# Critical assessment of the Kendrick mass defect analysis as an innovative approach to process high resolution mass spectrometry data for environmental applications

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**Abstract**

The growing application of high resolution mass spectrometry (HRMS) over the last decades has dramatically improved our knowledge about the occurrence of environmental contaminants. However, most of the compounds detected remain unknown and the large volume of data generated requires specific processing approaches. Therefore, this study presents the concepts of mass defect (MD), Kendrick mass (KM) and Kendrick mass defect (KMD) to the expert and non-expert reader along with relevant examples of applications in environmental HRMS data processing. A preliminary bibliometric overview indicates that the potential benefits of KMD analysis are rather overlooked in environmental science since only a limited but growing number of papers could be retrieved from this field in web of science. In practice, a simple calculation allows transforming a mass from the IUPAC system (normalized so that the mass of $^{12}C$ is exactly 12) to its corresponding KM normalized on a specific moiety such as $CH_2$ (the mass of $CH_2$ is exactly 14). Then, plotting the KMD according to the nominal KM allows revealing groups of compounds that differ only by their number of $CH_2$ moieties. For instance, data processing using KM and KMD was proven particularly useful to characterize natural organic matter in a sample, to reveal the occurrence of polymers as well as poly/perfluorinated alkylated substances (PFASs), and to search for transformation products (TPs) of a given chemical.

# 1. Introduction

The occurrence of severe droughts, floods and other extreme weather events has increased public awareness about environmental problems over the last two decades. In particular, the anthropic pressure on water resources has become a major concern worldwide that strongly influences research activities and has caused several paradigm shifts in water management (Villarín and Merel, 2020). For instance, water scarcity in arid areas has triggered research aiming at understanding the domestic water consumption (Villarín, 2019; Villarin and Rodriguez-Galiano, 2019; Wang et al., 2021) in order to plan actions that should lower the water demand like the Water Smart Landscapes program (WSL) and the initiative "cash for grass" launched by the Southern Nevada Water Authority (Wang et al., 2021). In addition, water quality is also a major environmental and public health concern. Indeed, conventional wastewater treatment plants poorly attenuate trace organic contaminants and the discharge of treated wastewater effluents is a reason of their occurrence in receiving waters. Depending on the ability of natural as well as engineered processes to attenuate them, some of these trace organic contaminants can even be detected in drinking water (Benotti et al., 2009; Mompelat et al., 2009). Moreover, with the large development of water reuse strategies for irrigation and even for direct potable reuse (Roccaro, 2018; Salgot and Folch, 2018; Villarín and Merel, 2020), public concern regarding water quality keeps on growing and the need for a comprehensive analysis of water composition is a major challenge.

The targeted analysis of trace organic contaminants is often performed routinely using tandem mass spectrometry preceded by a chromatographic separation. This common approach allows the specific, robust and sensitive quantification of dozens or even hundreds of preselected contaminants in a single analysis. Moreover, the constant progress in analytical chemistry keeps improving the detection limits while allowing a higher throughput. For instance, modern apparatus using online solid phase extraction achieve remarkable detection

capabilities with only a few milliliters of sample (Anumol and Snyder, 2015) while several liters were necessary two decades ago (Snyder et al., 2001). In addition, the direct injection of the sample (80−100 μL) onto the analytical device might even allow the detection of contaminants in the ng/L range in wastewater effluents (Anumol et al., 2015). However, with an analytical strategy based on the targeted analysis of preselected contaminants, all the known and unknown contaminants not included in the method remain undetected. Hence, for a more comprehensive assessment of contaminants in a sample, the conventional targeted analysis should be complemented by a non-targeted analysis (NTA).

The development of NTA was made possible through the progressive spread of high resolution mass spectrometry (HRMS) over the last decades. HRMS allows the exhaustive detection of all the components in a sample as long as they satisfy both of the following conditions: the source present on the instrument can ionize them and their concentration (eventually after enrichment) is such that the corresponding signal passes the minimum signal to noise threshold. Consequently, NTA through HRMS generates a large amount of data where each compound is initially considered as an unknown chemical that has to be identified a posteriori. An unknown compound is characterized by: A) one or several accurate mass to charge ratios (m/z) that reflect the occurrence of naturally stable isotopes, B) a retention time (RT) when using a previous chromatographic separation, C) potential fragments if the analytical method allowed their acquisition, and D) a collision cross section (CCS) for state of the art instruments combining HRMS and ion mobility spectrometry (Bijlsma et al., 2019; Celma et al., 2021; Regueiro et al., 2016).

The processing of HRMS data requires specific and resource intensive approaches that usually demand a high performance computing environment for data treatment as well as human time for data evaluation and the assignation of a confidence level (Schymanski et al., 2014a) to the compounds considered relevant. A common approach, referred to as suspect

screening, consists in comparing the acquired data to MS² spectra libraries. This allows for the rapid tentative identification of contaminants previously reported and characterized by other laboratories without the need for an analytical standard. Yet, the discovery and the identification of unknown environmental contaminants and transformation products that have not been previously characterized in the literature and that are not included in MS² spectra libraries remains a major challenge. However, the application of mass defect (MD) and Kendrick mass defect (KMD) analysis in environmental sciences is a potential opportunity to tackle this challenge.

The concept of MD has been successfully applied in pharmaceutical chemistry, and particularly for the characterization of drug metabolites (Zhang et al., 2009; Zhu et al., 2011). Moreover, it has been further completed with the concept of KMD. The initial objective of the KMD analysis was to screen the acquired HRMS data in order to visualize all the compounds that formed series of homologues differing by a given number of $CH_2$ moieties (Kendrick, 1963). Nowadays, the KMD analysis is still frequently used in several research fields. For instance, it is largely applied in petroleomics for the characterization of crude oils (Hughey et al., 2001) as well as in proteomics for peptide and protein tagging (Sleno, 2012). However, the concepts of MD and KMD seem rather overlooked in environmental sciences, even though the characterization of transformation products of trace organic contaminants and the identification of homologue compounds like poly/perfluorinated alkylated substances (PFAS) are major research focus. Therefore, this study aims to assess the potential application of MD and KMD analysis as an innovative approach for HRMS data processing in environmental sciences, with a critical consideration of limitations and perspectives.

## 2. Bibliometric overview of MD and KMD

The bibliographic search was performed in order to assess the magnitude of the application of MD and KMD analysis when processing HRMS data, with a particular focus on environmental purposes. As described in previous bibliometric studies (Merel et al., 2013; Villarín and Merel, 2020), the peer-reviewed literature was assessed through all databases and the core collection of web of science, using "Mass Defect", "Kendrick Mass", "Kendrick Mass Defect" and "Kendrick Mass Analysis" as search entries for the "search by topic" algorithm.

As a result, a total of 27,144 items were retrieved. After focusing on article and review papers published in English, 24,616 items were considered. A large number of the literature corresponded to the following research areas: Physics (22%), Materials Science (20%), Chemistry (15%). Publications in research areas from the field of environmental sciences were significantly lower: Environmental Sciences Ecology (1.2%), Public Environmental Occupational Health (0.7%), and Water Resources (0.1%). This observation tends to indicate a rather limited significance of MD and KMD for HRMS data processing in environmental analytical chemistry. Overall, 446 items corresponding to environmental sciences were retrieved in web of science. However, a trend can be observed and the number of publication keeps increasing since the 1990 (Fig. 1). In addition, most of the literature refers to MD while KMD represents only 15% of the articles. This reveals the lack of awareness regarding the potential environmental applications of the KMD analysis that this paper aims to address.

## 3. The concept of mass defect

### 3.1. Definition and calculation of mass defect

In physics, it is a known fact that the mass of an atom is slightly less than the sum of the masses of its constituents (protons, neutrons, and electrons). The reason is that maintaining together the positively charged protons that form the nucleus requires energy, which results in

a mass consumption (Audi, 2006; Thurman and Ferrer, 2010) due to the mass-energy equivalence (E = mc²). Physicists define this mass converted to binding energy as mass defect.

