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Review

New methods for identification of disinfection byproducts of toxicological relevance: Progress and future directions

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ABSTRACT

Disinfection byproducts (DBPs) represent a ubiquitous source of chemical exposure in disinfected water. While over 700 DBPs have been identified, the drivers of toxicity remain poorly understood. Additionally, ever evolving water treatment practices have led to a continually growing list of DBPs. Advancement of analytical technologies have enabled the identification of new classes of DBPs and the quantification of these chemically diverse sets of DBPs. Here we summarize advances in new workflows for DBP analysis, including sample preparation, chromatographic separation with mass spectrometry (MS) detection, and data processing. To aid in the selection of techniques for future studies, we discuss necessary considerations for each step in the strategy. This review focuses on how each step of a workflow can be optimized to capture diverse classes of DBPs within a single method. Additionally, we highlight new MS-based approaches that can be powerful for identifying novel DBPs of toxicological relevance. We discuss current challenges and provide perspectives on future research directions with respect to studying new DBPs of toxicological relevance. As analytical technologies continue to advance, new strategies will be increasingly used to analyze complex DBPs produced in different treatment processes with the aim to identify potential drivers of toxicity.

Introduction

Since the early 1900s, the development of routine drinking water disinfection processes has largely eliminated the threat of waterborne diseases in the developed world (CDC, 2012). The routine application of these processes stands as one of the greatest public health achievements to date. However, chemical disinfectants used to kill pathogens can react with natural or anthropogenic organics present in source water to form disinfection byproducts (DBPs) (Bellar et al., 1974). DBPs present an issue for water treatment because of potential health concerns. Epidemiological studies consistently identify potential, albeit weak, associations between chronic exposure to chlorinated drinking water and an increased risk of developing bladder cancer, as well as other adverse health effects (Bull, 2012; Hrudey, 2009; ; Hrudey and Fawell, 2015; Säve-Söderbergh et al., 2020). These findings led to the development

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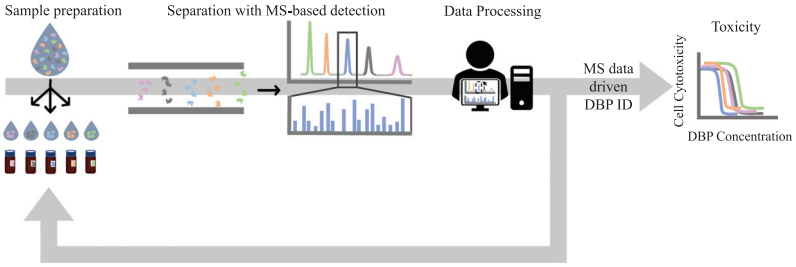

Fig. 1 – MS data driven identification of DBPs of potential toxicological relevance.

of regulatory limits for several DBPs observed at relatively high concentrations (e.g., trihalomethanes and haloacetic acids) as a proxy for reducing DBP exposure. DBPs formed unintentionally during the water treatment process are a chronic source of chemical exposure in disinfected drinking water. However, the context of potential chronic risk becomes more complicated when comparing DBP exposure to waterborne pathogens that present a significant and acute risk to public health (Hrudey et al., 2006; Hrudey, 2009; Hrudey and Fawell, 2015). DBPs remain a relevant public health issue due to their prevalence in disinfected water coupled with population wide exposure through drinking water. The discovery of previously unknown DBPs through emerging advanced analytical techniques is critical to understand the total DBP exposure load, but toxicological evidence is necessary to support the identification and occurrence of a novel compound as an emerging DBP of toxicological relevance (Hrudey and Fawell, 2015; Li and Mitch, 2018).

Since the initial discovery of DBPs, research continues to evolve with a major focus on the identification and quantification of novel DBPs in attempts to identify toxicity drivers responsible for the observed adverse health effects (Li and Mitch, 2018). Although over 700 DBPs have been identified (Richardson and Kimura, 2020), most organic halogen products resulting from chlorination remain unidentified. Further, new disinfection strategies and drinking water sources have led to an ever-increasing number of potential toxicity drivers (Dong et al., 2017; Krasner, 2009; Prasse et al., 2015). For instance, different treatment paths lead to different formation potentials for carbon, nitrogen, and iodo-DBPs (Hou et al., 2012; How et al., 2017; Zhang et al., 2017). One of the many challenges is a lack of comprehensive analytical methods for both regulated and emerging DBPs, which consist of a huge number of compounds with vastly different physiochemical properties. Additionally, DBP researchers are characterizing DBP precursors and their formation mechanisms to better predict the DBPs that can be produced from specific source waters. For example, nitrosamines can form from amine containing organics, and this knowledge can better help monitor nitrosamine DBPs in water (Krasner et al., 2013). Monitoring the removal and temporal variation of precursors can assist water treatment facilities to reduce the concentrations of more toxic DBPs (Qiu et al., 2020). Further, the concept of dechlorination has been suggested to lower the toxicity of disinfected water. While the mechanisms of these dechlorination agents are beginning to be proposed, many questions still surround the subsequent DBP transformation products (Pan et al., 2019). Therefore, there is a need to quantify diverse classes of compounds (precursors, DBPs, and transformed DBPs) as we better understand our water systems. As analytical technologies advance, DBP researchers can adopt new strategies to identify novel DBPs and discover toxicity drivers.

