


POLICY BRIEF

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High-resolution mass spectrometry to complement monitoring and track emerging chemicals and pollution trends in European water resources

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Abstract

Currently, chemical monitoring based on priority substances fails to consider the majority of known environmental micropollutants not to mention the unexpected and unknown chemicals that may contribute to the toxic risk of complex mixtures present in the environment. Complementing component- and effect-based monitoring with wide-scope target, suspect, and non-target screening (NTS) based on high-resolution mass spectrometry (HRMS) data is recommended to support environmental impact and risk assessment. This will allow for detection of newly emerging compounds and transformation products, retrospective monitoring efforts, and the identification of possible drivers of toxicity by correlation with effects or modelling of expected effects for future and abatement scenarios. HRMS is becoming increasingly available in many laboratories. Thus, the time is right to establish and harmonize screening methods, train staff, and record HRMS data for samples from regular monitoring events and surveys. This will strongly enhance the value of chemical monitoring data for evaluating complex chemical pollution problems, at limited additional costs. Collaboration and data exchange on a European-to-global scale is essential to maximize the benefit of chemical screening. Freely accessible data platforms, inter-laboratory trials, and the involvement of international partners and networks are recommended.

Challenge

Chemical monitoring according to the European Water Framework Directive (WFD) [1] currently addresses 45 priority substances (PS) [2] to establish the chemical status together with different sets of nationally defined River Basin Specific Pollutants (RBSP). Approximately 300 RBSPs are considered (in total) across the different EU Member States. However, this selection only reflects a very small fraction of all chemicals that may occur in European water bodies [3]. Recently, complementing PS and RBSP component-based monitoring with the application of effect-based methods (EBM) was suggested, to

assess the likelihood that chemical contamination causes harm to human health or aquatic ecosystems, as well as to develop measures to reduce chemical pollution impacts [4]. This EBM approach will help to identify, detect, and quantify groups of chemicals affecting toxicological endpoints of concern and identify hot spots of toxic risks. However, neither WFD component nor effect-based monitoring and assessment in their current forms are able to detect, identify, and quantify individual chemicals of potential concern beyond PS and RBSPs, i.e., 99.8% of the chemicals in commerce, and their mixtures. Thus, newly emerging chemicals, unexpected spills and chemicals with increasing concentrations remain unrecognized until toxicity thresholds are exceeded and an identification of the drivers of the measured effects for example using effect-directed analysis (EDA) [5] is triggered. Early warning of the emergence of new chemical threats

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would help to initiate efficient abatement even before EBMs indicate toxicity. At the same time, source identification is often the key for targeted abatement measures [6], but may be challenging without any information on the nature of the newly emerging chemicals in the water body of concern. Thus, the current status-related monitoring must be complemented with wide-scope target, suspect, and non-target screening (NTS) (Fig. 1), combined with component- and effect-based methods to protect against and assess the presence and risks of complex mixtures. This is the challenge that needs to be overcome on the way towards a more holistic and solution-oriented protection, monitoring, and assessment [7].

