary widely. The primary pathway of pharmaceuticals, PCPs and their metabolites entering the water cycle is through human usage in or on the body, and excretion or washing off Use of pharmaceuticals in veterinary practice and aquaculture can also lead to emissions (Boxall et al., 2004; Yao et al., 2015).

From the first papers reporting pharmaceuticals as environmental contaminants in waters (Daughton, 2004; Daughton and Ternes, 1999; Kolpin et al., 2002), there has been an impressive increase in the number of publications on occurrence of pharmaceuticals in waters around the world (e.g. Alder et al., 2010; Bartelt-Hunt et al., 2009; Campanha et al., 2015; Ghoshdastidar et al., 2015; ter Laak et al., 2014; van Nuijs et al., 2015; Wu et al., 2015). The development of sophisticated analytical techniques has undoubtedly played a key role in their emergence (Richardson and Kimura, 2016). Most of research performed until now is focused on parent pharmaceuticals, and only a limited number of metabolites/TPs is commonly included in analyses (Bletsou et al., 2015; Fatta-Kassinos et al., 2011; Ibáñez et al., 2017; Kern et al., 2010), and their impact on ecology or human health is often lacking (Escher and Fenner, 2011). Since some classes of pharmaceuticals have indirect effects such as the development of antibiotic resistance, it is a challenge to determine these effects and the associated risks (Boxall et al., 2012; Richardson, 2017; Singer et al., 2016). The evaluation of the hazards of PCPs is a current priority in regulatory water quality monitoring (Brack et al., 2017, 2012; Loos et al., 2009).

The occurrence of pharmaceuticals and PCPs in the aquatic environment is mainly a consequence of the poor removal efficiency of WWTPs for these organic micro-pollutants

Therefore, improvements of such efficiency are necessary using additional treatment systems, such as advanced oxidation processes, among others. The comprehensive control of these processes requires monitoring not only the elimination of the parent compound under study, but also the identification of potential degradation/transformation products that can be formed during the process. To this aim, advanced analytical techniques (e.g. LC-HRMS) are required.

Per- and polyfluorinated alkyl substances are a prominent group of emerging contaminants. They are persistent, resist degradation and have been linked to adverse health effects (de Voogt and Sáez, 2006). Sources of PFAS in the environment include a variety of industries, firefighting foams, landfills and WWTPs among others (Buck et al., 2011; Busch et al., 2010; Dimzon et al., 2017; Hu et al., 2016; Lau et al., 2007; Lindstrom et al., 2011; Eschauzier et al., 2011). Drinking water and drinking-water based beverages may also play a substantial role in the human exposure to these compounds (Sharma et al., 2016; Sun et al., 2016; Vestergren and Cousins, 2009)

Most of the research and analysis of PFAS have focused on the perfluorinated sulfonic acids (PFSAs) and perfluorinated carboxylic acids (PFCAs). Several studies (Miyake et al., 2007; Willach et al., 2016) have shown that identified and quantified PFAS in water usually account for less than 50% of the total organic fluorine content of the sample. This can be partly explained by the limited target lists investigated in low resolution MS methods, and lack of standards. Hence, a major part of organic fluorine remains unknown suggesting the occurrence of other fluorinated acids in addition to the known precursors. More than 3000 PFASs have been marketed (Wang et al. 2017). Although in recent years many new anthropogenic PFASs have been detected (Xiao, 2017; Gebbink et al. 2017; Barzen-Hanson et al. 2017) a clear picture of the full range of individual substances is still lacking and reveals the need to investigate in depth the occurrence of fluorinated compounds in the environment Kotthoff and Bücking (2018).

The replacements of banned or regulated substances, such as perfluoro-octanesulfonic acid (PFOS) and perfluoro-octanoic acid (PFOA), by per- and polyfluorinated alternatives, such as short chain PFCAs and PFSAs and perfluorinated ethers, has led to an increase in their levels in environment (Arp and Slinde, 2018; Schaider et al. 2017). For example, heptafluoropropoxy propanoic acid (HFPO-DA), a replacement of PFOA in the production process of polytetrafluoroethylene (PTFE), has been reported to occur in rivers close to manufacturing sites where PFOA was previously found, e.g. in the river Rhine (Heydebreck et al., 2015) and Cape Fear river (Sun et al., 2016).

While PFAS manufacturers have shifted from the production of long-chained to short-chain (CF<7) PFASs, the shorter chain PFAS are equally persistent in the environment (Ritter, 2015) and have higher aqueous solubility than their long-chain homologues. As a result, their removal from water is less efficient and breakthrough in treatment processes used for drinking water production has been demonstrated to occur (Eschauzier et al., 2012; McCleaf et al., 2017). Recently, a suite of persistent halogenated methanesulfonic acids including trifluromethanesulfonic acid has also been shown to occur in groundwater, surface water and drinking waters (Zahn et al., 2016). These findings highlighted the need for further development of advanced analytical methodologies to unravel the full spectrum of PFAS present in the environment (D'Agostino and Mabury, 2014; Y. Liu et al., 2015; Ruan and Jiang, 2017; Strynar et al., 2015, Dimzon et al, 2017).

Flame retardants are another group of great interest from the point of view of exposure science. These chemicals are widely applied to materials such as textiles, plastics and electronic products, to delay combustion in case of ignition. Several FRs have been detected in various environmental and food samples (Covaci et al., 2011; Law et al., 2014; Reemtsma et al., 2008; van der Veen and de Boer, 2012). Polybrominated diphenyl ethers (PBDEs) have been extensively used until two PBDEs mixtures (Penta and Octa-mix) were banned, because of their persistence, toxicity and bioaccumulation in the environment and biota (EC, 2003; Environment Canada, 2015, accessed 14.01.19 ; https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/polybrominated-diphenyl-ethers-pbdes, accessed 14.01.19). As a result of the halt in manufacture of these PBDEs in many countries, other FRs, such as deca-bromodiphenyl ethane (DBDPE), and other brominated and phosphorus FRs (PFRs) have replaced PBDEs (Covaci et al., 2011; Law et al., 2014; van der Veen and de Boer, 2012). This highlights that the continuous modification in law and use of many chemicals around the world forces analytical chemists to address these new families of contaminants.

A number of studies have been performed on these "new" FRs and identified them in the environment (Richardson and Kimura, 2016). Tris(chloropropyl)phosphate (TCPP) has been reported as the PFR most frequently found in surface waters (van der Veen and de Boer, 2012). In drinking water from eight different Chinese cities, TCPP was also found dominant together with tris(2-butoxyethyl)phosphate (TBEP) and triphenylphosphate (TPP) (Li et al., 2014).

Despite some PBDEs have been banned, they will remain in the environment for decades to come, and should therefore be monitored. For example, BDE209 (the major component of the deca-mix PBDEs product) was found dominantly present in sewage sludge samples from several countries (Law et al., 2014; Richardson and Kimura, 2016). BDE209 can

also degrade down to lower brominated diphenylethers (Gerecke et al., 2005), which, in contrast to BDE209 can bioaccumulate.