In recent years, DBP research has advanced by taking advantage of new mass spectrometry (MS) technologies for nontargeted analysis. Particularly, modern high-resolution MS (HRMS) instruments, such as time-of-flight (TOF) and orbitrap, provide both accurate molecular weight and structural information, enabling increasingly comprehensive identification and analysis of both known and novel DBPs. Additionally, the combination of enhanced ionization and separation techniques make the analysis of a large variety of chemical classes of DBPs possible. Gas chromatography (GC) has been the main separation technique used for discovery and analysis of nonpolar, volatile, or semi volatile DBPs (Richardson and Kimura, 2020). DBP analysis has increasingly used electrospray ionization (ESI) interfaced with liquid chromatography (LC) and MS to detect a variety of new large, polar, and/or thermally labile DBPs that cannot be detected by GC-MS (Hua et al., 2020; Jiang et al., 2020). The combination of LC with HRMS has been a popular method for both targeted and nontarget analysis since the late 2000s (Richardson, 2009). New GC-MS and HPLC-ESI-MS technologies have given researchers the ability to develop methods capable of identifying many chemically different DBPs in a single analysis. Many excellent reviews have been written on current advancements in the field of DBPs (Li and Mitch, 2018; Richardson and Kimura, 2020; Richardson and Postigo, 2014). Herein, we will discuss an overview of typical MS based workflows in DBP literature along with their limitations, and possible future directions for MS based analysis of DBPs.

1. Overview of workflows for DBP analysis

Fig. 1 illustrates a general workflow of applying MS technologies for comprehensive analysis of DBPs. Three key steps are highlighted: sample preparation, separation with MS-based detection, and data processing. This process is inherently cyclical as each phase influences decisions in the next cycle of sample processing. For nontargeted analysis, when putative identifications have been made, it is necessary to validate their identity with standards (Schymanski et al., 2014). Further, it is important to evaluate if the novel DBP is of toxicological relevance. For comparative purposes, Chinese hamster ovary (CHO) cell based cyto- and genotoxicity assays make up the largest existing database for known DBPs (Lau et al., 2020; Wagner and Plewa, 2017). Lastly, surveys to determine the prevalence of these emerging DBPs are needed to map exposure and identify areas of significance. We will discuss the importance of each step and how it can inform future decisions in the workflow for water DBP research. Later sections detail how these techniques are being used in literature to investigate a wide variety of DBPs.

Sample preparation is a key component when considering DBPs existing at trace concentrations with diverse physiochemical properties. A typical sample preparation procedure involves filtration followed by extraction. Filtering water is necessary to remove any large particles present, especially in source water as particulates may cause blockages during the extraction or separation step, slowing analysis. Next, ex-

Table 1 – Selected examples of common SPE sorbents used for extraction of DBPs.

SPE Sorbent	Description	Precursors and DBPs	Reference
XAD resins	Hydrophobic interactions	Soluble organics, TOX and organic matter	Chen et al., 2011; Daignault et al., 1988; Kimura et al., 2017; Suffet, 1980
C18: Bond Elut C18, Sep-Pak C18	Reverse phase retention, strongly hydrophobic	Nontargeted peptide derived DBPs, iodinated and brominated DBPs, DBP precursors	Wang et al., 2016b; Zhang and Yang, 2018; Tang et al., 2016
C18: Hypersil GOLD aQ column	Short column	Online SPE for nitrosamine precursors	Farre, et al., 2016
Anion Exchange: Oasis MAX	Reverse-phase/strong anion exchange, acidic compounds	N-chloro-acetamides, iodoacetic acids, iodo-aromatic DBPs	Yu and Reckhow, 2017; Hu et al., 2018
Cation Exchange: Oasis MCX	Reverse-phase/strong cation exchange, basic compounds	Nontargeted amino compounds	Liu et al., 2019
Oasis HLB	Water-wettable polymer, reverse phase retention	Haloacetamides, Halobenzoquinones, N-halo dipeptides	Chu et al., 2016; Cuthbertson et al., 2020; Huang et al., 2018; Huang et al., 2017; Tang et al., 2016
LiChrolut EN	Polymer, reverse phase interactions	nitrosamines	Charrois et al., 2004; Qian et al., 2015

traction is necessary to reduce interferences and, commonly, to enrich trace levels of compounds to detectable levels for MS analysis. DBPs in treated water typically occur at concentrations of ng/L to μg/L. Many different extraction methods are commonly used due to the varying polarity, hydrophobicity, and size of DBPs.