With these considerations on binding energy and mass defect in mind, the mass of $^{12}$C is expected to be 12.098943 when summing the masses of its constituents (6 protons, 6 neutrons and 6 electrons) but 12.0000 is reported by accurate mass spectrometry. Therefore, in the early 1960s, the standard accurate masses were changed (Cameron and Wichers, 1962) from an oxygen based system (where $^{16}$O has an exact mass of even 16) to a carbon based system (where $^{12}$C has an exact mass of even 12). With this currently used carbon based system, which is referred to as the IUPAC system in the rest of the paper, the accurate mass reflects the correct mass defect while the mass of the hydrogen atom (1.0078) is consistent with the rest mass of the proton and the electron (Thurman and Ferrer, 2010).

The masses obtained from HRMS analysis are expressed in the IUPAC system based on $^{12}$C, as explained previously. However, the users of mass spectrometry have developed another definition of mass defect, referred to as MD in the rest of the paper. Indeed, for mass spectrometrists (Thurman and Ferrer, 2010), MD is the difference between the nominal mass (NM) of a compound (exact mass rounded to the closest integer) and its exact mass (M), as indicated in Eq. (1).

$$MD = NM - M \qquad \qquad \text{Eq. (1)}$$

### 3.2. Application of mass defect for environmental purposes

The concept of MD in mass spectrometry is particularly useful to achieve data reduction. Indeed, HRMS generates a large volume of data that needs to be filtered in order to discard signals that are not relevant to answer the research question of the analyst. In this context, MD is particularly used in the field of pharmaceutical development for the investigation of

metabolites (Zhang et al., 2009). This application was developed in 2003 after observing that the monoisotopic ions of the parent drug and its metabolites (phase I and phase II) typically have the same MD within a 50 mDa tolerance (Zhang et al., 2003). For instance, MD is shifted by -5 mDa for a hydroxylation, -16 mDa for a dehydrogenation, -23 mDa for demethylation, +32 mDa for glucuronitation or -43 mDa for a sulfation. However, it is important to keep in mind that such data filtration might lead to discard some heavier conjugates like glutathione, which results in a +68 mDa shift compared to the MD of the parent drug. In environmental sciences, the concept of MD is poorly used for HRMS data processing. Yet, the application of such data reduction would result particularly useful for the assessment of transformation products (TPs) resulting from the degradation of organic contaminants by engineered (i.e., ozonation, chlorination…) or natural (i.e., photodegradation, biodegradation…) processes. However, for such environmental application of MD, it is important to conduct a specific evaluation. Indeed, it is important to consider that advanced oxidation processes might lead to a stronger oxidation than phase I and phase II metabolism. In addition, rather than a simple demethylation, advanced oxidation processes could lead to the cleavage of a significant part of the parent contaminant. Therefore, the associated TPs might have a MD that differ by more than 50 mDa from that of the parent contaminant, which implies that the MD range applied for data reduction might need to be adapted. Finally, it is also important to consider that the HRMS analysis of environmental samples like wastewater effluents usually reveals the occurrence of several thousands of components. Hence, when assessing the potential TPs of a given contaminant, data reduction by MD-based filtering could be impaired because a significant number of unrelated compounds might have a similar MD.

The concept of MD is also applied in environmental science for the identification of contaminants containing specific atoms like chlorine or bromine. In fact, the mass spectra of environmental contaminants reveal several naturally occurring isotopes separated by

approximately one mass unit. Therefore, the concept of relative MD (RMD) has been introduced to quantify the difference between the masses of two isotopologs and to assess its deviation from the mass unit (Thurman and Ferrer, 2010), as shown in Fig. 2 as well as in Eq. (2-4).

$$RMD_{A+1} = M_A - M_{A+1} - 1 \qquad \qquad \text{Eq. (2)}$$

$$RMD_{A+2} = M_A - M_{A+2} - 2 \qquad \qquad \text{Eq. (3)}$$

$$RMD_{A+X} = M_A - M_{A+X} - X \qquad \qquad \text{Eq. (4)}$$

A detailed definition of RMD and its application for the identification of pesticides is provided in the original literature (Thurman and Ferrer, 2010). Briefly, the examination of RMD and particularly $RMD_{A+2}$ could improve the identification of environmental contaminants. Indeed, environmental contaminants are often a simple combination of C, H, O, and N atoms with a major contribution of C and H. Therefore, the isotopolog A+1 is usually due to the occurrence of a single $^2H$ or $^{13}C$ atom in the molecule. Similarly the isotopolog A+2 is often due to the occurrence two $^2H$ atoms, two $^{13}C$ atoms or one atom of each. Since both $^2H$ and $^{13}C$ have positive $RMD_{A+1}$ (Fig. 2), the $RMD_{A+1}$ and the $RMD_{A+2}$ of the contaminants will be positive. However, if an environmental contaminant encloses at least one Cl atom or one Br atom, its isotopolog A+2 is mostly due to the occurrence of a single $^{37}Cl$ or $^{81}Br$ atom and its $RMD_{A+2}$ will be negative. As an example, a peak observed on the chromatogram of a wastewater effluent can be examined through the associated isotope pattern (Fig. 2). The calculation of $RMD_{A+1}$ (257.0185 - 256.0151 - 1 = 0.0034) is consistent with the occurrence of a $^{13}C$ atom but the $RMD_{A+2}$ (258.0122 - 256.0151 - 2 = -0.0029) suggests the occurrence of a $^{37}Cl$ atom. Moreover, the calculated $RMD_{A+4}$ (260.0092 - 256.0151 - 4 = -0.0059) even suggests the occurrence of a second $^{37}Cl$ atom in the molecule. Therefore, when applying the formula generation ($C_{0-100}$, $H_{0-200}$, $O_{0-20}$, $N_{0-20}$, $P_{0-5}$, $S_{0-5}$, $Cl_{0-5}$), the algorithm could be forced to include

2 Cl atoms and the number of potential formulae within 5 ppm decreased from 34 to 2 possibilities ($C_5H_{10}Cl_2N_6P$ and $C_9H_7Cl_2N_5$). A search in chemspider retrieved no result for the potential formula $C_5H_{10}Cl_2N_6P$ but the formula $C_9H_7Cl_2N_5$ was tentatively associated with the pharmaceutical lamotrigine (Fig. 2).

Despite the relevance of MD and RMD, a potential lack of awareness about these concepts leaves them rather overlooked in the field of environmental sciences. Moreover, the concept of MD can be further refined in order to obtain additional valuable information from HRMS data. However, as detailed afterwards, this requires additional calculation in order to obtain the Kendrick mass defect referred to as KMD.

## 4. Going further with the concept of Kendrick mass defect

### 4.1. Definition and calculation of the Kendrick mass defect

In a sample, some compounds might form homologue series differing by a given number of repeating unit (RU). For instance, in wastewater samples collected from Switzerland, a study has reported the occurrence of several polymers differing by n number of $CH_2$ groups (Schymanski et al., 2014b). A traditional plot of the mass (M) as a function of the retention time (RT) doesn't really provide a clear evidence of such homologue series in the sample (Fig. 3A). However, when plotting the mass defect (MD) obtained from Eq. (1) as a function of the nominal mass (NM), clear series can be observed with homologue compounds forming a slanting line (Fig. 3B). Indeed, with the addition of a $CH_2$ group the NM increases by 14 amu but the MD also shows a constant shift since the mass of the RU is not an integer. Nonetheless, observing such slanting line in a sample with thousands of compounds detected might remain complex. In order to further develop the discovery of homologue compounds, converting measured data from the IUPAC system to the Kendrick system is a substantial improvement.