3. Analytical strategies and tools

The analysis of environmental samples involves dealing with high complexity, low concentrations, unknown and sometimes even transient substances, with a broad range of physico-chemical properties. Mass spectrometry, coupled to GC or LC, is commonly the technique of choice to investigate the presence of OMs due to its strong identification potential and because it covers a wide selection of substances compared with other analytical methods. Analytical investigation of OMs can follow different strategies: target, suspect and non-target analysis **(Figure 2).**

In target analysis, the main objective is reliable identification and quantification of known substances for which reference standards are available in house. The analytical methods are optimized to allow highly sensitive and selective quantification of a limited number of substances typically present at sub-ng to µg/L levels. Modern targeted methods are mostly based on GC and LC coupled to (low resolution) tandem mass spectrometry (MS/MS) with ion trap (IT) or triple quadrupole (QqQ) analyzers. GC-MS/MS and LC-MS/MS methodologies have excellent performance in terms of sensitivity and selectivity (and less sample treatment as a consequence of the better sensitivity), and are the most commonly used in recent quantitative target analysis. Analytes of medium/high polarity are more compatible with LC-MS/MS analysis, for example many pesticides, pharmaceuticals, illicit drugs, veterinary drugs (Botitsi et al., 2011; García-Galán et al., 2016; Hernández et al., 2012, 2014; van Nuijs et al., 2011). In contrast, both GC-MS and GC-MS/MS, are the techniques of choice for less polar and/or highly volatile contaminants, such as classical priority pollutants (polychlorinated biphenyls (PCBs), organochlorine pesticides or polycyclic aromatic hydrocarbons (PAHs)), as well as siloxanes, PBDEs, and certain pesticides (Barco-Bonilla et al., 2010; Hernández et al., 2013; Law et al., 2014; Pitarch et al., 2010; Portolés et al., 2015).

An enrichment step (e.g. solid phase extraction (SPE), solid phase micro extraction (SPME), or solvent extraction) is typically applied prior to MS analysis, and can also result in some sample clean-up. However, the excellent sensitivity of new LC-MS/MS systems allows quantification at low ng/L levels with direct injection of water samples, even prior dilution with ultrapure water (Boix et al., 2015; Causanilles et al., 2016). Identification is achieved through acquisition of at least two MS/MS transitions in the Selected Reaction Monitoring (SRM) mode, and matching of the retention time (RT) and ion-intensity ratios between reference standards and samples (SANTE/11945, 2015). Looking into the (near) future, new technological

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developments are expected to allow the expansion of targeted methods to detect, identify and quantify several hundreds of targets accurately, with sensitivity down to pg/L (Hernández et al., 2014; Pinhancos et al., 2011; Vergeynst et al., 2015).

Suspect analysis involves looking for compounds expected in the sample on the basis of existing lists of (emerging) substances e.g. NORMAN suspect list exchange (Norman network, 2018a) , but for which standards are not available in-house. HRMS is the technique preferred when using this approach, as it allows searching for a large number of suspects based on the accurate-mass full-spectrum acquisition. Detected "suspects" can be tentatively identified with the valuable information provided by HRMS(/MS), RT and even spectral library matching, and can be confirmed retrospectively via reference standard purchase, which is a cost-effective strategy that has led to the increasing popularity of this approach (Hernández et al., 2015a; Moschet et al., 2013; Schymanski et al., 2015; Sjerps et al., 2016). Ion mobility Spectrometry (IMS) adds a new dimension to the chromatographic-TOF MS separations, which notably facilitates the identification process. The collisional cross-section (CCS), measured in IMS, depends on the geometry/shape of the ionized molecule, and is a valuable parameter that may help to solve problematic identifications (e.g. isomers, some analytes in highly complex matrices). Prediction of CCS has been successfully applied to improve identification of suspects and will surely be an efficient tool in suspect and non-target screening in the near future (Bijlsma et al., 2017; Mollerup et al., 2018; Zhou et al., 2016).

Suspect screening has huge potential for the identification of emerging contaminants and regulated substances (discussed further below), because it can speed up the evaluation of unknown peaks. Of great value is the use of databases of relevant compounds to be searched in the environmental samples. Considering the huge number of chemicals that are compiled in databases (e.g. the CompTox Chemistry Dashboard from the US EPA (Williams et al., 2017) or in the NORMAN Suspect List Exchange (Norman network, 2018a), a prioritization is needed to facilitate the detection and (tentative) identification of these compounds. Such prioritization can be based on key parameters, such as known or predicted toxicity, knowledge on uses and consumption, persistence in the environment, bioaccumulation, as well as previous data on occurrence (Howard and Muir, 2010).

Even after extensive target and suspect screening, many thousands detected components remain unknown (Fuhrer and Zamboni, 2015; Peisl et al., 2018). As identification of unknowns is very time-consuming, these are often prioritized for further elucidation using various methods depending on the research question, e.g. high intensity, specific isotope pattern, (Hoh et al., 2012; Schymanski et al., 2014b), mass defect (Chiaia-Hernandez et al., 2014; Merel et al., 2017; Thurman et al., 2014), linkage analysis for TPs (Schollée et al., 2015)

and various statistical measures (Schollée et al., 2016). Experimental design, such as sampling before and after a treatment, along a spatial gradient or over time can prioritize further masses for identification (Hollender et al., 2017). Spectral library searches are also used for non-target identification, especially in GC-MS where extensive standardized libraries are available, but increasingly also in HRMS(/MS). The confirmation of the identity and quantification of the compounds tentatively identified can be performed in a later stage if reference standards are available (Ruff et al., 2015; Schymanski et al., 2014b).

Insert Figure 2

In contrast to target analysis, suspect and non-target screening are less mature forms of data exploration and many different possibilities exist, from vendor software through to open access/open source solutions. Non-target strategies differ between the established low resolution GC-MS with electron ionization (EI), for which extensive libraries exist, and HRMS techniques (Schymanski et al., 2015). The NIST library is one of the most extensive collections of GC-EI-MS spectra (>200,000 substances) and retention indices (>83,000 substances) (Vinaixa et al., 2016), and is a valuable resource for the identification of unknowns as two orthogonal pieces of information are available (Schymanski et al., 2014a). If a substance is not in the library, identification e.g. via structure generation remains possible but challenging due to the low-resolution information (Brack et al., 2016; Schymanski et al., 2012). As the exact mass is not generally available, compound database searching has not really established itself for EI-MS.

Accurate-mass full-spectrum measurements are of great value for identification purposes, especially when using soft-ionisation techniques, irrespective of whether GC or LC is used. Recently, GC has been coupled to QTOF-MS using an atmospheric pressure chemical ionization (APCI) interface, providing accurate-mass spectra rather similar to those of LC-QTOF MS. The low fragmentation compared to EI, and high abundance of the protonated/molecular ion molecule are of great help to determine mass and often the molecular formula, making GC (APCI)-MS based methods more attractive for screening purposes of organic residues. (Portolés et al., 2014). The complementary use of GC and LC, both coupled to HRMS(/MS), facilitates a comprehensive analysis for known and unknown compounds within a wide range of polarity and volatility. This combination allows to advance towards the desired universal screening of organic contaminants (Hernández et al., 2015b).