Once sample preparation is complete, the extracted organic compounds require separation for sensitive and robust detection in MS. LC and GC are the most common separation techniques for DBP analysis. However, other separation methods used for environmental analysis, such as supercritical fluid chromatography (SFC), could be applied to DBPs. Differences in the physicochemical properties of DBP class(es) being investigated require specific separation techniques. Additionally, for MS detection, different ionization sources and mass analyzers are best suited for use with particular separation techniques and analytes of interest. In particular, the choice of ionization source has a significant influence on the class(es) of DBPs that can be analyzed.

Finally, data analysis is necessary to manage the large volume of data generated from these workflows. Sophisticated computational tools are required to facilitate fast and accurate peak selection, database searching, and identification, as well as quantification and statistical analysis. Ideally, these processes would be automatic and capable of batch processing. Currently, notable focus has gone into the development of software, code writing, and assembling libraries. MS based DBP research can be categorized into two main types of analysis: nontargeted and targeted. Nontargeted analysis does not require prior knowledge about the compounds to be analyzed and makes use of highly selective and sensitive HRMS detection. Exact masses, retention time, fragmentation patterns, and isotopic distributions are used to identify novel DBPs. Comparatively, targeted analysis focuses on detection or quantification of a selected class, or group of compounds, present in a sample. Targeted analysis requires information on the exact mass and fragments of each analyte, typically acquired from prior nontargeted analysis. Nontargeted and targeted analysis are frequently used in conjunction due to their inherent complimentary nature.

We describe a general workflow for a MS data driven identification (DDI) (Fig. 1) to uncover as many DBPs as possible, because data garnered in each step can influence the next. Each subsequent analysis can expand the understanding of known DBPs and help to identify novel DBPs. After identity confirmation, the novel DBP should be tested for its potential toxicity. Therefore, the cyclical process of DDI of novel DBPs, as shown in Fig. 1, is completed by comparing the toxicity of novel DBPs to known DBPs. By doing so, researchers can continue to untangle the relationship between the observed toxicity of disinfected water with the countless number of unknown and uncharacterized DBPs (Li and Mitch, 2018).

2. Workflow steps

2.1. *Sample preparation and extractions*

The variability in the physiochemical properties of DBPs, and their similarity to matrix constituents, present a significant challenge for development of a single method that can extract and enrich all known and unknown DBPs from water matrixes. Therefore, current DBP researchers have tended towards the discovery and quantitation of as many analytes as possible, through simple, fast, and generic methods.

A common sample pre-treatment is a single liquid liquid extraction (LLE), often with methyl tert-butyl ether (MtBE) (Cuthbertson et al., 2020b; Liberatore et al., 2017; Zhang et al., 2019b). However, a single extraction may not effectively extract organic analytes. Current literature shows that multiple extractions can improve the efficiency of total organic halogen (TOX) extraction from water samples (Han et al., 2017). Because nonpolar solvents are commonly used for LLE, many known and regulated DBPs are suited for extraction with LLE due to their lack of polarity (U.S. EPA, 1995), especially for volatile and semi volatile analytes. However, many new DBPs being identified are of relatively high hydrophilicity and thus, are not well captured with typical LLE procedures because of the nonpolar solvents used for extraction.

Another popular sample preparation technique, solid phase extraction (SPE) is commonly used for many environmental analyses (Liska, 2000) due to its high enriching efficiency, reproducibility, and wide array of sorbent materials. The choice of sorbent material allows SPE to be well suited for extraction of specific classes of compounds depending on physiochemical properties, such as hydrophobicity or hydrophilicity, and ionic characteristics (cations or anions). The major benefit of SPE is the ability to develop or modify sorbents to extract a specific class of DBPs or capture diverse classes of DBPs, as shown in Table 1. Typically, in DBP research

general SPE sorbents such as hydrophilic-lipophilic balance (HLB) are often used. Activated carbon and XAD resins are also popular for extraction of TOX and organic matter from water samples for GC analysis (Chen et al., 2011; Daignault et al., 1988; Kimura et al., 2017; Suffet, 1980). However, a challenging aspect of developing sorbents that can capture a wide variety of compounds is that they typically have low selectivity (Stalter et al., 2016; Wang et al., 2016a), resulting in potential interference from unintentionally extracted matrix molecules. Additional challenges for SPE processes include time and labor-intensive procedures as well as the significant production of single use plastic waste. One strategy to overcome these problems is the development and improvement of on-line SPE extractions. In on-line SPE, a sample is pumped through a short column for extraction followed by elution into an LC system to achieve the desired separation. These systems typically use a separate pump for each column and a quick-change valve between them. Many commonly used SPE sorbents have been made into on-line columns and are often reusable. By combining extraction and analysis of a sample into one process these methods reduce sample preparation time and lead to higher sample throughput, while increasing reproducibility (Cuthbertson et al., 2020; Farre et al., 2016). For example, Farre et al. used on-line SPE with ultra pressure LC (UPLC)-MS to quantify 15 NDMA precursors in less than 10 minutes (Farre et al., 2016). Another variation of SPE is solid phase microextraction (SPME) that combines sampling, extraction, and preconcentration into a single step. This technique has been shown to reduce the cost, use of solvents, and matrix effects while being simple and amenable to automation (Mijangos et al., 2018). DBP research commonly uses headspace SPME, where a polymer coated fiber is exposed to the headspace of a vial containing a water sample. This method has been well used for extraction of THMs, HAAs, HANs, and HNMs (Luo et al., 2014; Maia et al., 2014; Sa et al., 2012).