The Kendrick system is nothing else but a simple change of mass referential. Indeed, the mass of a compound is measured and expressed using the IUPAC system where the mass of $^{12}C$ is set exactly to 12 amu. The mass of any other element is a real number (set $\mathbb{R}$ in mathematics) whose decimal expansion includes several digits with at least one non-null. As a consequence, the mass of an environmental contaminant is also a real number with several digits (HRMS usually considers only the first four digit as significant). The Kendrick system was introduced in 1963 in order to convert masses from the IUPAC system based on $^{12}C$ = 12.0000 to a mass referential based on $CH_2$ = 14.0000 for the identification of homologue compounds differing only by their number of $CH_2$ moieties (Kendrick, 1963). The mass of every detected compound is converted to the Kendrick mass (KM) using the nominal mass ($NM_{RU}$) and the exact mass ($M_{RU}$) of the repeating unit (here RU = $CH_2$) according to Eq. (5). Then, the Kendrick mass defect is calculated using the nominal Kendrick mass (NKM) according to Eq. (6). In such Kendrick system, all the homologues have the same KMD while their NKM is shifted by a multiple of $NM_{RU}$. As a consequence, compounds forming homologue series can be easily observed since they are displayed on horizontal lines in plots showing the KMD as a function of the NKM. For instance, this is the case for the previously mentioned $CH_2$ homologues detected in wastewater (Fig. 3C).

$$KM = M * NM_{RU}/M_{RU} \qquad \text{Eq. (5)}$$

$$KMD = NKM - KM \qquad \text{Eq. (6)}$$

As an example, the analysis of a river sample might reveal the occurrence of multiple compounds, including four specific ones: compound A with mass 191.1310 Da, compound B with mass 177.1154 Da, compound C with mass 193.1103 Da and compound D with mass 209.1052 Da (Fig. 4). While a conventional suspect screening would result in the tentative

identification of compound A as DEET, an insect repellent frequently detected in water matrices (Kolpin et al., 2002) and nearly ubiquitous (Merel and Snyder, 2016) even in winter season (Merel et al., 2015), all three other compounds would remain unknown. In an attempt to identify additional compounds, applying Eq. (5) and Eq. (6) with O and $CH_2$ as RU allows KM and KMD to be derived from each individual mass measured in the IUPAC system (Fig. 4). When considering $CH_2$ as RU, DEET and compound B had a 0.0824 MD. Therefore, since NKM of both compound differed by 14 Da, compound B was tentatively identified as desmethyl-DEET, which is consistent with the photolysis of DEET reported in river water (Calza et al., 2011; Merel and Snyder, 2016). Similarly, when considering O as RU, Desmethyl-DEET as well as the compounds C and D had a -0.1717 MD while the NKM were shifted by a multiple of 16. Therefore, the compounds C and D were respectively tentatively identified as hydroxy-desmethyl-DEET and dihydroxy-desmethyl-DEET, also known transformation products resulting from the photolysis of DEET (Calza et al., 2011; Merel and Snyder, 2016).

## 4.2. Workflow for HRMS data processing using Kendrick mass defect

Environmental samples cover a wide range of matrices (i.e., water, sediment, biota, aerosols...) that can require specific preservation and preparation steps before HRMS analysis. Whether data acquisition is performed through MS scan or MS² scan with data dependent or data independent analysis, HRMS detects a large number of unknown compounds for each sample. Such data can be processed using different approaches but two common initial steps of data processing are "peak picking" and "componentization" (Celma et al., 2021). While the "peak picking" recognizes which accurate m/z can be associated with a compound from those due to background noise, the "componentization" consists in merging into a single feature all the signals that have distinct m/z but belong to the same chemical (isotopes or formation of several adducts in the ionization source). Afterwards, the features can be processed according

to several independent approaches depending on the objective of the study. Common approaches might include a suspect screening for a quick tentative identification of selected compounds using spectra libraries, an analysis of common fragments to find some transformation products of a given chemical, an examination of the isotope pattern to find chlorinated compounds, or a fingerprint analysis for a global overview of sample composition. Within this panel of existing and rather well known approaches, the KMD analysis is an emerging data processing option with a relatively simple workflow (Fig. 5) able to provide a quick visualization and a relevant reduction of HRMS data for deeper evaluation. A first step of the KMD workflow consists in selecting the repeating unit (RU) of interest for the question that the analyst aims to address. Afterwards, the mass of each feature resulting from the "peak picking" and "componentization" steps can be converted from the IUPAC system to the corresponding KM according to Eq. (5) and the KMD can be determined according to Eq. (6). Then, data can be visualized by plotting KMD as a function of NKM and data reduction can be achieved to reveal homologue series by pairing the features in order to keep only those having both the same KMD (within a selected tolerance t expressed in amu) as in Eq. (7) and a NKM differing by a multiple of $NM_{RU}$ as in Eq. (8). Finally, the remaining features shall be identified through the examination of their product ions either by comparison with an MS² spectra library or performing a structural elucidation.

$\Delta KMD = 0 \pm t$          Eq. (7)

$\Delta NKM = n * NM_{RU}$          Eq. (8)

## 4.3. Application of KMD for the characterization of organic matter

The goal of HRMS data processing using KM and KMD is mostly to reduce the amount of data to evaluate by revealing groups of chemicals of particular interest. This rather global

approach of HRMS data makes KMD analysis particularly suitable for scientists already used to global parameters like total organic carbon (TOC), total nitrogen (TN) or specific UV absorbance (SUVA) to characterize organic matter. In fact, the results of a KMD analysis provide additional information regarding functional groups, which greatly supplement the measurement of the previously mentioned bulk parameters (TOC, TN, and SUVA). For instance, several studies have used the KMD analysis to characterize organic matter in soil (Ohno et al., 2014), river water (Rakruam et al., 2021; Sanchis et al., 2020), rain water (Mead et al., 2015), drinking water (Phungsai et al., 2018) or fractions of fulvic acid from the Suwannee River (Stenson, 2008). While $CH_2$ is the most common RU considered in the literature, some studies also assessed organic matter in different samples using other RU like $CO_2$ (carboxyl group) for the KMD analysis (Chasse et al., 2015; Guigue et al., 2016; Li et al., 2018). Such analysis of organic matter might be particularly relevant since a recent study revealed that the presence of carboxyl groups was linked to the ability of the material to sequester pollutants such as Pu (DiDonato et al., 2017). In addition, for the characterization of organic matter, KMD analysis is often associated with van Krevelen plots (Guigue et al., 2016; Ohno et al., 2014; Sanchis et al., 2020) that provide further information regarding the source and maturity of organic matter by examining the molar H/C ratios with respect to the molar O/C ratios (Burnham, 2018).

## 4.4. Application of KMD for the characterization of groups of contaminants

Although the KMD analysis is mostly a HRMS data reduction strategy that provides global results, as explained for the characterization of organic matter, analysts focusing on the identification of contaminants might also find an unexpected interest in this data processing approach. Indeed, while the identification of contaminants is often performed through suspect screening that reveals specific but discrete chemicals, KMD analysis could reveal their

potentially related homologues that would otherwise remain unnoticed. For instance, selecting the appropriate RU, the KMD analysis can be used to reveal specific polymers (Table 1). Hydraulic fracturing is a source of wastewater that has been so far rather overlooked (Villarín and Merel, 2020) and some rare studies have relied on the KMD analysis to assess the occurrence of surfactants in such matrix. Using $C_2H_4O$ as RU to reveal groups of ethoxylates, a rather recent study showed the occurrence of polyethylene glycol (PEG) with formula $C_{2n}H_{4n+2}O_{n+1}$ as well as PEG-carboxylates with formula $C_{2n}H_{4n}O_{n+2}$ in flowback and produced water from hydraulic fracturing (Thurman et al., 2017). Then, in a similar matrix, an additional study reported the occurrence of PEG aldehyde with formula $C_{2n}H_{4n-2}O_n$ (Sun et al., 2019) while another article showed for the first time the occurrence of three groups of amine-containing PEGs: amino-PEG with formula $C_{2n}H_{4n+3}NO_n$, amino-PEG-carboxylate with formula $C_{2n}H_{4n+1}NO_{n+1}$, and amino-PEG-amine with formula $C_{2n+2}H_{4n+8}N_2O_n$ (Sitterley et al., 2018). Similarly, selecting $C_3H_6O$ as RU, several studies were able to report the occurrence of polypropylene glycols with formula $C_{3n}H_{6n+2}O_{n+1}$ in water resulting from hydraulic fracturing activities (Sun et al., 2019; Thurman et al., 2017) as well as in agricultural soils (Gravert et al., 2021). Finally, using multiple successive KMD analysis with multiple RU ($C_2H_4$; $C_3H_6$; $C_5H_8$; $C_4H_6$; $C_8H_8$; $C_{10}H_8O_4$; $C_2H_6OSi$; CHON) two studies reported the occurrence of microplastics and nanoplastics in the Ebro Delta (Mediterranean Sea) as well as in tap water of a major Spanish urban area by characterizing the associated polymers, which included polyethylene, polypropylene, polyisoprene, polybutadiene, polystyrene, polyamide, and polydimethylsiloxanes (Llorca et al., 2021; Vega-Herrera et al., 2022).