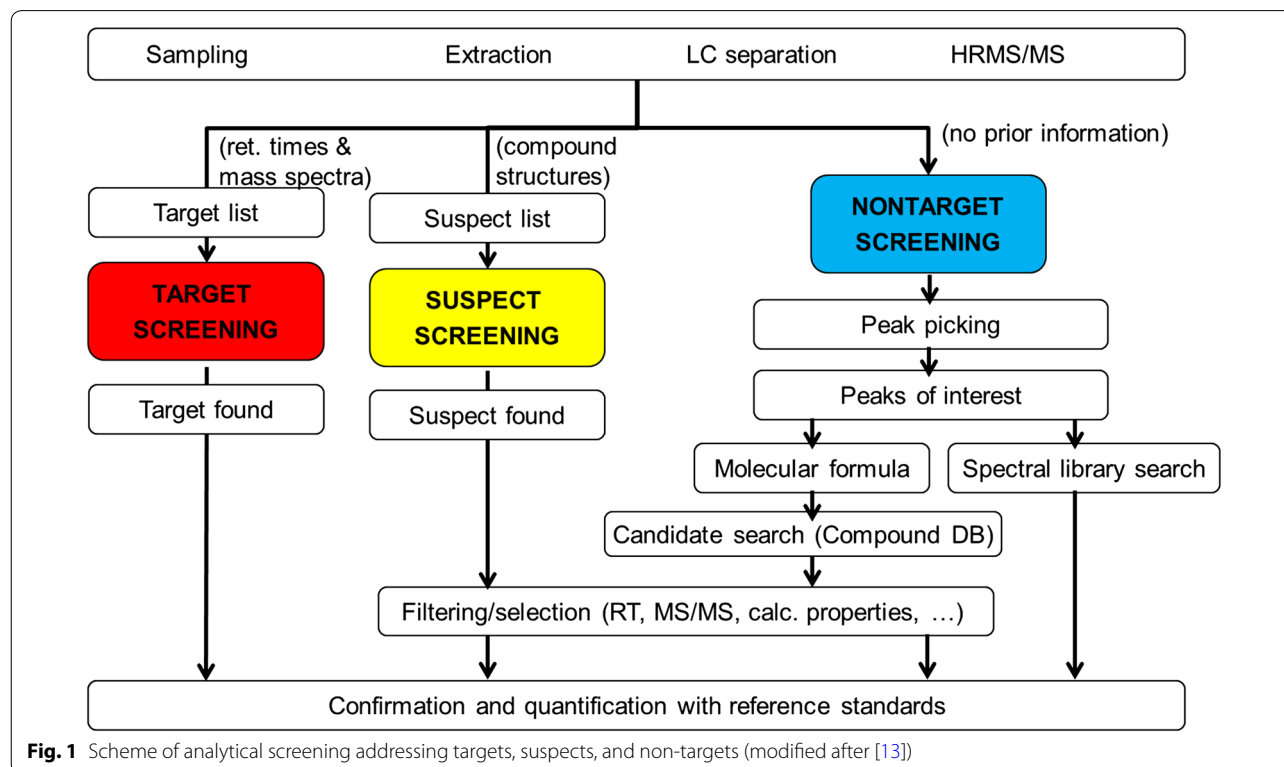
Powerful LC-HRMS- and GC-HRMS-based screening methods are increasingly available [8–12]. Thus, this paper wants to encourage monitoring practitioners, water managers, and policy makers to consider these new techniques to achieve a more holistic water quality assessment and to enhance awareness on the multifold potential to make abatement and management of water pollution more efficient.

Recommendations

- Apply analytical screening wherever possible, to comprehensively assess chemical pollution beyond the PS and the RBSP. Non-target screening (NTS) with

state-of-the-art gas- and liquid-chromatography high resolution mass spectrometry (GC-HRMS and LC-HRMS) is able to provide an increasingly comprehensive picture of the presence of dissolved chemicals in a water body strongly supported by rapidly developing automated data analysis workflows. This provides management-relevant information even if only a minority of the signals can be annotated with compound names. Management-relevant information from NTS can be gained in different ways:

- Screen NTS data for hundreds to thousands of known compounds of possible concern using state-of-the-art computational workflows. This will greatly extend the list of chemicals monitored and potentially considered in future risk and impact assessments. Combining target screening with toxicity data [14] can be used to estimate the likelihood of impacts on the water quality status applying toxic units (TU) [15] or the multi-substance potentially affected fraction of aquatic organisms (msPAF) [14, 16].
- Use NTS data to establish source-related contamination fingerprints [7]. Fingerprints may be defined as combinations of NTS signals or compounds that are characteristic for specific domestic, industrial or agricultural activities. Identifying