Comprehensive analysis of DBPs requires the capture of as many compounds as possible during the extraction step. Multi-SPE approaches have been adapted to encompass the diverse chemical nature of organics in water. For example, Tang et al. used three types of SPE cartridges, Oasis HLB, Bond Elut C18, and Bond Elut ENV, in parallel to extract compounds with a broader polarity range from water samples (Tang et al., 2016). Multilayer mixed-mode SPE with different polarity sorbents has also been reported. For example, graphitized carbon black, WCX, and WAX sorbent phases were combined into a single SPE cartridge for the extraction of halomethane sulfonic acids (Zahn et al., 2016; Zahn et al., 2019). This multilayer mixed-mode approach was applied to 26 polar environmental contaminants and found to have a much better recovery than HLB cartridges (i.e., 65% of compounds retained vs 30% with HLB) (Koke et al., 2018).

Extraction of some compounds, particularly very polar ones, can pose a significant challenge. To detect these compounds, several groups have used methods for the enrichment of water samples without any extraction. For example, Koke et al. used a sample preparation method consisting solely of evaporation of a water sample in a vacuum centrifuge. This method had a low enrichment factor and significant matrix effects, however they were able to detect analytes that were not extracted with typical SPE methods (Koke et al., 2018). Similarly, other work has shown that conventional extraction techniques, such as LLE, underestimates the toxicity of DBP mixtures compared to freeze-drying or rotoevaporation (Han and Zhang, 2018). Therefore, evaporative or freeze-drying enrichment methods may be necessary to detect larger portions of the unknown TOX in drinking water that are lost with extraction methods. However, these enrichment techniques rely more heavily on the separation to sufficiently distinguish analytes from each other and the matrix.

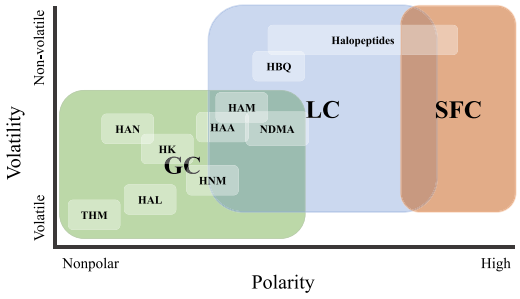

Fig. 2 – Diversity of volatility and polarity of different DBP classes and their general compatability with common separation strategies coupled to mass spectrometry detection.
THM: trihalomethanes (example reference et al. 2049)
HAN: haloacetonitrile
HAL: haloacetaldehydes
HK: haloketons
HNM: halonitromethanes
HAA: haloacetic acids
HAM: haloacetamides
NDMA: nitrosodimethylamine
HBQ: halobenzoquinone
Halopeptides.

Innovative approaches to sample preparation have been developed to decrease the complexity of the final data set. For example, in conjunction with HRMS detection, stable isotopic labeling has been applied to detect amino compounds (Liu et al., 2019). Creative sample preparation methods can also lead to detection of typically indistinguishable compounds. For example, ascorbic acid pre-treatment enables the distinction of isomeric N-chloro- from C-chloropeptides in water samples (Jiang et al., 2017). These types of sample preparation methods enhance researchers' ability to identify new DBPs by simplifying interpretation of the collected MS data and allow for detection of emerging DBPs.

2.2. *Separation*

Recently, an excellent review was published by Yang et al. highlighting current methods of DBP analysis in drinking water (Yang et al., 2019a). Many different approaches have been used to separate DBPs for identification and quantification. As seen in Fig. 2, volatility and polarity are two properties with great influence on the selection of separation techniques. This section provides an overview of common strategies and identifies how each can encompass a wide variety of DBPs within a single method for both targeted and nontargeted analysis. Additionally, it draws attention to analytical techniques that have been successfully applied to environmental samples and could be used to characterize unknown TOX.