Some MS/MS spectral libraries are now available and contain a wide range of environmentally-relevant substances, especially NIST17 MSMS (Yang et al., 2017), MassBank

(Schulze et al., 2012) and mzCloud (HighChem, accessed 5.30.18); for a more extensive overview see (Brack et al., 2016; Peisl et al., 2018; Vinaixa et al., 2016). If a compound detected is not present in any library, a variety of non-target software approaches exist for identification. The first step usually involves detecting masses of interest (termed peak picking or feature finding), either using commercial (vendor) software or one of the open source approaches such as XCMS (Smith et al., 2006), enviMass (Loos et al., 2016) or MZmine2 (Pluskal et al., 2010). Grouping of the resulting masses into components by summarizing isotope and adduct signals is essential to reduce the identification effort (see e.g. (Schymanski et al., 2015, 2014b). This also provides valuable information for calculation of the molecular formula.

When fragment information is available, *in silico* approaches can be applied to first find candidates (by searching compound databases on exact mass or formula), then these need to be matched with the experimental spectrum using the structural information provided by the fragments (Dührkop et al., 2015; Ruttkies et al., 2016; Schymanski et al., 2017). The combination of suspect screening with spectral libraries, and *in silico* methods, shows huge potential for rapid and comprehensive screening of emerging contaminants. While the *in silico* methods are improving greatly, it is still vital that tentative structures are confirmed with reference standards before a confident identification is claimed. Other powerful elucidation techniques that do not have much application in the environmental field yet, such as LC-NMR, can play a relevant role in the near future for confirmatory purposes.

The huge number of (non-overlapping) resources available, and the increasing volume of data, which requires consistent and more efficient workflows, both remains challenges for non-target screening with high resolution data. Exchange of information between institutes is essential to facilitate and improve workflows (Schymanski et al., 2015). Some initiatives to improve the European-wide exchange of information, such as a compilation of suspects lists, have been recently reported (Norman network, 2018a, 2018b). Looking towards the future, a degree of standardization that would come with greater maturity would help non-target methods, providing a valuable contribution for identification purposes.

4. The role of effect-directed analysis

Effect-directed analysis (EDA) is a powerful approach for the identification of emerging chemical risks. In EDA, EBTs are combined with sample fractionation using chromatography and HRMS to isolate the compounds responsible for the effects observed in the bioassay used. With this approach, an intrinsic prioritization is applied and the identification efforts are focused on those fractions that showed to be biologically active. The combination of

biological/toxicological and chemical analytical tools for environmental quality assessment has a long history and has led to complementary approaches developed in the United States and in Europe (Burgess et al., 2013). Toxicity Identity Evaluation (TIE) was developed primarily for land remediation sites, thus focusing on sediment, in vivo bioassays and bioavailability, whereas the development of EDA was stimulated by the EU WFD and the need to investigate the drivers of chemical water quality.

Typically, the EBTs used in EDA are rapid screening tools in multi-well plate format based covering a wide range of toxicological endpoints, such as endocrine disruption, genotoxicity, oxidative stress, etc. Both total extracts (prior to fractionation) and all fractions are tested in the selected bioassay, which enables the assessment of eventual losses during fractionation and antagonistic or synergistic effects (Weiss et al., 2009). Recently, an in-depth overview of EDA supporting monitoring of aquatic environments has been published (Brack et al., 2016), focusing on toxicity testing, sampling, extraction and identification strategies. The advantages of the implementation of integrated tools on effect-based and chemical identification and the monitoring of organic pollutants were highlighted in a European demonstration program (Tousova et al., 2017).

Although some EDA studies reported the identification of compounds, e.g. photosynthesis inhibitors in coastal waters (Booij et al., 2014) and mutagenic aromatic amines in river water (Muz et al., 2017), and despite the technological advancements of HRMS, significant progress with regard to the identification of chemicals responsible for observed effects in EBTs has not been truly achieved. From the perspective of acceptance of EDA for e.g. investigative monitoring in the WFD, the studies were too laborious and time consuming. To tackle these two aspects, the EDA approach was transformed to a high throughput tool using very small scale fractionation, i.e. the collection of fractions only a few seconds wide and thus small volumes, ideally enabling a more straightforward coupling of the biological activity to the chemical identity. For high-throughput EDA (HT-EDA), a high-resolution fractionation platform was developed for fractionation into 96-well plates and used with an estrogenicity assay to direct the analysis (Jonker et al., 2015). The direct fractionation of EDA extracts into 96-384-1536 well plates demands the downscaling of toxicity assays, such as the transthyretin binding assay using a fluorescent probe for high throughput screening of thyroid hormone disruption in environmental samples (Ouyang et al., 2017). Other assays that have been miniaturized for use in HT-EDA cover genotoxicity, (anti-)estrogenicity and (anti-) androgenicity and arylhydrocarbon receptor (AhR) binding (Zwart et al., 2018a, 2018b).

Complementary to the ubiquitously used LC fractionation, strategies for GC fractionation were developed in order to cover a larger part of the chemical space by focusing on volatile

513 compounds. An example focused on the AhR-binding assay and the identification of PAHs
514 (Pieke et al., 2013) in sediments. Improvement of the GC fractionation platform for bioactivity
515 screening of toxic compounds was demonstrated by the analysis of a mixture of test
516 pesticides, which after fractionation into a 384 well plate were tested in a post-column
517 acetylcholinesterase (AChE) assay (Jonker et al., 2016). Using a similar approach, (anti)
518 androgenicity testing using the AR-Ecoscreen in 384 well plate format has been reported
519 (Jonker et al., 2017).
520 Very small fractions may also be obtained by LCxLC, using two LC columns with different
521 (orthogonal) functionalities (Ouyang et al., 2016). A strategy based on LC×LC fractionation
522 resulting in microfractions of 9 s into 4x96 well plates, an AChE inhibition assay and parallel
523 identification by TOF-MS resulted in the identification of 3 psychoactive drugs in the effluent of
524 a WWTP. Apart from the high resolution fractionation that can be achieved by the
525 implementation of LCxLC, compounds were identified by two-dimensional retention alignment
526 as well as their AChE inhibition activity, which significantly contributes to the reliable
527 identification of bioactives in the aquatic environment.
528 Compound identification in EDA is carried out using non-target screening, following
529 analogous identification pipelines as described above. For a first check of reported toxicity of a
530 tentatively identified compound, toxicity databases such as the CompTox Chemistry
531 Dashboard (Williams et al., 2017), ToxCast and PubChem Bioassay may be consulted. To
532 facilitate identification, dedicated databases for e.g. a specific toxicological endpoint or a
533 specific sample matrix have been developed. Thus, large databases of compounds showing
534 thyroid hormone disrupting activity (Weiss et al., 2015) or directed towards the identification
535 of chemicals in house dust (Lucattini et al., 2017) have been reported. In addition to compound
536 libraries and toxicity databases, identification efforts are expected to greatly benefit in the
537 future from the implementation of less commonly used MS interfaces such as APCI and APPI
538 for specific compound classes.
539 The HT-EDA platforms based on LC and GC fractionation into ≥ 96 well plate for rapid
540 toxicity screening and parallel identification using HRMS/MS, comprehensive compound
541 databases (e.g. ChemSpider or PubChem, that contain properties such as accurate mass, log
542 Kow, etc), in addition to mass spectral libraries, are expected to contribute to an improved
543 framework for investigative monitoring in the environment.
544 Other approaches than EDA could be followed to reduce the complexity of the analysis,
545 such as the use of molecular imprinted polymers (Kubo & Otsuka, 2016) for very specific
546 extractions, or the use of antibodies (Li et al., 2017), among others. However, a complete
547 description would be far beyond the scope of the paper.

