



## Tales of the tides: Pattern-based non-target analysis of the Elbe River

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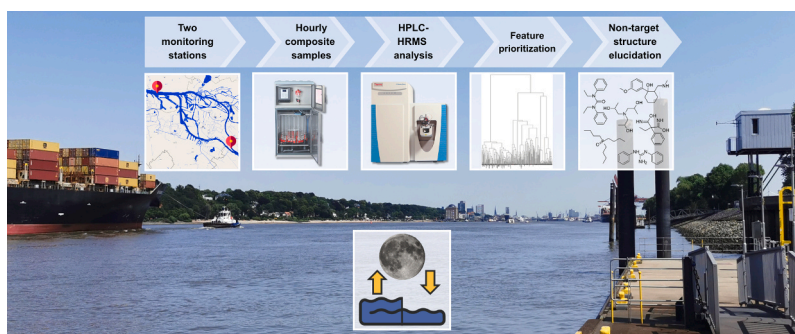
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### HIGHLIGHTS

- Tidal river dynamics significantly influence organic pollutant behavior.
- Pattern-based non-target analysis identified seven untargeted micropollutants.
- Accessible workflow using standard monitoring equipment and basic statistics.
- High-frequency sampling captures concentration patterns.
- Spatial analysis allows approximation of source locations.

### GRAPHICAL ABSTRACT



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### ABSTRACT

The goal of this study was to identify previously undetected organic micropollutants (OMPs) in a tidal river system using pattern-based non-target analysis (NTA). Tidal rivers are complex hydrological systems with constantly changing water levels, flow rates, and flow directions, posing significant challenges for monitoring contaminant behavior and fate. In a previous study, we demonstrated that these conditions create distinctive spatiotemporal pollutant patterns for target analytes, differing fundamentally from unidirectional river systems, ranging from tidally oscillating pesticide plumes to stable pharmaceutical concentrations from continuous wastewater inputs. Here, we employed high-frequency sampling with NTA and statistical methods to unravel additional contaminants with tidal-related patterns in the Elbe River, Germany. Two sampling campaigns (August 2022, February 2023) were conducted at upstream and downstream locations spanning Hamburg's metropolitan area. We analyzed 404 hourly composite samples using high-performance liquid chromatography coupled to high-resolution mass spectrometry (HPLC-HRMS). Statistical methods (differential analysis, correlation analysis, variance analysis, hierarchical cluster analysis) prioritized non-target features based on similarity to target micropollutant patterns exhibiting tidal-related dynamics. Seven micropollutants were identified and

**Abbreviations:** BU, "Bunthaus" sampling station; CE, collision energy; CV, coefficient of variation; ddMS<sup>2</sup>, data dependent fragmentation; HCA, hierarchical cluster analysis; HCD, higher-energy collisional dissociation; HESI, heated electrospray ionization; HPLC-HRMS, high-performance liquid chromatography-high resolution mass spectrometry; HU, Institut für Hygiene und Umwelt Hamburg; ISTD, isotopically labelled internal standard compound; LOD, limit of detection; LOQ, limit of quantification; NTA, non-target analysis; OMP, organic micropollutant; PCA, principal component analysis; QA/QC, quality assurance and quality control; R<sup>2</sup>, correlation coefficient; RT, retention time; SH, "Seemannshöft" sampling station; WWTP, wastewater treatment plant.

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confirmed: pharmaceutical metabolites (phenylethylmalonamide, N-desmethyltramadol, O-desmethyltramadol), industrial additives (triisopropanolamine, 1,3-diphenylguanidine), and niche chemicals (tributylphosphine oxide, ethyl centralite), several have rarely been reported in surface waters. This study provides novel insights into micropollutant dynamics in tidal rivers, highlighting the importance of high-frequency sampling for capturing contamination in tidally influenced waters. Importantly, our workflow was implemented by a single analyst using standard regulatory equipment, demonstrating that comprehensive chemical characterization of complex tidal systems is achievable for routine monitoring laboratories.