- them in surface waters will help understanding complex contamination patterns in surface waters not only as mixtures of individual compounds but as an overlay of source-related fingerprints with background signals and site-specific individual components. This will help to estimate, prioritize, and abate contributions of pollution sources.
- *Screen NTS data for newly emerging signals*, signals with changing trends over space or time, which may indicate emerging chemical hazards even if the identity of chemicals involved is initially unknown [17]. This can be used to trigger efforts on compound and source identification and source-related abatement measures.
 - *Screen NTS data for ubiquitously occurring peaks* that might be of Europe-scale concern, as well as for rare and site-specific peaks that help to identify specific local sources of contamination for abatement measures [18]. Chemicals containing heteroatoms and halogens, often indicating anthropogenic and possibly toxic compounds, can be identified as well [8, 12, 19, 20].
 - *Use NTS for the identification of transformation products* for example in wastewater treatment plant effluents if applied together with knowledge on biotransformation reactions and multivariate statistics [21–23].
 - *Correlate NTS data with effect-based monitoring data* or ecological information to identify potential drivers of toxic impacts [24].
- *Harness this progress in chemical analysis and integrate NTS into ongoing WFD chemical monitoring activities.* Monitoring of many PS and RBSPs at concentrations below the Environmental Quality Standards (EQS) in many cases already applies modern LC-HRMS techniques. These techniques are becoming increasingly available in laboratories of water suppliers, monitoring stations and in commercial labs. Thus, complementing current analyses methods with NTS requires limited additional analytical efforts, but provides great opportunities to protect against, monitor, and manage so far unknown or unexpected contamination that affect the ecological status of surface waters or drinking water production.
 - *Participate in international networks* that are advancing NTS and transferring this to policy, such as NORMAN (Network of reference laboratories, research centres and related organisations for monitoring of emerging environmental substances, <https://www.norman-network.net>), and benefit from collaborative trials that have been performed [25, 26].
 - *Store NTS data in repositories for retrospective analysis and support open science for identifying emerging chemicals* (See also [27]). Freely available community database resources with high quality data are essential for data exploration via rapid retrospective screening for the temporal and spatial occurrence of newly identified compounds [28, 29]. Community support with curation of chemical structures and relevant information for suspect prioritization including compound properties, toxicity data, use information, production tonnages, and previous detections is encouraged [30]. NTS repositories will help to understand long-term trends of contamination even for compounds that are not currently monitored, so many parties can benefit from the rapidly improving analytical technology as well as from globally increasing data exchange.
- ### Requirements
- The technology for GC- and LC-HRMS based NTS is fit for purpose [17] and continuously advancing. Automated workflows for data evaluation are opening up this technology for routine monitoring. Front runners in official monitoring in many European Member States already perform NTS of European surface waters [17]. The large-scale implementation requires a paradigm change with the:
- Awareness that chemical pollution is much more than a chemical and ecological status of a water body based on PS and various sets of RBSPs and the understanding that NTS of the entire mixture complemented with component and/or effect-based methods is essential for early warning of new contaminants, recognizing undesired trends in pollution, providing data for future retrospective assessment and for triggering cost-efficient management measures;
 - Upgrade of existing laboratories with HRMS technology and the training of the staff in NTS to enable monitoring groups in all EU Member States to address complex chemical mixtures analytically. Learn from monitoring stations that are already routinely applying NTS for example at the River Rhine [17].
 - Willingness of free data exchange and international collaboration. The establishment and/or continuing support of free data exchange platforms will strongly enhance the success rate of identification of compounds in the environment. This data exchange should involve scientists and regulators but also industry.

- Preparedness to further advance NTS and to develop criteria and procedures to evaluate quality criteria concerning accuracy, precision, sensitivity, and reproducibility to enhance acceptance and to maximize the benefit from application for assessment and management [31].

Achievements

Using NTS for wide-scope target screening

While traditional target analysis often addressed only a limited number of contaminants, NTS now allows an “all-in-one” measurement and data can be directly used for target screening of hundreds to thousands of chemicals in monitoring studies [32, 33]. Examples are the screening for about 270 and 400 target chemicals in order to evaluate the impact of non-treated and treated wastewater effluents on the micropollutant burden in water in the River Danube [34, 35] and in small streams in Switzerland [36], respectively. In these studies, linking target screening with effect-based monitoring [4] was shown to help assess toxic risks, identify drivers of toxicity, quantify their contribution to mixture risks, and indicate the risk that is not explained by the limited selection of current target chemicals. In a study on wastewater treatment plant (WWTP) effluents, target screening helped to unravel seasonal dynamics in organic pollutant mixtures and related toxic risks [37].

Development and assessment of automated methods for small molecule identification

Software-based automated data processing methods play a critical role for the successful identification of compounds from NTS data. In general, NTS workflows start from detection of peaks by the peak picking software. To maximize the quality and number of detected peaks the performance of one of the widely used data processing software packages MZmine 2 was assessed for LC-HRMS data [14] and validated on both spiked and real surface water samples. This optimization workflow for MZmine 2 can be applied to data from other LC-HRMS instruments.

In compound identification, *in silico* MS/MS fragmentation prediction approaches are most widely applied to assign a compound structure to an unknown peak. The evaluation of the Critical Assessment of Small Molecule Identification (CASMI) 2016 contest [38] showed a substantial improvement in (semi-)automated fragmentation methods for small molecule identification. The inclusion of metadata information (e.g., commercial relevance of compounds) further improves the identification success for “real life” annotations of environmental contaminants [39].