548

549 **5. Relevance of transformation products**

550 Once released into the environment, most organic contaminants are subjected to
551 biotic and abiotic transformations. These transformations generate a great variety of TPs that
552 differ from the parent compound in both their environmental behaviour and (eco)toxicity.
553 Unfortunately, there is a significant gap between the knowledge on the occurrence of TPs and
554 their toxicity, making risk assessment difficult (Agüera et al., 2013; Farré et al., 2008).

555 Current legislation is almost exclusively directed towards regulating parent chemicals,
556 with very little mention of TPs. Usually, information is lacking on analytical determination,
557 occurrence, and toxicological effects of TPs. Therefore, there is a clear need to reveal the
558 quantitative and qualitative presence of TPs in the environment and their potential risks for
559 human health.

560 HRMS has been used for identification of TPs (Díaz et al., 2012; Hernández et al., 2014,
561 2011; Hogenboom et al., 2009; Ibáñez et al., 2017; Kern et al., 2009; Nurmi et al., 2012;
562 Schollée et al., 2015), but discovering TPs in environmental samples is still challenging, as they
563 are generated from many possible reactions and automated identification workflows are still
564 missing. In most cases, a time-consuming manual inspection is required followed by the
565 acquisition of reference standards. The latter step used to be one of the main limitations
566 because standards are in many cases unavailable for TPs.

567 TPs occurring in the environment can be formed from biotic or abiotic processes. Biotic
568 processes include the activity of microbial flora in natural or engineered environmental
569 compartments, like soils, surface water or wastewater, or human or animal metabolism.
570 Abiotic TPs are formed in the aquatic environment by hydrolysis and photolysis, as well as in
571 water-treatment processes such as oxidation by chlorination, chloramination, ozonation and
572 other advanced oxidation processes used for disinfection and removal of chemicals (Bletsou et
573 al., 2015; Fenner et al., 2013; Vughs et al., 2018).

574 Simulating the transformation processes in laboratory experiments under controlled
575 conditions is a useful approach for identification of TPs (Boix et al., 2016b, 2013; Helbling et al.,
576 2010). Batch experiments can be performed under biotic or abiotic conditions at realistic or at
577 high concentrations of the compounds. During such experiments, spiked and blank samples
578 are run in parallel, together with sterilized blank samples as well as ultrapure water for
579 correcting abiotic processes (Wick et al., 2011).

580 Even under laboratory-controlled conditions, the identification of TPs is a time-
581 consuming process as commonly many products are generated; therefore, prioritization of
582 relevant TPs is recommended. This can be performed using time trends (the TP is observed to

583 form, or form and then transform further), abundance (the most intense peaks are identified),
584 prediction (transformation processes are predicted using *in silico* methods) or using observed
585 toxic effects. The latter assumes that if increased toxicity is observed, toxic TPs are likely to be
586 formed (Escher and Fenner, 2011) and it is worth to invest time and effort to identify them
587 (see above section on EDA).
588 Once the laboratory experiments are completed and the main TPs identified, the next
589 step is analysing real-world environmental samples to test their possible presence in the
590 samples (Bijlsma et al., 2013; Boix et al., 2016a, 2014; Duester et al., 2017; Kolkman et al.,
591 2015; Vughs et al., 2018). LC-HRMS(/MS) is the most common technique for investigation of
592 TPs as these are generally more polar than parent compounds. In addition, HRMS(/MS) allows
593 the application of different workflows for efficient identification: target analysis for already
594 known TPs with standards available; suspect screening for potential TPs reported in literature
595 or predicted by *in silico* models; and non-target analysis for discovering unknown, non-
596 reported nor previously identified TPs.
597 The formation of TPs by bacteria degradation can be predicted using different *in silico*
598 tools, such as the Eawag-Pathway prediction system (enviPath, formerly UM-PPS) (Wicker et
599 al., 2015) or MINE (Jeffryes et al., 2015), whereas other comprehensive knowledge-based
600 software programmes, like Meteor Nexus-Lhasa, predict the metabolic fate of chemicals,
601 among other processes. It is, however, noteworthy that the latter tools are often not freeware.
602 Obviously, these predictors have limitations yet they have also shown its value in different
603 fields of research. More applications can be expected for environmental toxicology in the near
604 future (Miller et al., 2018).
605 After prediction, suspect screening of expected exact masses of TPs is conducted in
606 HRMS data, usually comparing versus a control sample. The plausibility of RT, isotopic pattern
607 and ionization mode can be used to reduce the candidate peaks, as well as MS/MS fragment
608 peaks if available. Another interesting possibility to investigate the presence of TPs in waters is
609 a directed non-target analysis, which implies the search of unknown compounds within a
610 limited chemical space. This approach relies on the assumption that many TPs maintain
611 similarity in their chemical structure with the parent compound, and therefore present several
612 common fragment ions (Hollender et al., 2017; Ibáñez et al., 2017; Zonja et al., 2015). Thus,
613 the investigation of TPs for a given compound is not a truly non-target analysis, because the
614 searching is limited to those compounds that share a given chemical structure or fragment.
615 Searching for common fragments is a powerful strategy, able to detect and tentatively identify
616 TPs/metabolites in *the* samples, although it is time-consuming and requires a notable
617 knowledge of mass fragmentation rules. This approach benefits when all-ion-fragmentation

(AIF) acquisitions (also known as MS^E, all ion or broad-band CID) are performed during HRMS screening (Castillo et al., 2016; Gómez Ramos et al., 2019; Hu et al., 2017; Kinyua et al., 2015; Telving et al., 2016). This allows to obtain simultaneous information on intact molecules (low collision energy, LE) as well as their fragments (high collision energy, HE) without precursor ion selection. After a detailed study on mass fragmentation, it is possible the tentative identification of the TP.

The common fragments strategy can be extended to the metabolites/TPs identified in the samples, which means that some TPs can be discovered in an iterative process because they share fragments, not with the parent molecule but with other TPs previously identified in the samples (Boix et al., 2016a). Interesting extensions to this approach in metabolomics includes the application of text-mining to interpreting fragmentation data (van der Hooft et al., 2016) as well as molecular networking (Wang et al., 2016).