## 1. Introduction

Tidal rivers present unique hydrological challenges for monitoring organic micropollutants (OMPs) due to constantly changing water levels, flow rates, and flow directions driven by ebb and flood dynamics. These hydraulic conditions significantly influence contaminant fate and transport, making them fundamentally different from unidirectional river systems [1,2]. In a previous study, we demonstrated through high-frequency sampling and target analysis that OMPs in the tidal Elbe River exhibit distinct spatiotemporal patterns, depending on contaminant source and environmental behavior: transient contamination events of pesticides with tidal-related peaks, stable pharmaceutical concentrations from continuous wastewater treatment plant (WWTP) inputs, and seasonally varying dynamics of a pharmaceutical transformation product [3]. While the applied targeted approach successfully characterized 135 known compounds, the amount of environmentally relevant contaminants extends far beyond available analytical reference standards, leaving vast proportions of anthropogenic contamination undetected and uncharacterized [4].

Non-target analysis (NTA) using high-resolution mass spectrometry (HRMS) offers a solution to unravel contaminants beyond target analysis but requires strategic filtering of the tens of thousands of detected features to focus identification efforts on environmentally relevant compounds. Effective and adaptive extraction, prioritization, and annotation of compound features are crucial for any suspect screening or non-target analysis [5]. Several studies have successfully applied spatiotemporal and similarity analysis in order to prioritize unknowns in freshwater systems. Nikolopoulou et al. [6] applied trend and factor analysis to 30 consecutive days of upstream/downstream sampling to classify chemical trends. Carpenter et al. [7] collected daily composite samples for one year in a small stream and used hierarchical clustering analysis (HCA) to prioritize non-target features based on their similarity to target micropollutant profiles. At the Rhine River, multiple studies combined spatial and temporal sampling with NTA to track pollution sources and reveal pollution patterns [8–10]. All these studies were successful in identifying unsuspected pollutants within surface waters of unidirectional flow. However, no studies have specifically addressed tidal river systems, where bidirectional flow and enhanced mixing create pollutant transport patterns fundamentally different from unidirectional streams. High-frequency monitoring has proven essential for capturing short-term dynamics of physicochemical parameters in estuarine systems and tidal rivers [3,11–13], demonstrating that conventional sampling approaches (e.g. [14–16]) fail to capture the variability of these systems. The application of high-frequency sampling for NTA of organic micropollutants in tidal rivers thus addresses a significant knowledge gap.

A critical barrier to implementing comprehensive NTA monitoring is the perception that extensive resources, specialized expertise, and sophisticated data analysis capabilities are required. Many regulatory monitoring agencies and research institutes, the majority of which have limited budget and personnel, may view high-frequency sampling and NTA as operationally infeasible. However, when built upon existing monitoring infrastructure and leveraging open-source tools, pattern-based NTA can be implemented with comparatively low cost and effort. The key is to combine pragmatic sampling strategies with straightforward statistical approaches that do not require advanced data science expertise yet remain effective for feature prioritization and

source identification. Such accessible methodologies are essential to expand comprehensive chemical monitoring beyond time-limited research projects and to enable broader assessment of emerging contaminants in diverse tidal river systems worldwide.

This study demonstrates a practical, accessible approach to NTA in tidal rivers. We applied pattern-based feature prioritization to high-frequency sampling data from the tidal Elbe River, analyzed using high-performance liquid chromatography coupled to high-resolution mass spectrometry (HPLC-HRMS) as described in our previous study [3]. We prioritized features using univariate statistical analyses (differential analysis, correlation analysis, variance analysis) and hierarchical cluster analysis, implemented in open-source R software. Features were selected for structural elucidation if they exhibited distinct patterns based on thresholds defined in our previous study (e.g. strong correlation with water levels or remarkably low variance) and clustered with known target compounds. The aim of this study was to demonstrate that effective pattern-based NTA in complex tidal systems can be implemented without extensive personnel resources using standard regulatory monitoring equipment and general statistics, providing a replicable framework for comprehensive chemical characterization accessible to resource-limited monitoring laboratories worldwide.

## 2. Materials and methods

### 2.1. Chemicals

Detailed information on the chemicals and reagents used for this study as well as on the employed analytical standards, consisting of 427 reference standard compounds and 35 isotopically labelled internal standard compounds (ISTDs), are provided as [supplementary material](#).

### 2.2. Study area

Study area was a section of Tidal Elbe in the federal state of Hamburg, Germany. River water was sampled simultaneously at two water quality monitoring stations operated by the Free and Hanseatic City of Hamburg and located 19 river kilometers apart, as depicted in [Fig. 1](#). The first station (Bunthaus, BU) is located east and upstream of Hamburg's urban area, while the second station (Seemannshöft, SH) is positioned west and downstream of the inner city of Hamburg, its central wastewater treatment plant, the harbor and the majority of the region's industrial facilities. The study area and river system are described in detail in the material and our previous publication ([3], [Section 2.2](#)).