Nowadays, poly and perfluorinated alkylated substances (PFASs) are another group of contaminants of particular concern for the environment and public health. Besides the well-known PFOA and PFOS often measured by LC-MS/MS using a targeted approach, several other compounds might occur in a sample with a different $CF_2$ chain length. While some of

these other compounds might be available as analytical standard for their detection with the same targeted approach, some might not. In fact, with 455 new PFASs characterized in multiple matrices over the period 2009-2017 (Villarín and Merel, 2020; Xiao, 2017), most of these compounds should be detected using NTA. Then, data processing using a KMD analysis would be a suitable approach to reveal their occurrence (Table 1). For instance, several recent studies have successfully used the KMD analysis with $CH_2$ as RU, revealing novel substances such as chlorinated perfluoroalkyl carboxylic acids (Cl-PFCAs) and perfluoroalkylether carboxylic acids (PFECAs) in German and Chinese rivers (Joerss et al., 2022), or the occurrence of polyfluoroalkylsilanes in commercial antifingerprint liquid products (Zhu et al., 2019). Similarly, the same KMD approach also revealed the occurrence of 160 PFASs from 42 classes in products for land application derived from organic waste (Munoz et al., 2022), and the occurrence of 57 classes of PFASs (including 40 new ones) in aqueous film-forming foams as well as impacted groundwater (Barzen-Hanson et al., 2017). However, due to the large variety of PFASs, some recent studies considered that $CF_2$ shall not be the only RU considered (Bugsel and Zwiener, 2020; Jia et al., 2021). Indeed, while $CF_2$ as RU allowed revealing a total of 70 homologues series containing at least 3 compounds with consistent RT shift (increasing RT with increasing number of RU) in samples from contaminated soils, additional data evaluation considering $CF_2O$ and $C_2F_4O$ as RU respectively revealed 23 and 13 homologue series with a minimum of 5 compounds. Although some of these homologue series remain unidentified, such results illustrate the large number of PFASs in the environment as well as the capability of the KMD analysis to discover groups of contaminants that would otherwise remain unnoticed in a large variety of environmental matrices.

Finally, besides polymers and PFASs differing in their chain length, other groups of contaminants of particular interest are those differing by the number of hydrogen atoms substituted by chlorine or bromine. Indeed, some known contaminants like chlorinated

paraffins, PCBs (polychlorinated biphenyls) or PCDEs (polychlorinated diphenylethers) might have congeners with a different degree of substitution that remain unnoticed with current monitoring techniques based on a target approach. In addition, during drinking water disinfection by chlorine or during wastewater ozonation, one or several halogenation might occur for some molecules like cyanotoxins and other peptides (Hureiki et al., 1994; Merel et al., 2010; Merel et al., 2009). While these types of compounds are not homologue series with an increasing number of atoms, they can still be revealed through a KMD analysis considering a "simulated" RU defined as [X - H] consisting in the addition of the halogen atom X combined with a loss of H (Taguchi et al., 2010). For instance, in order to reveal the substitution of H by Cl in a molecule, KMD should be performed with [Cl - H] as RU (Table 1). Therefore, in Eq. (5) $NM_{RU}$ would be 34 (nominal monoisotopic mass of hydrogen subtracted from the nominal monoisotopic mass of chlorine) and $M_{RU}$ would be 33.96102 (exact monoisotopic mass of hydrogen subtracted from the exact monoisotopic mass of chlorine). In fact, an open solution (HaloSeeker) was developed to mine HRMS data and reveal such substitution by halogen atoms (Léon et al., 2019). This approach was successfully used to process HRMS data from an extract of Lake Ontario lake trout, revealing the occurrence of several groups of chlorinated chemicals such as chlorinated terphenyls, degradation products of the pesticide DDT (dichlorodiphenyltrichloroethane), chlorinated anthracenes/phenanthrenes, PCBs (polychlorinated biphenyls), PCDEs (polychlorinated diphenylethers) and other unidentified groups (Jobst et al., 2013). Similarly, more recent studies also used the same approach to reveal halogenated organic contaminants such as PCBs, chloroanisoles and chlorothioanisoles in surface water (Zhang et al., 2020), Polychlorinated terphenyls, Polybrominated diphenyl ethers (PBDEs) and other halogenated contaminants in dust collected from an electronics recycling facility (Ubukata et al., 2015), and chlorinated paraffins in indoor dust and cat hair (Brits et al., 2020).

**4.5. Application of KMD for the characterization of specific contaminants like TPs**

The application of KMD analysis to process HRMS data is not limited to assess the overall composition of a sample (characterization of organic matter) or the occurrence of certain groups of chemicals (polymers). Indeed, selecting the suitable RU and comparing relevant samples, the KMD approach can provide significant results for scientists interested in the identification of specific chemicals such as the transformation products (TPs) of a given chemical or group of chemicals (Table 1). For instance, the KMD analysis successfully revealed TPs of organic contaminants during the ozonation of wastewater effluent (Merel et al., 2017). Considering that the decreasing abundance of some wastewater contaminants (precursors) after ozone exposure should be associated with the increasing abundance of their transformation products (TPs), the KMD analysis using O as RU revealed the precursors and their related oxygenated species (OSs). Moreover, additional consideration on the retention time shift between a precursor and its OS also revealed whether the oxygenation was most likely an hydroxylation or the formation of an N-oxide. Then, the identity of some precursors (sulpiride, tiapride, lidocaine, tramadol, venlafaxine…) was established by suspect screening and the identity of their corresponding N-oxide was determined by structural elucidation through a detailed examination of MS² product ions. Similarly, a recent study also used a KMD analysis to characterize the formation of N-nitroso compounds (substitution of a H atom on an amine moiety by a NO group) during biological wastewater treatment (Brienza et al., 2020). In particular, using [NO - H] as the "simulated" RU, N-nitroso-ciprofloxacin and N-nitroso-hydrochlorothiazide could be observed and identified. Another example is the application of the KMD analysis to characterize the environmental fate of the anticonvulsant carbamazepine (Raeke et al., 2017). While the photodegradation of carbamazepine was shown to form 3-quinolinecarboxylic acid (3-QCA) with the chemical formula $C_{10}H_7NO_2$, a KMD analysis using

3-QCA as RU revealed that the photodegradation of carbamazepine in the presence of dissolved organic matter (DOM) would generate 160 additional TPs resulting from the covalent binding of 3-QCA with DOM.

## 5. Environmental application of the KMD analysis: value, limitations and perspectives

The processing of HRMS data using the KMD analysis remains rather insignificant in the field of environmental sciences, as described by the preliminary bibliometric overview. However, over the last years, the community of environmental analytical chemists has perceived and explored its potential. Nowadays, a growing number of studies report its successful application for purposes ranging from the global characterization of organic matter to the identification of groups of contaminants and TPs.