Unfortunately, the information available on TPs in databases is still very limited and the success rate in the identification is low in non-target screening. Scientists performing such studies should ensure that their data can be reused by making this accessible (Schymanski and Williams, 2017). Additional techniques, as NMR, are often critical for an unambiguous identification of TPs where positional isomers are likely to occur, but it is rare that sufficient amount of analyte can be isolated for NMR measurement in environmental samples. Unfortunately, reference standards for TPs are not always available; therefore, identification of TPs in water samples mostly relies on (accurate) mass data interpretation and communicating the confidence of the identification is critical (Schymanski et al., 2014a).

6. Early warning systems

Monitoring long-term trends and changes in water quality is the first step towards a deeper understanding of water resources. Beyond event monitoring, establishing baseline water quality has become increasingly important for protecting source water as it is affected by urbanization, effluents from industry and agricultural activities. Continuous online monitoring is a key initiative and it can lead to smart water management and informed decision making by providing early warnings about changes in water quality.

Early Warming Systems (EWS) are characterized as being early in time to take measures (Early) against water quality exceeding defined standards (Warning) with a well-defined system (System). They can provide accurate and clear information, necessary to facilitate adequate decision-making, and have been used in a wide range of applications (Towhata and Uchimura, 2013), such as cyanobacterial blooms (Shi et al., 2013), water levels (Kuantama and

652 Saraswati, 2015), specific chemical compounds (Imen et al., 2015) and emerging contaminants
653 (Alygizakis et al., 2018).
654 The real time monitoring can be based on), physical (temperature, redox potential,
655 conductivity, turbidity, and spectroscopic techniques, such as fluorescence, HPLC-UV, LC-MS),
656 chemical (pH, ammonium, nitrate, chloride, fluoride, phosphate, oxygen) and biological
657 parameters (measuring live responses in Daphnia, fish, mussels and algae to water quality)
658 (Carstea et al., 2016). Chemical and biological monitoring are both valuable approaches for
659 water quality monitoring, but in most cases of an alarm, chemical analysis with identification
660 techniques (e.g., HRMS) is necessary for tracking the cause of the alarm and elucidating the
661 source of the pollution (de Hoogh et al., 2006; Hollender et al., 2017; van Leerdam et al.,
662 2014).
663 EWS present advantages, such as the continuous availability of the on-line information,
664 the combined information of the different systems and the low costs for running the system in
665 many cases. However, some drawbacks limit their application, as for example often relative
666 high detection limits compared to specific analysis in a laboratory. Improvements are required
667 for an unambiguous interpretation of data, and standardization is needed to increase the
668 comparability of results. Minimizing false positive and false negative responses and valid
669 quality assurance according to protocols also need to be improved in the near future. The
670 identification of specific (organic) compounds responsible of pollution events is surely the
671 most complex issue at present. The implementation of analytical measurements based on
672 HRMS for wide-scope screening and reliable identification of the compounds is among the
673 most urgent needs in the application of EWS and has already been showcased in the Rhine
674 River (Hollender et al., 2017) and for emerging contaminants in NormaNEWS (Alygizakis et al.,
675 2018).
676 EWS should be able to detect and identify signals of concern due to the presence of
677 chemicals. To this aim, several methodologies have been reported and the strengths and
678 challenges of different prioritization strategies for emerging pollutants in Europe have been
679 discussed (Brack, 2015; Dulio et al., 2013; Dulio and Slobodnik, 2015; Faust and Backhaus,
680 2015; Heiss and Küster, 2015). As an illustrative example, a prioritization approach based on
681 occurrence data and PNEC (derived from experimental data, QSAR or read-across predictions),
682 has been recently developed classifying chemicals into 6 categories depending on the
683 information available (Dulio and Slobodnik, 2015). These categories define the need for action,
684 including: 1) priority regular monitoring, 2) watch list monitoring, 3) extension of the
685 (eco)toxicological data set, 4) improvement of analytical methods, 5) extension of both
686 monitoring and (eco)toxicological data, and 6) compounds classified as low priority for regular

687 monitoring due to estimated low risks (Brack et al., 2017). The approach starts from a list of
688 compounds identified by experts as frequently discussed emerging substances. Monitoring
689 data of known hazardous compounds in water using multi-residue methods is the main source
690 of exposure information, and thus new and/or unknown hazardous substances that are out of
691 the scope of the analytical methods and monitoring programs cannot be traced. However,
692 most recent scientific data are included and risk is predicted despite data gaps to bring
693 potential emerging chemical risks to the attention of regulators. Using this approach several
694 compounds identified have been included into the Watch list to obtain more widespread
695 monitoring information for improved risk assessment.

696 Another example comes from the Dutch National Institute of Public Health and
697 Environment (RIVM) that developed a general methodology to identify, prioritize and suggest
698 follow-up regulatory measures for new and/or emerging risk chemicals (NERCs) for protection
699 of three vulnerable groups (workers, consumers and the environment), and to support
700 strategic and policy decision-making. The general strategy is based on several steps, involving
701 internet search systems, scientific literature, monitoring studies, and a multidisciplinary group
702 of experts that perform data evaluation (for more details, see (Bakker et al., 2014)). The first
703 crucial step is to pick-up early signals on possible NERCs for each vulnerable group, followed by
704 collecting relevant information on the potential NERCs identified. In the case of workers and
705 consumers, data collection is focused on adverse health outcomes related to exposure from
706 various sources, 'exposure first method'. For the environment, this process is severely
707 hampered by the complexity of samples, their unknown composition, the presence of
708 numerous other compounds/contaminants and their highly fluctuating concentrations.
709 Monitoring studies are of great relevance to get information on potential NERCs, as they help
710 to identify contaminants actually occurring in the environment that may be of concern (ter
711 Laak et al., 2015). Unfortunately, monitoring data are commonly limited and focused on well-
712 known and/or priority contaminants, and thus many potential hazardous compounds remain
713 ignored due to difficulties/limitations of the analytical methods. Therefore, it is rather difficult
714 to relate observed effects to a specific chemical or combination of chemicals. EDA is a
715 promising, but still challenging method, to deal with this complexity and improved non-target
716 screening approaches are likely to assist greatly in the next years (Hollender et al., 2017). It is
717 also likely that "big data" sciences may revolutionize the way we deal with non-target data in
718 the next decades (Aksenov et al., 2017).

719 Using the general strategy proposed by RIVM, NERCs have been identified for the three
720 vulnerable groups, including the recommendation of follow-up steps to reduce or eliminate
721 the risks. The necessity to have more monitoring data available has been recognized to get a

722 better picture of occurrence of NERCs in the environment (Bakker et al., 2014). Also, more
723 hazard information is needed, especially on chronic toxicity. Extensive lists with estimated
724 values(e.g. Norman network, 2018a) are a good start, yet more work is needed to incorporate
725 these in environmental investigations.