### 2.3. Sampling

A staggered sampling strategy was employed to balance logistical constraints with the need for extended observation windows and adequate temporal resolution, thereby ensuring robust capture of contaminant dynamics under tidal influence. Automated samplers at the two study sites collected one-hour composite samples by transferring 180 ml of river water into 2 L glass bottles every six minutes, providing hourly time-proportional samples. Field blanks, consisting of 1.5 L mineral water (VIO, Coca-Cola Services N.V., Brussels, Belgium), were poured into a randomly selected rinsed sampler container and left for at least 45 min before retrieval.

The first sampling campaign took place in August 2022. Samples were collected continuously over two periods separated by a two-day interval: August 23 to August 25 (48-h period) and August 28 to August 29 (24-h period). The second campaign was carried out from February 15 to February 26, 2023, covering fourteen days. Here, samples were collected every second day, covering the previous 24-h period. Each sampling period covered at least one semi-diurnal tidal cycle (two high waters and two low waters). In total, 404 samples from nine 24-h periods were collected and analyzed (62 per station in August and 140 per station in February). Fig. 2 visualizes sampling periods and tidal water levels for both campaigns.

Meteorological and hydrological conditions were typical for the respective season, sampling campaigns did not cover extreme events. Further details on the sampling procedure, as well as meteorological and hydrological data are provided as [supplementary material](#) and in our previous publication ([3], Sections 2.3 and 2.4).

#### 2.4. LC-HRMS analysis

Sample preparation included centrifugation (15 min at 1850 rcf) and spiking with isotope-substituted internal standards yielding 200 ng/L of each ISTD in the samples. If possible, analysis was started directly after sample preparation, else, samples were stored at  $-20\text{ }^{\circ}\text{C}$  for a maximum of seven days. Samples of each 24-h period batch were analyzed in randomized order to prevent systematic errors such as instrument drift within the data. Analysis was performed using Ultimate 3000 HPLC coupled to a Q Exactive Focus Orbitrap HRMS system with heated electrospray ionization (HESI) (all Thermo Fisher Scientific Inc., Waltham, MA, USA). Chromatographic separation was achieved with an Acquity PREMIER HSS T3 C18 column ( $2.1 \times 150\text{ mm}$ ,  $1.8\text{ }\mu\text{m}$  particle size; Waters Corp., Milford, MA, USA). A mobile phase gradient of water and methanol, both containing 0.0025% formic acid and 5 mM ammonium formate, was applied at  $350\text{ }\mu\text{L}/\text{min}$  shifting from 100% water to 100% methanol within 23 min. Sample injection volume was  $100\text{ }\mu\text{L}$ .

The mass accuracy of the HRMS instrument was calibrated (tuned) prior to each measurement batch. Data was acquired in profile mode for mass-to-charge-ratios ( $m/z$ ) ranging from 68 to 1020 at a nominal resolving power of 70,000 referenced to  $m/z$  200, and a mass error below 5 ppm for positive ionization and 7 ppm for negative ionization, respectively. Positive and negative ionization modes were applied in separate analytical runs for each sample. Data dependent fragmentation (ddMS<sup>2</sup>) was applied with stepped absolute collision energies (CE) of 10 eV, 50 eV and 100 eV, respectively, via higher-energy collisional dissociation (HCD) with a resolving power of 17,500 referenced to  $m/z$  200. Comprehensive information about the HPLC-HRMS instrumentation and analytical parameters, calibration, target analysis quantification, and the determination of operational limits of detection (LODs) and limits of quantification (LOQs) are provided as [supplementary material](#).

#### 2.5. Data processing

Suspect screening and non-target analysis were carried out using a self-established workflow within the software Compound Discoverer (version 3.3, Thermo Fisher Scientific Inc.), including data extraction, filtering, and feature annotation. A detailed description of the NTA workflow is provided as [supplementary material](#). Samples were processed per campaign and ionization mode, yielding four processing files. This improved evaluation efficiency and comparability, despite longer processing times and potential retention time (RT) shifts compared to processing batch-wise.