In another study, a data set of 78 diverse known micro-pollutants analyzed by LC-HRMS was used to assess two different MS/MS fragmentation and two retention prediction approaches. To combine scores from these different candidate selection tools, consensus score values with optimal weights were calculated to show the contribution of each approach and whether the combination could improve candidate selection [40, 41].

Automated small molecule identification approaches require reporting standards that reflect the confidence of the identification based on NTS data. The “Level system” proposed in [42] has been used in SOLUTIONS and NORMAN efforts for communicating NTS results [25].

NTS in routine monitoring—the River Rhine case study

The international Rhine monitoring station has showcased the use of NTS with automated workflows in routine monitoring [17]. This involves the automated screening for 320 target compounds for long-term trend analysis, suspect screening of 1500 compounds to identify peak events and emission patterns, and NTS to detect accidental spills of previously undetected compounds. Daily trend analysis revealed peak signal intensities triggering compound identification efforts. In 2014, ten major spill events of previously undetected compounds were recorded, representing a chemical load of more than 25 tons in the River Rhine.

Use of NTS to identify site-specific pollution

While the focus of chemical monitoring in Europe is on chemicals that are relevant on a European or basin scale, risks and impacts on water quality and ecosystems are quite often due to site-specific chemicals including many unexpected or unknown chemicals, which are typically overlooked or, in some cases, discovered via effect-based monitoring and identified by effect-directed analysis [24, 43]. Thus, an NTS-based approach has been developed and tested in case studies, which applies a rarity score based on detection frequency and ratios of maximum to median peak intensity on a set of sites of concern to identify water bodies with extensive occurrence of site-specific peaks [18]. Focusing identification efforts on these peaks allowed for the establishment of major sources of pollution that should be addressed by targeted abatement [6].

Integration of NTS with multivariate statistics to prioritize unknown transformation products

During wastewater treatment, about 50% of parent micro-pollutants are (bio)transformed but not completely mineralized [44]. As a result, transformation products (TPs) are of major concern in environmental monitoring. NTS and parent/TP similarity has been used

to identify TPs formed in wastewater treatment [22]. This approach combines principle component analysis (PCA) with difference analysis from known biotransformation pathways to prioritize NTS data and identify pairs of parent compounds and TPs. PCA and hierarchical clustering was also applied to prioritize TPs formed during ozonation of wastewater [21].

Exploring the potential of a global emerging contaminant early warning network

Alygizakis [28] introduced a pilot study for a global emerging contaminant early warning network, led by NORMAN, and supported by SOLUTIONS. Eight reference laboratories used archived NTS data from a range of samples for subsequent retrospective screening of a list of new and emerging contaminants contributed by members (https://comptox.epa.gov/dashboard/chemical_lists/normanews and <https://zenodo.org/record/2623816>). This revealed the widespread occurrence of drug transformation products (e.g., gabapentin-lactam, metoprolol acid, and 10-hydroxy carbamazepine), several surfactants (e.g., polyethylene glycols), as well as industrial chemicals such as 3-nitrobenzenesulfonate and bisphenol S.

This Policy Brief highlights the opportunities of HRMS screening for a holistic monitoring and assessment of chemical pollution with limited additional efforts, accentuates the benefit of recording, compilation and exchange of NTS data for retrospective analysis to understand trends of pollution, even for compounds which are not in the focus today, and highlights the need for establishing open science, international collaboration, and data exchange to maximize the benefit for environmental assessment and protection.

Abbreviations

CASMI: critical assessment of small molecule identification; EBM: effect-based methods; EDA: effect-directed analysis; EQS: environmental quality standard; GC: gas chromatography; HRMS: high-resolution mass spectrometry; LC: liquid chromatography; NORMAN: network of reference laboratories, research centres and related organisations for monitoring of emerging substances; NTS: non-target screening; PCA: principle component analysis; PS: priority substances; RBSP: river basin-specific pollutants; TP: transformation product.

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Authors' contributions

WB conceptualised and drafted the manuscript. JH, MLdA, CM, TS, ES, JS, and MK elaborated the manuscript and contributed specific aspects. All authors read and approved the final manuscript.

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Competing interests

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