2.2.1. *Gas chromatography*

GC coupled with mass spectrometry (GC-MS) is the most popular technique for chemical analysis of nonpolar, volatile, or semi volatile, DBPs. While GC only has a single mode of separation (i.e., partition chromatography); different functional groups can be bound to the solid phase coating the capillary column to provide a range of selectivity options. The biggest differentiating factor between GC-MS techniques is the MS ionization source. Electron ionization (EI) is advantageous for producing predicable fragmentation patterns that can be used

for structural identification of a compound. Like a unique fingerprint, a matching fragmentation pattern can be searched for in databases that contain real and predicted EI spectra for individual compounds. Therefore, GC-MS with EI methods are commonly employed analytical methods for determination of regulated and emerging DBPs (Cuthbertson et al., 2020b). Unfortunately, due to the robust fragmentation of EI, the molecular ion is often absent in mass spectra. To obtain the molecular ion, softer ionization techniques, such as chemical ionization (CI), can be used to complement EI for identification of unknowns. Additionally, CI can provide higher sensitivity for targeted quantification of some analytes, such as derivatized HAAs (Jia et al., 2003). Both EI and CI work well with nonpolar, or low polarity, and volatile DBP classes like THM or HAL. Other soft ionization techniques can be used to expand the range of ionizable compounds for MS detection. Atmospheric pressure chemical ionization (APCI) provides efficient ionization as well as reduced thermal decomposition leading to increased sensitivity. APCI has been used to achieve ng/L detection limits for common nitrosamines (Charrois et al., 2004). A similar technique, atmospheric pressure photo ionization (APPI), excels at ionizing nonpolar analytes. As commercial GC-MS with APPI instruments become available, its potential applications will likely increase. Additionally, both APCI and APPI can be performed with either LC- or GC-MS. Both APCI and APPI are better suited for more polar or less volatile DBPs than those analyzed for EI and CI. For examples, classes of DBPs like HNM, HAA, or NDMA would be better suited to APCI or APPI.

One GC specific technique is two-dimensional gas chromatography (GCxGC). Two columns are connected to provide orthogonal separation, which greatly increases the resolving power, separation efficiency, and can provide more reliable quantification. GCxGC has begun to build momentum as a tool to analyze a large variety of environmental contaminants. One study applied the technique to water analysis for the discovery of DBPs, and tentatively identified over 500 compounds (Li et al., 2016). This is a promising technique that is likely to become more prominent in its application for DBP analysis.

2.2.2. *Liquid chromatography*

LC is a very popular separation technique for a variety of compounds, especially polar, high molecular weight, and/or thermally labile compounds that cannot be analyzed by GC. LC-MS DBP methods typically use reversed phase LC (RPLC) with ESI (Rubirola et al., 2019; Zhang et al., 2019a). Typical RPLC columns can include C4, C8, and C18 that are effective at separating nonpolar or lowly polar DBPs. Examples of classes well separated on these columns are haloacetic acids (HAAs) (Hu et al., 2018), haloacetamides (HAMs) (Chu et al., 2016), and nitrosodimethylamines (NDMAs) (Chen et al., 2016). Additionally, these classes of compounds work well with ESI ionization. ESI is a soft fragmentation technique that is useful for small polar molecules, but less effective at ionizing large, or more nonpolar, compounds. The United States Environmental Protection Agency's (EPA) proposed regulation on perchlorate highlighted the importance of LC-ESI-MS as it is much more specific than previous methods relying on ion chromatography (U.S. EPA, 2007). Other aforementioned ionization techniques, such as APCI, though less commonly used, can be implemented to facilitate the detection of less polar analytes. While RPLC can separate more nonpolar and hydrophobic compounds, other separation types like hydrophilic interaction liquid chromatography (HILIC), can be used for highly polar analytes. Amine, silica, and zwitterionic HILIC columns are well suited to separate DBPs like halogenated methanesulfonic acids (Zahn et al., 2016) as well as halopeptides or other amino acid containing DBPs (Tang et al., 2016) because of their increased polarity and hydrophilicity. However, while HILIC provides retention of very polar analytes, it has complex retention mechanisms and variability in retention times between runs (Backe et al., 2014; Salas et al., 2017). Therefore, unlike RPLC, it is harder to compare HILIC chromatograms between samples and perform corresponding blank subtractions.

When trying to detect a large number of compounds in a sample, separation techniques can be combined to increase the coverage of compounds in a sample (Tang et al., 2016). This is a powerful technique but decreases the throughput of samples because samples are often analyzed by two or more separate methods. Parallel coupling of different separations have been developed to separate nonpolar, polar, and very polar analytes in the same sample. One example of this concurrent separation is the use of HILIC and RPLC for quantitative metabolomics (Klavins et al., 2014). Klavens et al. simultaneously injected two aliquots of a sample using a dual column setup to increase throughput. Each sample was separated on one of the columns and the eluents were combined prior to introduction into the MS. Since different retention of compounds was achieved on each column, two peaks for each analyte were obtained at separate retention times. Most compounds were well retained on one column but unretained or retained too long on the other. The best peak for each compound was selected for quantification using scheduled MRM. This analysis combined the benefits of two different separation mechanisms with high throughput capabilities of a single method. This approach is not useful for nontargeted analysis, because there are two peaks for each compound in the sample which complicates data analysis. However, it may be useful to quantify larger and complex sets of known DBPs within a single method.