The following filtering procedure aimed at extracting high-quality features for subsequent statistical evaluation and compound identification. 1) background removal: any feature in a sample had to exhibit a peak area at least five times higher than that observed in system and field blanks; 2) RT window: set from 1.60 to 21.0 min to remove insufficiently resolved peaks occurring early and very late in the chromatogram; 3) peak rating: excluding features with poor peak shapes (rating  $\geq 5$  in at least three samples, based on prior experiments); 4)



Fig. 1. Map of the metropolitan area of Hamburg with locations and photos of the two monitoring stations Bunthaus “BU” and Seemannshöft “SH”. General direction of flow at low tide is from east to west, i.e. from BU to SH [17].

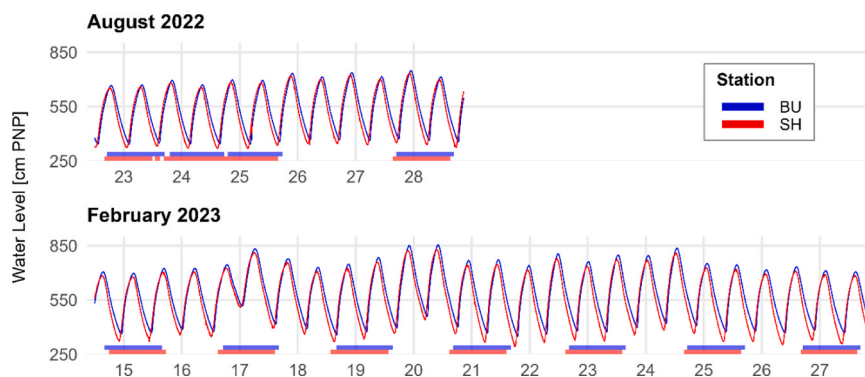


Fig. 2. Tidal water levels and sampling periods for the sampling stations Bunthaus “BU” (blue) and Seemannshöft “SH” (red). Sampling periods are displayed as colored bars at the bottom of each graph.

structure elucidation criteria: requiring both  $MS^2$  data and predicted chemical formulas for each feature. Filtered features were exported for statistical analysis and visualization using an in-house R script [18].

Two data treatment strategies were evaluated to ensure reliable identification and prioritization of unknown compounds: handling missing values and normalization with internal standards. Firstly, when no peak is detected, low arbitrary values instead of zeros or NAs can be assigned to a sample. These values derived either from trace areas or spectrum noise present in the chromatogram, or were simulated with a Gaussian fit algorithm when no spectral traces were detected. Although artificial, these values improve statistical quality by increasing data density and reducing variability, and were therefore included in all calculations. Secondly, feature intensity normalization using 15 ISTDs (ESI+) and 3 ISTDs (ESI-) was evaluated, including averaging across multiple ISTDs and the assignment of single ISTDs to a feature based on retention time-based matching or chemical similarity to tentative structure proposals [9,19]. However, comparison with parallel target analyses showed no overall improvement in data quality (see supplementary material), which was also reported previously [20]. Since most statistical evaluations were performed batch-wise and the instrumental analysis exhibited high in-batch stability, normalization was generally unnecessary. Normalization improved consistency for some analytes but introduced additional variability for others. Therefore, non-normalized data were used as the primary basis for analysis, though both datasets were reviewed to ensure comprehensive interpretation.

## 2.6. Prioritization of unknown features

A full characterization and structure elucidation for all features was not feasible due to the large number of filtered unknowns (~5700). Prioritization therefore focused on features that exhibited distinct concentration patterns and clustered with known target compounds identified in our previous study. Selection was guided by multiple statistical criteria and hierarchical cluster analysis.

## 2.7. Statistical analysis

Statistical analysis aimed to identify distinct analyte concentration patterns and was comprised of: 1) Differential analysis based on the Wilcoxon rank-sum test as well as principal component analysis (PCA) to compare sampling stations or seasons. 2) Correlation analysis, calculating Spearman's rank correlation coefficients ( $R^2$ ) for the analyte peak areas to water levels across individual sampling days. 3) Variance analysis, determining the coefficients of variation (CV) for the analyte concentrations over different temporal scales, including single tidal cycles, individual sampling days, and entire sampling campaigns.

Analogous to our previous study utilizing target analysis, features with noticeable patterns were identified by 1) significant differences ( $p < 0.05$ ) between sample groups, 2) elevated correlation coefficients

( $|R^2| \geq 0.5$ ), or 3) coefficients of variation marked by either exceptionally high ( $CV \geq 50\%$ ) or remarkably low ( $CV \leq 10\%$ ) values.