One of the main advantage of the KMD analysis is the significant amount of data reduction that can be achieved without any preliminary information regarding sample composition, only by selecting a suitable RU. In addition, although the KMD analysis aims at data reduction, it might still be particularly useful when trying to identify chemicals. Indeed, since the KMD analysis reveals homologue series, identifying one chemical (for instance by suspect screening) will allow identifying all the homologues in the series but an investigation of MS² product ions should still be performed to propose a detailed structure for each of them. Another two advantages of the KMD analysis are the high simplicity and the rapidity of this approach (Fig. 6). In fact, after selecting the suitable RU to address his research question, the analyst only needs to convert the accurate mass measured in the IUPAC system to the KM system using Eq. (5) and Eq. (6). This can be easily performed in a simple computing spreadsheet that can also be used to plot the results. However, the need for a computing spreadsheet might also be the first limitation for the application of the KMD analysis. Indeed,

since the KMD analysis is not commonly used, software packages from vendors usually don't include the option for such HRMS data processing. For instance, Agilent Technologies through the MassHunter software or Waters Corporation through the UNIFI software allow filtering HRMS data according to a certain range of MD defined by the analyst. As described previously in the paper, this is particularly useful to investigate TPs and metabolites. However, no further option appears available in order to perform data filtration based on KMD. In fact, in order to perform a KMD analysis, analysts seems to rely on their own calculation spreadsheet (Merel et al., 2017), their own MatLab code (Bugsel and Zwiener, 2020) or other in-house solution (Kune et al., 2019; Léon et al., 2019) that are made available or could be obtained upon request. Some solutions are also available in R, for example through the enviGCMS package. Nonetheless, despite the high simplicity of the KMD analysis, the overall lack of a built-in options to perform it probably greatly prevents its application beyond rather advanced HRMS users.

The KMD approach also has two main limitations. The first limitation is the fact that the user must select an RU to perform the analysis. Although this is a fairly simple decision to make for a very specific application such as tracking the formation of oxygenated species after water treatment by any advanced oxidation process, it might be much more complex for other tasks like revealing all potential poly/perfluorinated compounds in a sample. Indeed, this task was shown to require the consideration of several RU, which points to the second limitation of the KMD analysis. Indeed, each RU requires its own conversion from the IUPAC to the KM system and its own processing. For instance, when searching for TPs of contaminants after wastewater ozonation, a KMD analysis performed with O as RU would reveal oxygenated species and another KMD analysis performed with $CH_2$ as RU would reveal potential dealkylations but TPs resulting from an oxygenation combined with a dealkylation would remain unobserved. Consequently, even though the KMD analysis proved efficient for the

discovery of specific TPs, its application is highly driven by the analyst who selects the RU. In fact, TPs resulting from an unexpected chemical reaction would remain undiscovered.

Perspectives for the application of KMD analysis include the use of 2D KMD plots (Fig. 7). For instance, the antioxidant ethoxyquin (EQ) has been shown to degrade into multiple TPs (Merel et al., 2019; Negreira et al., 2017) resulting from dealkylation as well as hydration of a double bound among other oxidation mechanisms. Therefore, some TPs of EQ should be observed with a KMD analysis using $CH_2$ and $H_2$ as RUs. When using $CH_2$ as RU, the TP referred to as DEQ and corresponding to the loss of $C_2H_4$ can be observed (Fig. 7A). When using $H_2$ as RU, the TP referred to as DHEQ and corresponding to the gain of $H_2$ can be observed (Fig. 7B). When elaborating the 2D KMD plot with each axis representing the KMDs calculated according to a specific RU (Fig. 7C), several other compounds that might have been observed on regular KMD plots now appear to be clearly EQ TPs, including DHMEQ that several quantitative structure–activity relationship (QSAR) tools reported to be potentially genotoxic (Rasinger et al., 2022). Adding another dimension to obtain a 3D plot would certainly reveal additional TPs of EQ. However, the oxidation of EQ is complex and all the TPs observed so far cannot be characterized with only 3 RUs. Therefore, designing an approach allowing the exhaustive observation of TPs represents a major perspective for the application of the KMD analysis. In addition, it would also represent a major breakthrough in the field of environmental analytical chemistry since the exhaustive discovery and identification of TPs remains challenging despite all the recent technical progress in detection capabilities.

## 6. Conclusion

The constant progress in detection capability and the growing application of HRMS in environmental sciences have dramatically improved our knowledge of contamination in all sorts of environmental matrices. However, as most of the components detected in a sample

remain unknown, the analytical challenge is progressively switching from "how can we detect more chemicals at lower concentration?" to "how can we efficiently handle and make sense of this large volume of data that HRMS generates?". Therefore, processing method are being improved or imported from other research fields.  In this context, the KMD analysis that is well-known in the field of fuel chemistry is progressively gaining interest in the field of environmental chemistry. Although only a rather limited amount of publication mention it for the analysis of environmental samples, it proved useful for multiple applications such as the characterization of organic matter, the discovery of polymers and the assessment of TPs. However, commercial software packages provided with high resolution mass spectrometers usually don't include the option to perform a KMD analysis, which probably limits the broad use of this quick and efficient data processing approach. In addition, further research is still required to better adapt the KMD analysis to environmental applications. Particularly, developing a global KMD approach that would allow revealing all the potential TPs of a given chemical without having to select multiple repeating units would be a major advance in environmental analytical chemistry.

**Declaration of Competing Interest**

The author declare no conflict of interest and that he has no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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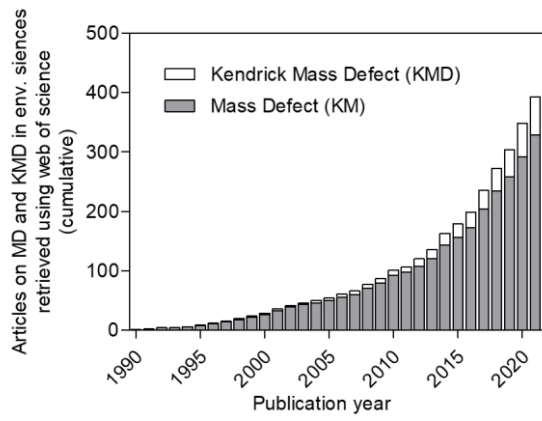
## Figure and Tables



**Fig. 1:** Bibliometric overview of the peer-reviewed literature on mass defect and Kendrick mass defect in research areas related to environmental sciences.

**Accurate mass and relative mass defect (RMD) for a suite of common atoms**

| Isotopolog | H | C | N | O | F | P | S | Cl | Br | I |
|---|---|---|---|---|---|---|---|---|---|---|
| A | $^1$H (99.9885%) 1.00783 | $^{12}$C (98.93%) 12.00000 | $^{14}$N (99.632) 14.00307 | $^{16}$O (99.757%) 15.99491 | $^{19}$F (100%) 18.99840 | $^{31}$P (100%) 30.97377 | $^{32}$S (94.93%) 31.97207 | $^{35}$Cl (75.78%) 34.96885 | $^{79}$Br (50.69%) 78.91834 | $^{127}$I (100%) 126.90447 |
| A+1 | $^2$H (0.0115%) 2.01410 | $^{13}$C (1.07%) 13.00335 | $^{15}$N (0.368%) 15.00011 | $^{17}$O (0.038%) 16.99913 | N.A. | N.A. | $^{33}$S (0.76%) 32.97146 | N.A. | N.A. | N.A. |
| A+2 | N.A. | N.A. | N.A. | $^{18}$O (0.205%) 17.99916 | | | $^{34}$S (4.29%) 33.96787 | $^{37}$Cl (24.22%) 36.96590 | $^{81}$Br (49.31%) 80.91629 | N.A. |
| RMD$_{A+1}$ | 0.00627 | 0.00335 | -0.00296 | 0.00422 | N.A. | N.A. | -0.00061 | N.A. | N.A. | N.A. |
| RMD$_{A+2}$ | N.A. | N.A. | N.A. | 0.00425 | N.A. | N.A. | -0.00420 | -0.00295 | -0.00205 | N.A. |