2.2.3. *Other separation techniques*

In addition to LC and GC, alternative separation techniques show promise to increase the diversity of compounds that can be resolved. SFC and its modified variant, ultraperformance convergence chromatography (UPC^2), are classic techniques with increasing popularity in recent literature. Both techniques use compressed carbon dioxide as a mobile phase, though UPC^2 adds organic cosolvents allowing for more control over analyte elution. These methods allow for the separation of analytes that are not typically retained in LC, as well as having the ability to separate small molecules from complex matrices (West, 2018). Bieber et al. showed that a single SFC separation could attain similar separation to sequential HILIC and RPLC (Bieber et al., 2017). While SFC has been used for screening of environmental samples, neither SFC or UPC^2 have gained traction for DBP research (Bieber et al., 2017). SFC could be implemented in the determination of amino acid based DBPs, as SFC was recently used to successfully separate enantiomers of underivatized amino acids (Lipka et al., 2019).

2.3. *Data analysis*

Targeted MS methods for the detection and quantification of known DBPs rely on compound specific information gathered from previous nontargeted HRMS analysis during identification and subsequent confirmation steps. Analysis of pure standards provides retention time, molecular mass, and major fragment ion information. Nontargeted MS data analysis typically includes background subtraction, library searching, manual interpretation of peaks, determination of exact mass and molecular formula, and finally confirmation of unknowns with standards. Things to consider for nontargeted data analysis include: MS scan strategies, availability of databases and computational tools, and data storage for future analysis. While targeted analysis is relatively straightforward, data analysis could be considered the most difficult step for nontargeted DBP investigations. The massive amount of data generated by nontargeted analysis requires conversion

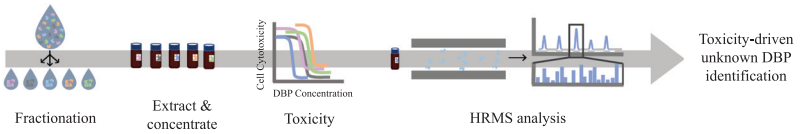

Fig.. 3 – Effects Directed Analysis (EDA) of unknown DBPs in drinking water (Recreated from Dong et al. 2020).

into a format that can be interpreted to better identify DBPs. Nontargeted techniques are becoming more prevalent in DBP research, however there are still challenges that limit its application.

One such difficulty in nontargeted analysis is quantification of analytes. A recent review published by Kruve et al. discusses five different methods for quantitative conclusions when performing nontargeted HPLC-HRMS. Five approaches, commonly found in literature, are explained in greater detail in the review. Briefly, they utilize (1) peak areas directly, or in combination, with statistical data treatment, (2) isotope dilution, (3) radiolabelling, (4) structurally similar compounds for quantitation, and (5) predicted ionization efficiencies (Kruve, 2020).

MS scanning programs such as Precursor Ion Scan (PIS), Precursor Ion Exclusion (PIE), and SWATH are useful in order to increase the quality of collected data and allow detection of trace compounds in complex matrices. PIS is used to scan for a range of precursors in a given *m/z* range that can produce a specific fragment ion (Yang et al., 2019). PIE is used to exclude selected ions so that more time can be devoted to detection of other ions. The MS instrument, in a second analysis, is able to scan for low abundance ions because the now excluded high abundance ions were scanned in the previous run (Tang et al., 2016). SWATH (sequential windowed acquisition of all theoretical fragment ion mass spectra) is one approach to data-independent acquisition. A fairly narrow scan range (20 or 25 Da) is selectively fragmented. The product ions of these collisions are then analyzed to produce a fragment ion spectrum for all precursors within that *m/z* window. The same *m/z* precursor window is fragmented over the course of the chromatographic separation (Zhu et al., 2014).

MS software is typically equipped with computational tools capable of searching through large sets of nontargeted data for peak picking, database searching, database identification, quantification, and statistical analysis. A review by Hollender et al. summarizes the data analysis for nontargeted screening and its use in environmental analysis (Hollender et al., 2017). The provided workflow and information on MS analysis, available software, and current challenges can be translated to data analysis for identification of DBPs. However, the need for advanced software to meet more demanding applications has become increasingly evident not only for the DBP field, but also for all nontargeted water analysis (Hohrenk et al., 2020; Hollender et al., 2017). The majority of unknown DBPs cannot be found in MS libraries, thus it is important to collaborate by adding entries to existing libraries to further advance nontargeted DBP research. Future work could be done by DBP researchers in writing and coding their own programs with custom libraries to streamline the data analysis process.