726

727 **7. The protection of drinking water: a priority issue**

728 Providing high quality drinking water is an exigency of the society at present, and a
729 priority issue for exposure science (some examples are EU funded research projects, such as
730 EU project PROMOTE, and current initiatives by the German UBA who attempt to include
731 Mobility (of organic contaminants) as a criterion in REACH legislation). Producing safe drinking
732 water starts with knowledge about source quality and on potential contamination related to
733 activities within the catchment area that may affect water quality constantly or during a
734 calamity (e.g. industrial activities, agricultural activities, infrastructure and transport activities,
735 presence of residential areas and the activities within these areas, historical contamination).
736 Furthermore, the removal rates and robustness of the treatment process are essential for
737 knowing whether suitable drinking water can be produced from a certain source, and whether
738 the system is resilient against future changes of water quality and calamities.

739 Determine the chemical water quality of sources, the quality of the produced water
740 and the performance and robustness of treatment systems are key issues. The Drinking Water
741 Directive (Council Directive 98/83/EC) concerns the quality of water intended for human
742 consumption with the objective to protect human health from adverse effects of any
743 contamination. On February 2018, the European Commission adopted a proposal for a revised
744 Directive to improve the quality of drinking water and provide greater access and information
745 to citizens. In the Annex of this proposal, quality standards for chemicals are listed
746 (http://www.europarl.europa.eu/RegData/etudes/BRIE/2018/625179/EPRS_BRI(2018)625179
747 _EN.pdf). The fast detection of relevant changes in (source) water quality is of great
748 importance to take timely measures, when necessary. The analytical tools range from fast
749 generic biological and chemical sensors and automated chemical analysis for fast detection of
750 (large) changes in water quality to very sensitive chemical analysis of a wide array of
751 compounds, as well as bioassays to assess (adverse) effects of substances (Altenburger et al.,
752 2015; Bäuerlein and Kolkman, 2016; Storey et al., 2011). Regular monitoring of sources and
753 produced drinking water is mostly done with target analysis of priority/relevant contaminants
754 (e.g. pesticides is one of the groups of highest concern). However, it is questionable whether
755 this is sufficient for appropriate quality control with the seemingly endless numbers of

substances that remain unmeasured or unidentified. Biological and chemical non-target screening approaches have been applied to evaluate technical processes e.g. chlorination, ozonation or UV-peroxide during water treatment, as it offers the possibility of assessing the effectiveness without knowing the identity of the substances that are eliminated or newly formed during a particular process (ter Laak et al., 2012). Even if identification is not achieved, the non-target analysis is still a valuable tool as it allows comparing different samples (Bader et al., 2016; Müller et al., 2011; Nürenberg et al., 2015).

The identities and concentrations of chemical contaminants in source waters determine the type of treatment required for their removal. In particular, persistent compounds that are also mobile (PMOCs), as a result of their high aqueous solubility, can constitute a threat to the quality of our water resources (Reemtsma et al., 2016). Highly polar or ionic substances can pass through WWTPs as well as natural barriers (river banks, sand dunes) and thus become present in source waters. Treatment processes applied in drinking water production may not be able to completely remove such substances, and some processes may even result in the generation of new, even more recalcitrant polar compounds. Examples are TPs generated in e.g. disinfection (chlorination, ozonation, UV-peroxide) treatment, some of which have been shown to be particularly hazardous (Kolkman et al., 2015; Richardson et al., 2007; Richardson and Kimura, 2016; Schmidt and Brauch, 2008). The control of such processes requires sophisticated LC-HRMS methodologies to identify the possible products generated.

The lack of appropriate analytical methodologies is one of the major gaps in knowledge on occurrence of highly polar PMOCs in water samples (Reemtsma et al., 2016). This is so because their polarity range - characterized by negative values of log D - makes them hardly amenable to either GC or reversed-phase LC separation. Possible solutions may be found in hydrophilic interaction liquid chromatography (HILIC) (Zahn et al., 2016), mixed-mode LC (Montes et al., 2017; Ordoñez et al., 2012), combining HILIC and reversed phase LC (Bieber et al., 2017), ion-pairing LC or supercritical fluid chromatography (SFC).

Protection of drinking water requires often advanced methods of treatment for removal of emerging contaminants. While advanced oxidation methods have been shown to efficiently remove traces of non polar organic compounds, they may not sufficiently protect against the persistent mobile organics. Further refinement of such methods is underway and includes combinations of ozonation and/or UV-peroxide treatment with granular active carbon filtration (Bourgin et al., 2017). Even such combinations may not necessarily suffice, as demonstrated by the presence of polar compounds in drinking water (see text above). Membrane processes, such as nanofiltration and reverse osmosis (Farré et al., 2011; Fujioka et

al., 2012; Hajibabania et al., 2011; Verliefde et al., 2009) can remove polar and ionogenic compounds more efficiently than advanced oxidation processes, but still require more testing and understanding to guarantee their efficacy towards these compounds.

8. Wastewater: a valuable source of information on lifestyle and exposure to chemicals

Wastewater can provide anonymised but comprehensive and objective information on community-wide health status and lifestyle in real time, as urban water (sewerage system and receiving aqueous environment) pools anonymous urine, wastewater and runoff samples from thousands of households that are served by individual WWTPs. The monitoring of sewage for chemicals used as indicators of the collective status of human health (stress/disease) or any other facet relevant to determine trends in community-wide health is the basis of wastewater-based epidemiology (WBE), which is being used to monitor community-wide use of lifestyle substances such as illicit drugs, new psychoactive substances (NPS), alcohol, tobacco, doping substances and counterfeit medicines. WBE enables the retrieval of epidemiological information from wastewater via analysis of specific human (metabolic) excretion products (called biomarkers). This approach is currently used to report on world-wide illicit drug use trends e.g. (Ort et al., 2014; Thomas et al., 2012; Tscharke et al., 2016) and feeds into the Europe-wide evidence based EWS managed by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, accessed 11.7.18 ; SCORE, accessed 11.7.18).

Human excretion products of external or internal bodily origin resulting from intentional or unintentional exposure to foreign 'xenobiotic' agents and internal processes (e.g. metabolism of xenobiotics, xenobiotic triggered DNA damage leading to excretion of characteristic metabolites, proteins and DNA biomarkers) are pooled by the sewerage system. Analysis of appropriate biomarkers in wastewater provides valuable evidence of the quantity and type of xenobiotic substances to which a population is exposed by e.g., deliberate administration of illicit drugs, or accidental chemicals exposure to food, environmental toxicants or infectious agents (Daughton, 2018; Kasprzyk-Hordern et al., 2014). More information can be obtained for guiding investigation needed for preventing, avoiding, controlling or reducing human exposure risks, as well as for maintaining or promoting health.