**Application of relative mass defect (RMD) for the identification of the chlorinated pharmaceutical lamotrigine**
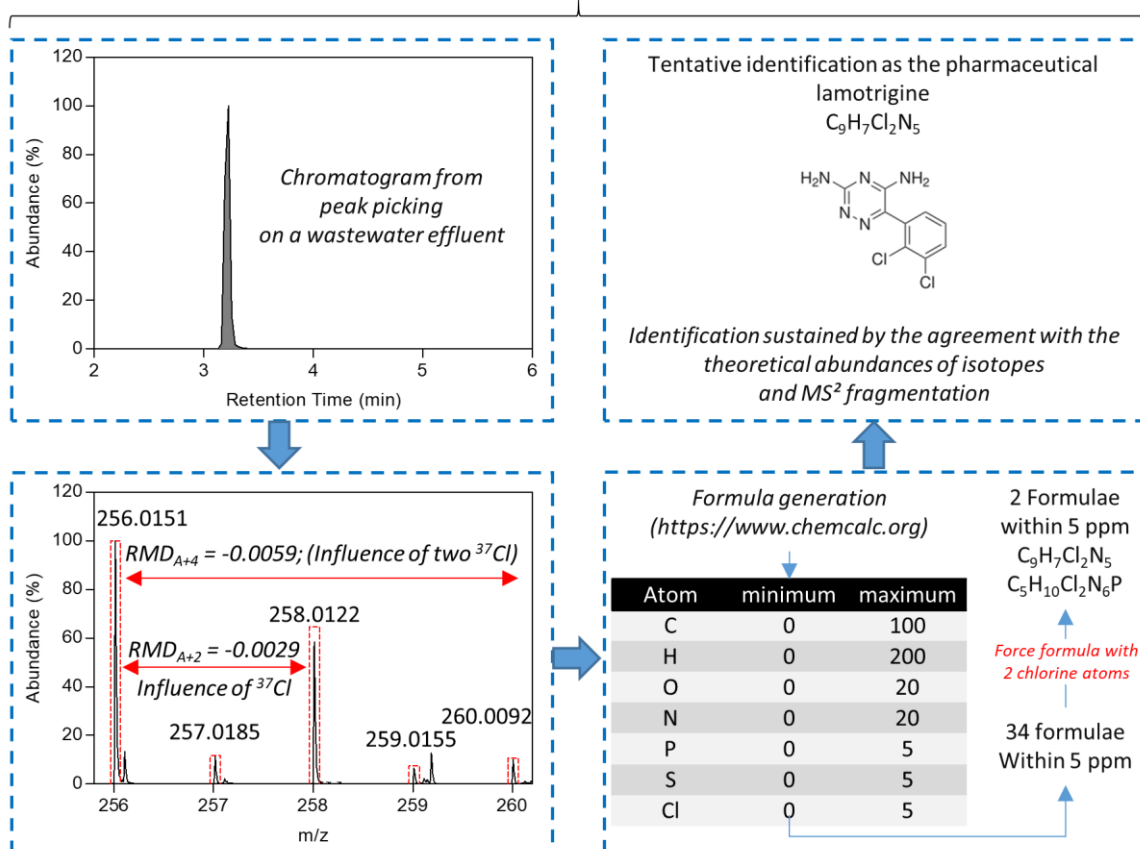


**Fig. 2:** Accurate mass and relative mass defect (RMD) for common atoms and example of application for the identification of a chlorinated environmental contaminant.
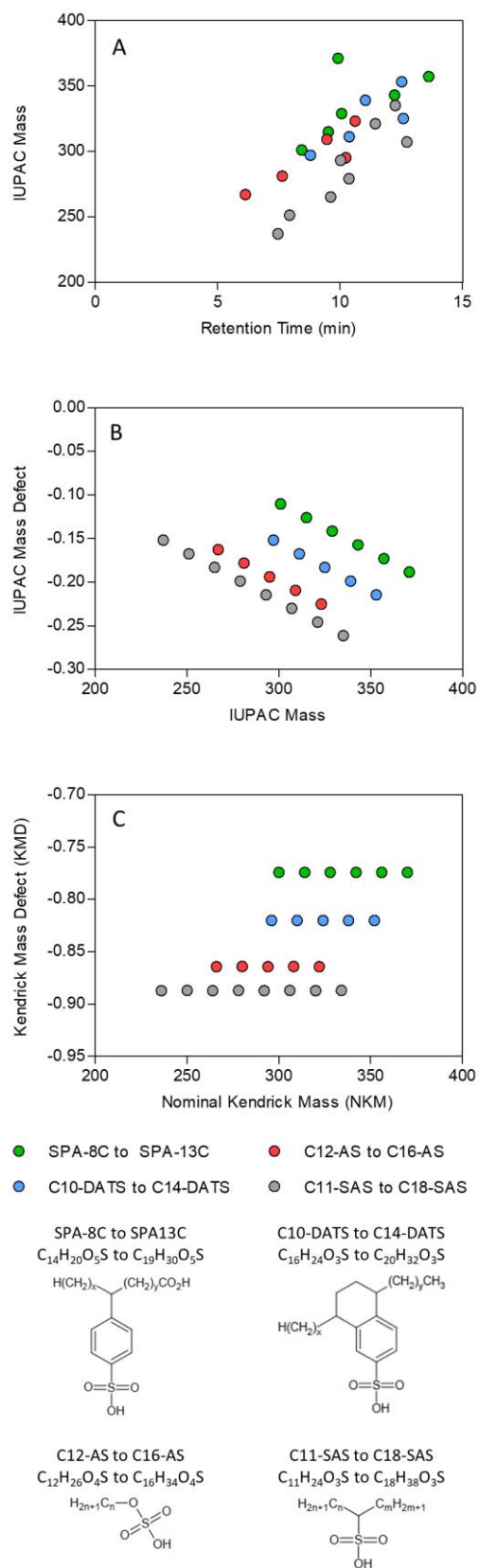
**Fig. 3:** Plots showing selected polymers through: (A) IUPAC mass vs. retention time, (B) IUPAC mass defect vs. IUPAC mass, and (C) Kendrick mass defect vs. nominal Kendrick mass.
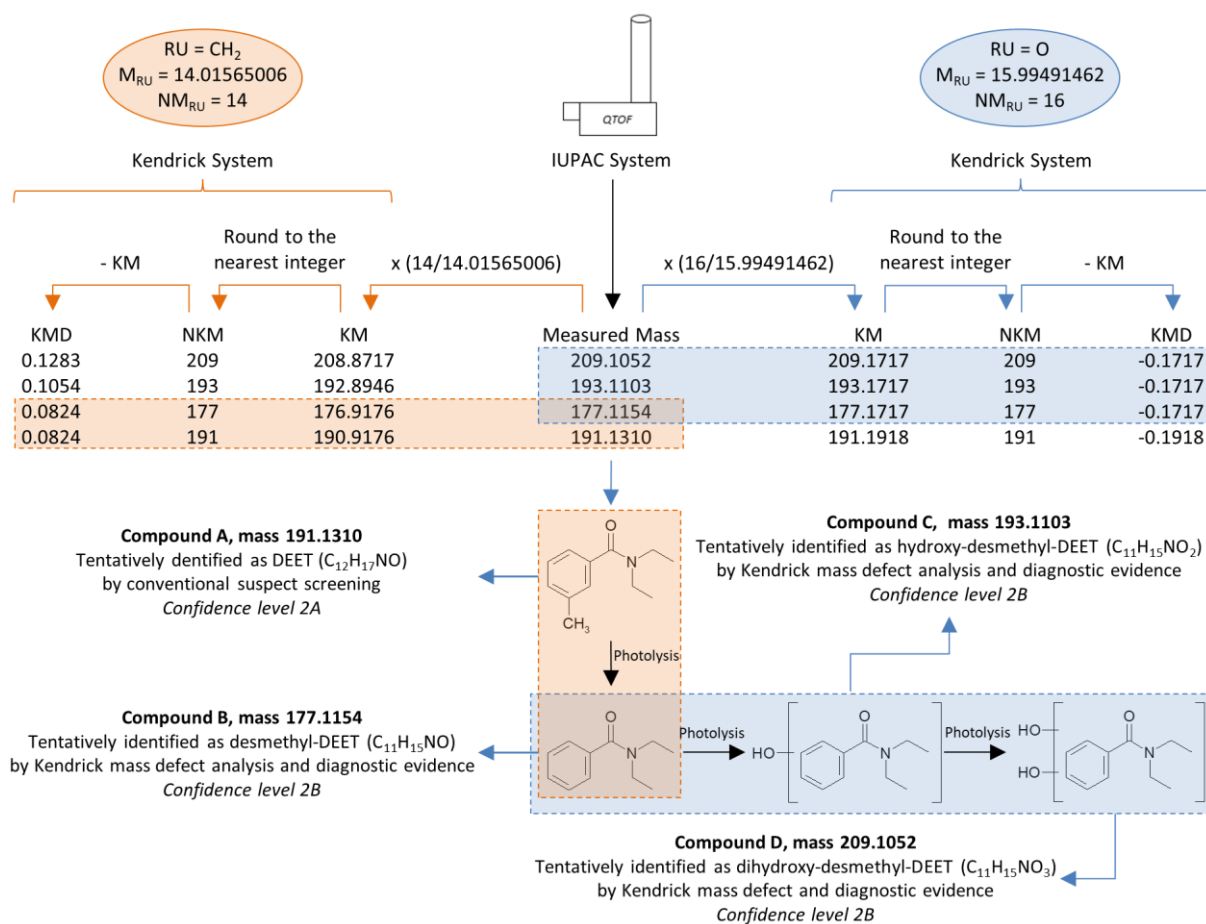
**Fig. 4:** Calculation example for KM and KMD leading to the tentative identification of unknown contaminants.
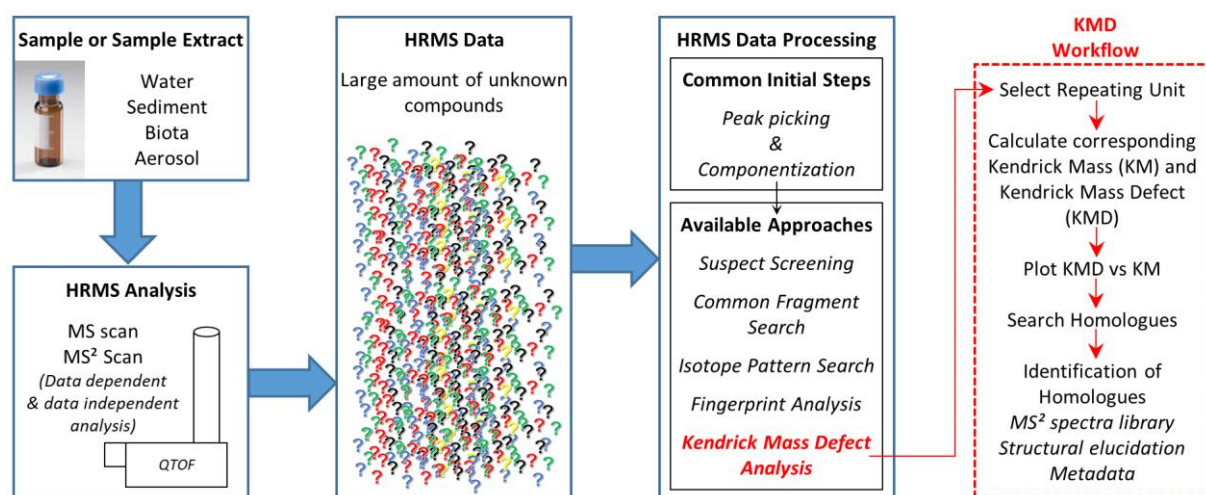