When collecting HRMS data it is important to prepare for the possibility of retrospective analysis of raw data as data analysis tools are constantly evolving, and databases are continuously growing. There are few studies that have reanalyzed existing data to uncover new information. However, a major benefit of this approach was demonstrated when Alygizakis et al. investigated spatial and temporal trends for concentrations of emerging global contaminants, previously omitted from aqueous environmental sample analysis (Alygizakis et al., 2018). To facilitate retrospective analysis and future collaboration through HRMS data sharing between many research groups, DBP researchers should establish a standardized format for archiving both MS and separation data. Further, standardized workflows are needed for direct comparison of stored data. The NORMAN network was created for this purpose, specifically looking at contaminants of environmental concern. This collection of research groups has agreed to use a common data format (mzML) independent from vendor software. This data is then "digitally frozen" and can be retroactively screened by exact mass, predicted retention time window, isotopic fit, and qualifier fragment ions (Alygizakis et al., 2019). The DBP community could similarly use a common data format to create their own network.

3. Future directions

Identification of new DBPs has focused on developing new sample preparation methods and analytical techniques to separate and detect larger numbers of DBPs in drinking water. Most DBPs that have been identified through conventional GC-MS techniques are low molecular weight semi volatile, or volatile, compounds. However, this does not necessarily mean that the majority of DBPs fall into this category. LC-MS methods, especially with softer ionization techniques, like ESI, have heightened possibilities for the detection of many more compounds. Further, continuously improving MS instrumentation has enabled the resolution and detection of more unique mass spectral peaks leading to enormous data sets. Together, advances in these analytical technologies have facilitated the identification, characterization and determination of novel environmental contaminants, including DBPs. However, quantification and prioritization of toxicologically relevant, emerging, known and unknown DBPs, is paramount. Researchers need to think critically about the relevance of newly discovered DBPs and how they fit into the overall chemical exposure that humans face through long-term consumption of disinfected drinking water.

Toxicity data can be used to prioritize classes of compounds to be identified with HRMS data. Recent literature has suggested that pre-screening sample fractions for toxicological relevance can focus efforts on potential toxicity drivers that may be present in complex mixtures. Effects directed analysis (EDA) is an established approach that has been proposed as a model workflow for DBP identification (Chen et al., 2018; Dong et al., 2020). EDA was used by the U.S. EPA to identify at least one DBP but has since not been commonly used by DBP researchers (Dong et al., 2020). Fig. 3 describes an EDA workflow for identification of DBPs, which differs from our DDI workflow in shown in Fig. 1. The basic principle of EDA is to first fractionate water samples based on the physiochemical properties. Next, perform toxicity analysis to prioritize the most toxicologically relevant fractions thereby simplifying subsequent analysis. The HRMS workflows can then be performed to identify toxicologically relevant DBPs in a less complex sample fraction. Because EDA puts a greater emphasis on fractionation, separation techniques can be chosen to better suit specific analyte characteristics (e.g., polarity) for each fraction. While this prioritization strategy overcomes the challenge of separating analytes with diverse physiochemi-

cal properties within one sample, EDA relies on a laboratory resource capable of high throughput toxicity tests (e.g., cytotoxicity, genotoxicity, mutagenicity, and developmental toxicity assays). Otherwise, toxicological ranking of fractions becomes an equally challenging and limiting step in EDA experimental design. Additionally, identifying specific analytes responsible for the observed toxicological potency of a fraction ultimately requires further toxicity testing. Therefore, individual research groups should determine if they are better equipped for toxicity testing or HRMS data analysis. Collaboration between chemists and toxicologists have led to significant advancements in DBP research and will be essential for EDA strategies to become commonplace. Computational toxicology prediction through quantitative structure-activity(toxicity) relationships may be able to assist with EDA-driven nontargeted HRMS discovery of new DBPs (Bull et al., 2006; Li et al., 2016) as an *in silico* assessment tool alternative to *in vitro* and *in vivo* laboratory toxicity testing.

Researchers in the DBP field are beginning to adapt omics approaches to better determine the possible health risk of DBPs. In light of the development of exposomics, which aims to quantify the total human exposure to environmental contaminants (Evlampidou et al., 2020; Vineis et al., 2017), several studies have demonstrated similar applications to quantify total DBP exposure from drinking water (Kimura et al., 2019; Plewa et al., 2017). Using GC-MS, Kimura et al. aimed to quantify the DBP exposome by analyzing 39 DBPs, thought to be key drivers of toxicity, in finished water samples (Kimura et al., 2019). We expect that methods like this, which seek to quantify a large variety of DBPs, will be increasingly used to discover spatial and temporal trends in DBPs exposure. Additionally, it is important to consider that humans are constantly being exposed to a mixture of chemicals, including DBPs. While DBP research has focused on identifying individual toxicity drivers, many questions still surround the toxicological effect of mixtures (Li and Mitch, 2018; Plewa et al., 2017) because the impact cannot be discerned when relating the toxicity of a specific drinking water sample with quantified DBP exposure (Krasner et al., 2013). One issue identified in past studies on DBP mixtures pointed out by Stalter et al., is the critical consideration of individual DBP potency (Stalter et al., 2020). Rather than preparing DBP mixtures at either equimolar or environmentally relevant concentrations for toxicity testing, they suggested preparing mixtures at concentrations relevant to their correlated toxicities. Otherwise very abundant or very toxic DBPs may dominate the mixture's observed toxicity.