The analysis of wastewater opens new perspectives within exposure science thanks to the vast amount of information contained in this type of samples. This is because wastewater analysis can provide information about the presence of stressors in the studied system as well as community-wide biological effects (e.g. prevalence of certain diseases). To this aim, the identification and quantification of appropriate urinary biomarkers of exposure (metabolic

residues of stressors) and effects (e.g. biomarkers of inflammation or oxidative stress) is required. Human biomarkers of exposure are typically present at very low concentrations in a very complex matrix, such as wastewater. LC-MS/MS QqQ is the technique most commonly used, although LC-HRMS is increasingly being used in this field too (Hernández et al., 2018). The concentrations of biomarkers can be used to back-calculate their daily mass loads in wastewater and to estimate daily exposure after taking into consideration knowledge (if exists) on human disposition, including metabolism (Castiglioni et al., 2013; Thomas et al., 2012).

Analysis of wastewater can be applied to assessment of spatial and temporal trends in (1) lifestyle and substance use (e.g. illicit drugs, alcohol, tobacco or NPS); (2) health status (e.g. stress) and (3) exposure to food and environmental toxicants (e.g. pesticides (Gracia-Lor et al., 2018; Roussis et al., 2016), chemicals in personal care products (antimicrobials and UV filters) (Lopardo et al, 2017, 2018), phosphorus flame retardants (Been et al., 2017), and phthalate plasticizers (Gonzalez-Mariño et al, 2017))

An interesting analytical approach is the use of chiral chromatography, which allows for understanding of origins of biomarkers in wastewater (i.e. differentiation between consumption/direct exposure and other disposal routes, e.g. direct disposal of unused drug (Castrignanò et al., 2018; Emke et al., 2014; Kasprzyk-Hordern and Baker, 2012; Petrie et al., 2016; Vazquez-Roig et al., 2014). Sensors have also been developed for cheaper and faster quantification of biomarkers (such as cocaine and prostate specific antigen (PSA)) (Yang et al., 2016, 2015a, 2015b). Tracking of infectious disease and linking exposure to air pollutants with respiratory diseases has been proposed with the ultimate goal of a comprehensive public health assessment, since urban water can be considered as a 'diagnostic medium for the health status of a city' (Daughton, 2018; Thomas and Reid, 2011; Yang et al., 2015a).

9. Regulatory issues

The regulation of chemicals on the market ensures consumer and environmental safety, yet the information required in the regulatory processes often remains confidential to some extent to protect commercial/trade secrets. Furthermore, many of these chemicals are not listed in public compound databases often used for screening. With an estimated 140,000 chemicals regulated under REACH, including confidential information, market use (tonnage, intended use) and hazard classifications for a subset of these (approx. 15-30,000 substances), the information held by regulatory authorities could provide valuable assistance for non-target and suspect screening. However, the majority of these are industrial chemicals and some level of curation is needed to apply this information for screening purposes. Strengthening the

collaboration between regulatory authorities and environmental laboratories would lead to mutual benefits – an example workflow of how to protect confidentiality yet yield vital information for screening of emerging chemical risks is given in **Figure 3**. Regulatory bodies could provide for instance accurate mass data instead of confidential substance structures as well as exposure indexes instead of confidential consumption or application data to laboratories for suspect screening purposes. In case of potential environmental or human risk, reported findings could result in additional confirmatory and regulatory actions. Beyond exchanging information with local regulatory authorities, for instance in the context of granting permits, there is also an increasing need to exchange information internationally, as the increasing use of imported products may also result in adverse human and environmental impacts. Initiatives such as the NORMAN Suspect Exchange (Norman network, 2018a) and the chemical lists on the CompTox Chemistry Dashboard (Williams et al., 2017) are important steps to improve the exchange of information. Both resources now contain chemical lists with exposure estimates. The ExpoCast list (Wambaugh et al., 2014) contains estimated data on 7968 chemicals, also available from the batch search to download. The KEMI Market List on the NORMAN Suspect Exchange contains information and associated exposure indexes and hazard scores on 30,748 chemicals (version provided 3 July 2017; further details about these scores provided on the Suspect Exchange). The Chemicals and Products Database contains reported and predicted information on >75,000 chemicals contained in >15,000 consumer products (Dionisio et al., 2018) and is also available through the CompTox Chemistry Dashboard.

Widening/improving suspect lists with the inputs from regulatory bodies is extremely beneficial for screening purposes, and the tasks of analytical laboratories would be notably facilitated, resulting in a more efficient screening, providing more realistic data on the presence of contaminants of concern in monitoring programs (Gago-Ferrero et al., 2018; Schulze et al., 2018). At the same time, a close collaboration would make easier the updating of regulation based on occurrence on harmful compounds in the environment. As an example, an exchange of information on PMOCs would be beneficial, as these contaminants have the greatest chances of appearing in drinking water, because they are mobile enough in the aquatic environment to enter drinking water sources and persistent enough to survive treatment processes. This identification and ranking procedure for PMOCs can be part of a strategy to better identify contaminants that pose a threat to drinking water sources (Arp et al., 2017).

However, exact mass or suspect screening, especially using large lists of compounds, is not sufficient. All “hits” detected in such a manner must be confirmed using additional

analytical information to avoid false positives. RT and fragmentation information can be used to provide additional evidence for a formula or exact mass hit and library spectra or reference standards should be used (as described further above) for additional confirmation. Progressive efforts are underway to integrate suspect lists containing exposure data into *in silico* fragmentation methods such as MetFrag (Ruttkies et al., 2016) to facilitate the connection between research and regulation. Efforts are also underway to improve the assessment of materials of Unknown and Variable composition, Complex reaction products and Biological substances (UVCBs), which make up a significant percentage of chemical substances in regulatory lists (Schymanski and Williams, 2017; Williams et al., 2017). For instance, 16,923 of 67,951 entries (25 %) in the April 2018 Toxic Substances Control Act (TSCA) are UVCBs.

Non-targeted analytical methods are suited to discover potential emerging chemical risks in the environment. With improved, rapid communication and increasing regulatory acceptance of screening methods, this has great potential to assist in the monitoring of this type of compounds

Insert Figure 3

Chemicals identified as substances of very high concern (SVHC) in accordance with the REACH Regulation are added to the so-called Candidate List, and then become subject to authorization. To date, all chemicals included in the Candidate List that are classified as either persistent, bioaccumulative and toxic (PBT), or very persistent and very bioaccumulative, are in principle considered to be hazardous to the environment. However, really polar, mobile chemicals have not been identified as SVHC. Thus, neither in the protection of surface water and groundwater nor in REACH regulation PMOCs have been considered specifically, yet. Although REACH does not specifically address PMOCs they can be covered under article 57 (f) by identifying them as substances of equivalent concern. Thus, there is a strong need to establish criteria for identifying PMOCs in order to prevent that this becomes a regulatory gap. Currently, the lack of analytical methods, monitoring, and modeling data hampers an evaluation of the magnitude of this gap (Reemtsma et al., 2016).