**Fig. 5:** Simplified workflow for the analysis of an environmental sample by HRMS and subsequent data processing by Kendrick mass defect analysis.
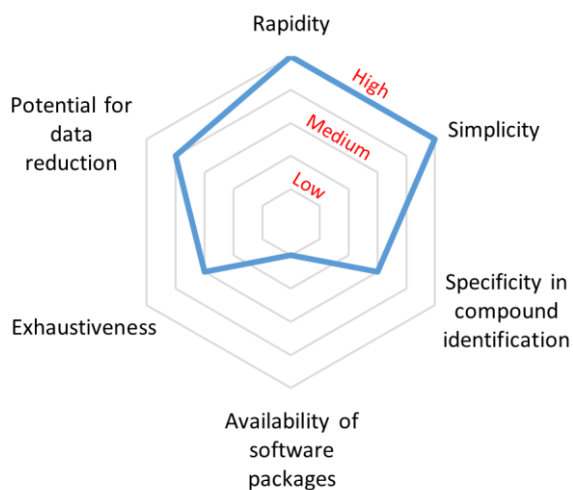
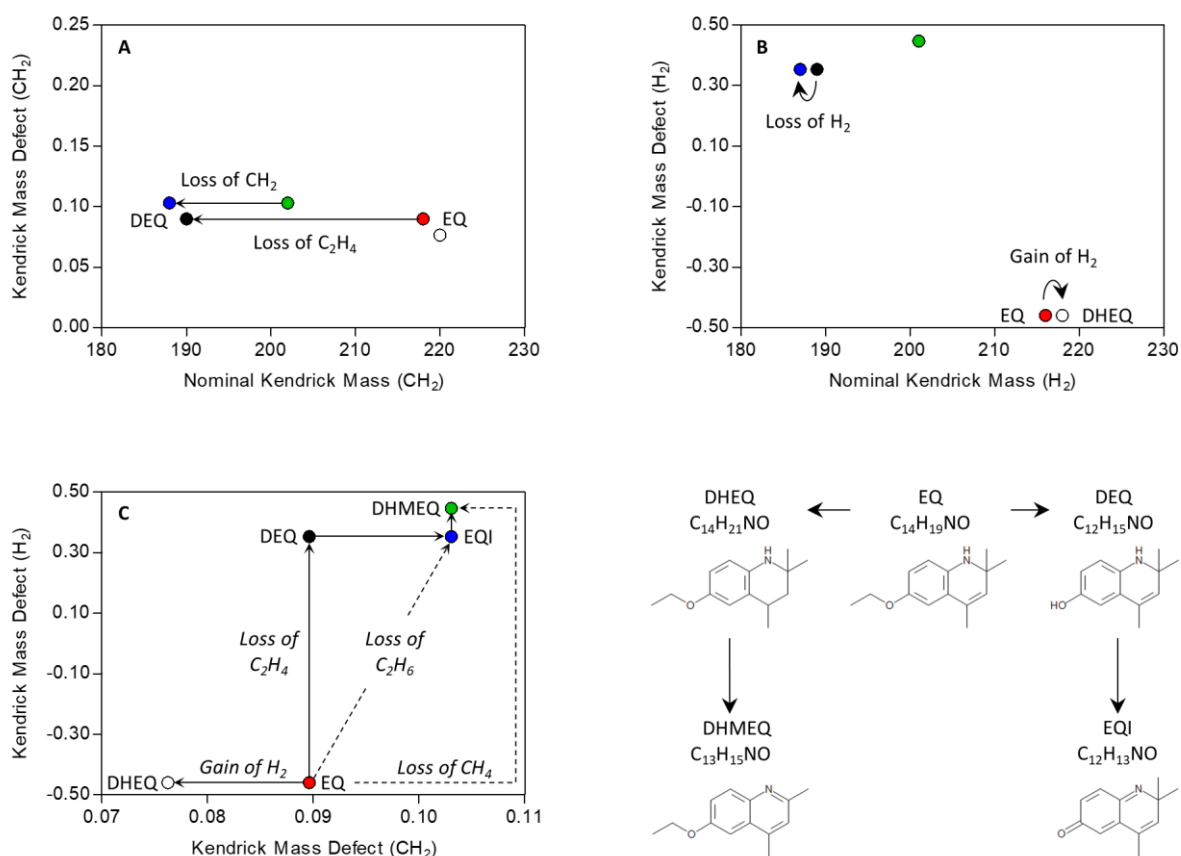**Fig. 6:** Qualitative evaluation of Kendrick mass defect analysis.