DBP research can also learn from the study of metabolomics to consider the metabolic pathway of DBPs after exposure. The effects of DBPs on the human metabolome may assist with identifying the toxicological mechanism of DBPs. The PISCINA II study sought to investigate biological responses to chemical exposure from swimming in chlorinated pool water (van Veldhoven et al., 2018). van Veldhoven et al. measured the external exposure (i.e., swimming pool water) and internal exposure (i.e., exhaled breath and urine) using GC-MS and LC-MS for specific DBPs. Then nontargeted metabolomic analysis of the same samples using UPLC-MS with ESI enabled the discovery of many known metabolites that may be correlated with DBP exposure. Occupational exposure to disinfectants may be another important source of elevated DBP levels in humans. A recent study that measured biomarkers of exposure (urinary THMs) to disinfectants in an occupational setting found that nurses were exposed to almost double the levels of total THMs and brominated THM than the general population (Ioannou et al., 2017). Results from these types of metabolomic analyses are increasingly important to understand the overall effects of DBP exposure in the race to identify the drivers behind the epidemiologically observed toxicity associated with long-term consumption of disinfected water.

Interpretation of DBP data is complicated by the fact that drinking water sources and treatment systems are all unique. A well-known issue with changing water treatment practices to reduce specific (i.e., regulated) DBPs is the formation of different and potentially more toxic DBPs (Li and Mitch, 2018). Therefore, a common philosophy in selecting drinking water treatment practices is to "know your system" (Hrudey, 2012). Many water treatment operators rely on proxy information (i.e., TOX, total organic nitrogen, and total organic carbon) to make water treatment decisions. While this is often a qualitative approach, the application of the DDI workflow (Fig. 1) for comprehensive analyses of important DBP classes would add a quantitative measure for DBP formation. If comprehensive quantitative methods are developed, capable of assessing total drinking water system DBP production, similar to exposome studies, they could be used to optimize drinking water treatment. Further, this could prevent unintentional production of more toxic DBPs. Machine learning has already been applied to predicting the formation of specific DBPs (Kulkarni and Chellam, 2010), and more generally, is increasingly used to investigate all aspects of drinking water quality (Wu et al., 2014). If methods for the comprehensive quantification of DBP exposure can be achieved they can be used to monitor and identify spatial and temporal trends in DBP production at different water treatment facilities.

The field of DBP discovery has benefited from advancements in analytical technologies to overcome previous challenges. New ionization sources have enabled discovery and analysis of DBPs that were previously not ionizable. Additionally, new very polar DBPs are being discovered with new separation techniques, such as HILIC, which are capable of retaining them. These same advancements have enabled targeted analysis of broader classes of DBPs within a single method. For example, development of SPE sorbents and even multilayer SPE cartridges has allowed for more extensive extraction of DBPs. Analysis automation, like on-line SPE, is a promising direction for the field to increase throughput and reduce cost by minimizing sample preparation time, consumables, and solvents. All these improvements to analytical analysis of DBPs have allowed researchers to detect a seemingly infinite number of compounds. However, the field lacks the ability to efficiently process and prioritize the massive amounts of data that are being produced. A further challenge is that the majority of unknown DBPs cannot be found in MS libraries. Therefore, careful consideration of sample preparation, separation, and MS scanning modes can help reduce the complexity and amount of resulting data. In order to prepare for new databases in the future, it is suggested that DBP researchers prioritize data archival in a common data format. This will allow researchers to reanalyze their data as databases grow and techniques for data analysis improve. Ever changing water sources and treatment technologies coupled with continuous advancement of analytical techniques has led to a constant discovery of novel DBPs through nontargeted analysis. Additionally, these new analytical strategies have allowed for the development of comprehensive targeted analyses of drinking water DBPs. This review seeks to highlight the common features of these increasingly complex methods and provide a discussion on possible workflows. The DDI approach described in Fig. 1 illustrates the most common workflow used in DBP discovery research. Within this workflow, new techniques for sample preparation, separation, detection, and data analysis are constantly being developed to both identify and characterize unknown DBPs and quantify increasing numbers of chemically diverse DBPs. Continuously evolving methods necessitate a regular re-evaluation of currently employed DBP water analysis strategies in comparison to similar fields using cutting-edge methods. The development and incorporation of emerging techniques will continue to drive the identification

of novel DBPs and more effectively interpret and manage the massive amounts of data produced.

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Appendix A. Supplementary data

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jes.2020.06.020.

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