Despite limitations in the regulation, many countries, water authorities and waterworks are taking advantage of the improved analytical capabilities and are increasing their efforts to cover a broad range of emerging chemical risks in their monitoring following the precautionary principle and due to public concern. Accordingly, most regulatory laboratories already have GC-MS and/or GC-MS/MS, as well as LC-MS/MS, at their disposal, and many have acquired HRMS instruments to broaden their analytical capabilities further.

This trend will most likely continue and result overall in better surveillance of water resources. Improved data processing techniques and acceptance will support these efforts further. The field is currently developing very rapidly and there is much reason to be positive for the future of non-target screening methods in regulatory contexts (Hollender et al., 2017).

10. Trends and perspectives

To conclude the information presented in this article, firstly several key issues are emphasized, then upcoming trends and perspectives are anticipated for the next few years in relation to the role of analytical chemistry in the field of exposure science.

- Early warning systems show great promise as both a pro-active and retrospective method to enable the timely capture of insufficiently characterized chemical threats in waters. To prevent potential risks from unregulated aspects of chemicals, emerging chemical risks must be traced and identified at the earliest possible stage (Bakker et al., 2014; Fahrenkamp-Uppenbrink, 2018). The lack of data on occurrence of many chemicals and their transformation products in the environment is a limitation at present. To fill this gap, the complementary use of gas and liquid chromatography hyphenated with high resolution mass spectrometry appears as one of the most powerful approaches for wide-scope screening. Environmental analytical chemistry will surely be a priority research area in exposure science in the next years.
- Working with large databases of compounds (e.g. in suspect screening) requires careful prioritization and confirmation efforts to focus on the most relevant compounds. Prioritization should be given to those chemicals where high exposure or potential risk to human and environmental health is expected, and relevant occurrence or risk data should be included where possible.
- Metabolites/TPs of organic contaminants are commonly present in waters at concentrations sometimes exceeding those of the parent chemicals, and therefore should be also considered as major environmental contaminants, e.g. those compounds that may remain biologically active. Further research is needed to identify and quantify these compounds in the aquatic environment, and to establish their potential hazards and eco-toxicological effects. Linking contaminant levels (exposure) obtained with mass spectrometry tools with biological responses (hazard) obtained with rapidly developing bioassay tools provides a promise for better and faster identification of those chemicals that represent a real threat to the environment and public health.

- The lack of multi-residue/ multi-class analytical methods for highly polar, persistent and mobile organic compounds implies gaps in terms of analysis, and consequently in monitoring data, water treatment measures and in regulation. New methods are expected in the new few years for the determination of these compounds, e.g. making use of chromatographic separations based on HILIC, Mix-Mode, ion-pairing or SFC.
- Wastewater analysis has allowed exposure science to gain a powerful tool to verify public and environmental health trends in near real time. Future developments are expected in this area aimed to identify (bio)markers of exposure in wastewater. Development of novel real-time, low cost and easy to operate sensors will surely be a relevant issue in the near future.
- The increasing awareness of potential risks of organic contaminants for aquatic ecosystems and human health fosters the scientific and public discussion and political action for further reduction of the input of these compounds to the aquatic environment. The information given by modern analytical chemistry will help in making choices on the best removal process of compounds from the environment, because it is possible to monitor the efficiency removal of the process applied and, at the same time, the possible formation of transformation/degradation products in the environment.
- Non-target analysis now makes possible the monitoring of both known and unknown chemicals in waters in near real time and trends of these chemicals over time. It allows comparing different samples and monitoring of unknown masses of interest. In this way, episodes of high contamination can be detected even if the unknowns remain unidentified. Especially for the evaluation of technical processes (i.e. ozonation during water treatment), non-target analysis offers the possibility of assessing the effectiveness without knowing the identity of the substances which are eliminated or newly formed during a particular process.
- The most recent data reported in the literature reveal that screening by LC-HRMS now leads to results similar to those from the regular target monitoring using specific (LC-MS/MS) analytical methods. Still, some challenges have to be faced in the coming years, such as (i) developing a further optimized quality assurance strategy, (ii) optimization of the LC, prediction of retention times (Aalizadeh et al., 2016; Bade et al., 2015a; McEachran et al., 2018; Miller et al., 2013; Stanstrup et al., 2015), and prediction of CCS in Ion Mobility MS (Bijlsma et al., 2017; Mollerup et al., 2018; Zhou et al., 2016) (iii) storage and exchange of measurement data e.g. (Wang et al., 2016) and

(iv) the identification of unknown compounds. The outlook is to incorporate non-target LC-HRMS(/MS) screening into regulatory monitoring in the near future and embedding this in a regulatory framework. As a result, a more complete overview of the occurrence of organic compounds in the water cycle will be generated and more realistic data will be available for appropriate risk assessment.

- Further strengthening and embedding of analytical chemistry within the field of exposure science will enhance the identification and prioritization of potential threats to health and the environment. The existing first steps outlined above with the NORMAN Suspect Exchange and the CompTox Chemistry Dashboard could be extended by setting up a European programme generating, assessing, exchanging, and communicating experimental and model-based exposure data in support of the European strategy for exposure science with a roadmap 2020-2025-2030 ("The European branch of the International Society of Exposure Science (ISES-Europe). Such activities will also be applicable on a global scale. Also on a global scale, and particularly in developing countries, UN Environment is investing since more than 10 years already in capacity building for the analysis of persistent organic contaminants (Van Leeuwen et al., 2013)
- New hazards are becoming hot topics in exposure science not related to specific chemical families but to new classes of contaminants like nanoparticles or microplastics (Pico et al., 2017, 2018; Wagner and Lambert, 2018). Nano-based technology has made enormous progress over the last decade with applications in cosmetic, pharmaceutical and medical fields using engineered nanoparticles consisting of carbon-based (eg. Fullerene) and inorganic (eg. TiO_2) forms, partly with functionalized surfaces (Bundschuh et al., 2018). The environmental concern on microplastics (i.e. fragments smaller than 1 mm) is related to their slow degradability and capability as carriers to concentrate and transport synthetic organic pollutants. Primary sources are related to cleaning and cosmetic products, while secondary sources arise as fibres coming from washing clothes, both entering aquatic system through household sewage discharge (Jiang, 2018). These have a whole new set of analytical challenges associated with them that have not been covered in this article
- A new trend is directed towards the study of the exposome, *i.e.* the totality of environmental exposures from conception onwards, where two broad complementary interpretations can be considered. One, called "top-down", is mainly interested in identifying new causes of disease based on *omics* technologies (internal exposome) (Turner et al., 2018). This approach utilizes methods such as metabolomics to generate

new hypotheses on disease causes. The second, called “bottom-up”, starts with a set of exposures or environmental compartments to determine the pathways by which such exposures lead to disease. Although the present article deals with the external exposome, focused on the aquatic environment, one should not forget that a comprehensive exposome concept also involves the internal exposome, in order to integrate the totality of environmental exposures. Analysis of the exposome (so-called exposomics) will require powerful analytical techniques, such as HRMS coupled to both GC and LC, combined with robust statistical tools and quick and trusty annotation applications, as discussed here.

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