**Fig. 7:** Benefits of using a 2D Kendrick mass defect plot with respect to conventional

Kendrick mass defect plots for the discovery of transformation products (example of the

antioxidant ethoxyquin)

# Tables

**Table 1:** Studies using the Kendrick mass approach retrieved from web of science in research areas related to environmental sciences.

| Selected Repeating Unit | Objective | Ref |
|---|---|---|
| $CH_2$ | Characterize organic compounds in aerosols | Kourtchev et al., 2013, 2014, 2016 |
| $CH_2$ | Characterize organic compounds in biomass burning aerosols | Smith et al., 2009 |
| $CH_2$ | Characterize natural organic matter in soil | Ohno et al., 2014 |
| $CH_2$ | Characterize organic matter in river water | Rakruam et al., 2021, Sanchis et al., 2020 |
| $CH_2$ | Characterize organic matter in rain water | Mead et al., 2015 |
| $CH_2$ | Characterize organic matter in drinking water | Phungsai et al., 2018 |
| $CH_2$ | Characterize organic matter in fractionated Suwannee River fulvic acid | Stenson, 2008 |
| $CH_2$ | Characterize organic matter and chlorinated disinfection byproducts in chlorinated Suwannee River organic matter solution | Lu et al., 2021b |
| $CH_2$ | Characterize organic matter and brominated disinfection byproducts in ozonated Suwannee River organic matter solution | Lu et al., 2021a |
| $CH_2$ | Characterize changes in disolved organic matter when changing the feed in recirculating aquaculture systems | Aguilar-Alarcon et al., 2020 |
| $CH_2$ | Characterize constituents unique to septic tanks in freshwater, salt water, groundwater, septic-influenced groundwater | Troxell et al., 2022 |
| $CH_2$ | Characterize organic contaminants in tap and surface water | Ng et al., 2022 |
| $CH_2$ | Characterize polycyclic aromatic hydrocarbons (PAHs) dissolved organic matter in wastewater in soils and sediments | Vila et al., 2020 |
| $CH_2$ | Characterize of polycyclic aromatic compounds in commercial pavement sealcoat products | Bowman et al., 2019 |
| $CH_2$ | Characterize polycyclic aromatic compounds in crude oils | Nocun and Andersson, 2012 |
| $CH_2$ | Characterize naphthenic acid compounds from oils sands in fluid fine tailing | Bowman et al., 2018 |
| $CH_2$ | Characterize naphthenic acids in oil sands processed water | Nyakas et al., 2013 |
| $CH_2$ | Characterize the degradation of naphthenic acid compounds from oil sands process-affected water in constructed wetland | Ajaero et al., 2020 |
| $CH_2$ | Characterize the biodegradation of oxidized oligomers from photo-oxidized polyethylene films | Eyheraguibel et al., 2017 |
| $CH_2$ | Characterize cyclic lipopeptides in crude extract from Pseudomonas sp. COW3 | Omoboye et al., 2019 |
| $CH_2$ | Characterize poly/perfluorinated compounds in whole fish | Crimmins et al., 2014 |
| $CO_2$ | Characterize humic-like substances in aerosols | Lin et al., 2012 |

| | | |
|---|---|---|
| $CO_2$ | Characterize organic matter in the water-extractable fraction from biochar | Smith et al., 2013 |
| $CO_2$ | Characterize dissolved organic matter in different soil organic horizons and a reference Pahokee peat soil (IHSS) | Chasse et al., 2015 |
| $CO_2$ | Characterize the organic matter in Pu-contaminated soil | DiDonato et al., 2017 |
| $CO_2$ | Characterize organic compounds in volcanic ash soil humic acid | Kramer et al., 2004 |
| $CO_2$ | Characterize dissolved organic matter in surface water | Li et al., 2018 |
| $C_2H_4O$ | Characterize polymer in a phytosanitary product | Sero et al., 2019 |
| $C_2H_4O$ | Characterize amino ethoxylates in wastewater from hydraulic fracturing | Sitterley et al., 2018 |
| $C_3H_6O$ | Characterize polypropylene glycols in agricultural soils | Gravert et al., 2021 |
| $CF_2$ | Characterize perfluorinated compounds in groundwater impacted by aqueous film-forming foams | Barzen-Hanson et al., 2017 |
| $CF_2$ | Characterize poly/perfluorinated compounds in contaminated groundwater and soil sample | Cody and Maleknia, 2020 |
| $CF_2$ | Characterize poly/perfluorinated compounds in river water | Joerss et al., 2022 |
| $CF_2$ | Characterize poly/perfluorinated compounds in almond hulls and black soldier fly larvae | Li and Bischel, 2022 |
| $CF_2$ | Characterize poly/perfluorinated compounds in biosolids, composts, and organic waste | Munoz et al., 2022 |
| $CF_2$ | Characterize poly/perfluorinated compounds (PFCs) in surface water and aqueous film-forming foam | Young et al., 2022 |
| $CF_2$ | Characterize poly/perfluorinated compounds (PFCs) in extract form coated vials exposed to light simultation | Zhu et al., 2019 |
| $O$ | Characterize contaminants and their oxygenated transformation products in ozonated wastewater effluent | Merel et al., 2017 |
| $C_{10}H_7NO_2$ | Characterize transformation products from the photodegradation of carbamazepine with Suwannee River fulvic acid | Raeke et al., 2017 |
| $[Cl - H]$ | Characterize chlorinated paraffins in indoor dust and cat hair | Brits et al., 2020 |
| $[Cl - H]$ | Characterize compounds with chlorine substitution in dust sample from an electronics recycling facility | Ubukata et al., 2015 |
| $[Cl - H]$ | Characterize halogenated organic contaminants in surface water | Zhang et al., 2020 |
| $[NO - H]$ | Characterize the formation of N-nitroso-compounds during the biological treatment of wastewater | Brienza et al., 2020 |
| $[NO_2 - H]$ | Characterize organic matter in tropospheric particle | Spranger et al., 2019 |
| $CH_2$; $[Cl - H]$ | Characterize chlorinated compounds in lake trout | Jobst et al., 2013 |
| $CH_2$; $CO_2$ | Characterize organic matter in the water-extractable fraction of soils | Guigue et al., 2016 |
| $C_2H_4O$; $C_3H_6O$ | Characterize organic matter in water from hydraulic fracturing of oil and gas wells | Kim et al., 2020 |
| $C_2H_4O$; $C_3H_6O$ | Characterize surfactants in flowback and produced waters from hydraulic fracturing | Thurman et al., 2017 |
| $CH_2$; $H_2$; $CO_2$ | Characterize the organic matter during $O_3/H_2O_2$ treatment of nanofiltration concentrates from landfill leachate | Gu et al., 2022 |
| $CH_2$; $CH_2O$; $O$ | Characterize isoprene oxidation in secondary organic aerosols | Nguyen et al., 2010 |

| | | |
|---|---|---|
| $CH_2$; $C_2H_4O$; $C_3H_6O$ | Characterize polymers in flowback and produced waters from hydraulic fracturing | Sun et al., 2019 |
| $CH_2O$; $C_6H_4O$; $C_9H_{10}O_3$ | Characterize lignin degradation products in lignin solution | Qi et al., 2016 |
| $CH_2$; $C_2H_4O$; $CF_2$; $[Cl - H]$ | Characterize dissolved organic matter in wastewater | Verkh et al., 2018 |
| $CH_2$; $H_2$; $CO_2$; $CO$; $OH$; $C_6H_5$ | Characterize dissolved organic matter in landfill leachates | Liu et al., 2022 |
| $CF_2$; $CF_2O$; $C_2F_4O$ | Characterize poly/perfluorinated compounds freeze-dried soil samples from contaminated areas | Bugsel and Zwiener, 2020 |
| $CF_2$; $CF_2O$; $C_2H_2F_2$; $C_3F_6O$ | Characterize poly/perfluorinated compounds in fluorocarbon paint | Jia et al., 2021 |
| $C_2H_4$; $C_3H_6$; $C_5H_8$; $C_4H_6$; $C_{10}H_8O_4$; $C_2H_6OSi$ | Characterize polymers from micro and nanoplastics in river water and seawater | Llorca et al., 2021 |
| $C_2H_4$; $C_3H_6$; $C_5H_8$; $C_4H_6$; $C_8H_8$; $C_{10}H_8O_4$; $C_2H_6OSi$; $CHON$ | Characterize polymers from micro and nanoplastics in tap water | Vega-Herrera et al., 2022 |