## 2.8. Cluster analysis

Agglomerative hierarchical cluster analysis based on Ward's method with squared Euclidean distance was applied to the feature lists of the 404 samples using the R package ‘stats’. Prior to cluster analysis, peak areas were scaled with the R-base function ‘scale’ to ensure all variables have equal variances. HCA was performed separately for positive and negative ionization modes on the following dataset configurations: 1) campaigns and sampling locations combined (2 datasets: 2 ionization modes); 2) campaigns separately, each combining both sampling stations (4 datasets: 2 campaigns  $\times$  2 ionization modes); 3) locations separately, each combining both campaigns (4 datasets: 2 stations  $\times$  2 ionization modes); 4) all station-campaign combinations separately (8 datasets: 2 stations  $\times$  2 campaigns  $\times$  2 ionization modes). Non-detects (i. e., imputed low random values) were retained in all datasets.

Since absolute dendrogram heights differed markedly between datasets, we used a depth-based rather than height-based approach to define clusters: clusters were defined as subtrees extending a maximum of five agglomerative steps (branch points) from a target compound. This threshold was derived experimentally from observations of target compounds with similar concentration patterns [3], and typically resulted in compact neighborhoods comprising fewer than 1% of all features. Features within these clusters that exhibited distinct group differences, strong correlations, or notable coefficients of variation (as described in Section 2.6.1) were flagged for structural elucidation.

## 2.9. Structure elucidation

Structural elucidation of flagged features was performed in Compound Discoverer through chemical formula prediction, comparison of experimental and theoretical patterns (isotopologue distributions, adducts, fragmentation spectra), and database matching. Searches included: 1) ChemSpider, based on predicted formulas or molecular weights [21]; 2) mzCloud, using MS and  $MS^2$  data [22]; and 3) an in-house library based on previously analyzed reference standards, matching  $m/z$  and RT. Features without database matches were manually investigated using the NORMAN Database System (<https://www.norman-network.com/nds/>), FOR-IDENT (<https://www.for-ident.org/>), and PubChem (<https://pubchem.ncbi.nlm.nih.gov/>). Ambiguous matches were prioritized based on likelihood of being present in the aquatic environment.

## 2.10. Quality assurance and quality control (QA/QC)

Robust data quality is essential for statistical pattern recognition to minimize false identifications. Quality assurance and quality control

(QA/QC) in non-target analysis is less straightforward than target analysis, as it cannot rely on reference standards or compound-specific internal standards. Although recent publications provide guidance [23–25], the complexity and flexibility of NTA preclude universal standardized procedures. Instead, QA/QC measures must be implemented across the entire workflow, from sample collection to data interpretation [26]. In this study, data quality was monitored through three approaches:

1) **Field blanks** identified potential contamination during sample collection and preparation. Compound Discoverer's automated background removal excluded features with intensities less than five times higher than system and field blanks (Section 2.5). When necessary, blank subtraction was performed prior to statistical evaluation via R. Tentative identifications were manually reviewed for blank occurrence (e.g., triisopropanolamine, Section 3.2).

2) **Isotopically labelled internal standards** (14 ESI+, 3 ESI-) were used in all samples and standards to assess matrix effects and instrument stability. Performance was stable with retention-time drift < 0.2 min and mass accuracy < 1.5 ppm (ESI+) and < 7 ppm (ESI-). Daily (batch-wise) CVs had medians of 6.9% (ESI+) and 13.2% (ESI-), and campaign CVs were at 20–39%. These values validate the statistical thresholds described in Section 2.6.

3) For **NTA validation** key metrics ( $R^2$ , CV) from automatically integrated NTA peak areas were compared with quantitative target analysis. For all six reference compounds evaluated, NTA-derived metrics closely matched target analysis: day-cases without correlation were nearly identical (70 target vs. 72 NTA), and among moderate to strong correlations ( $|R^2| \geq 0.5$ ) > 70% deviated by less than 0.1 (maximum deviation: 0.24). CVs showed high overall agreement.

Overall, these findings reflect the robustness and validity of the applied method. Comprehensive QA/QC results are provided as [supplementary material](#).

### 3. Results and discussion

#### 3.1. Feature prioritization

During the sampling campaigns, 32,373 features were detected. Data processing steps (Section 2.5) reduced this by 82% to 5700 high-quality features through background removal, retention time filtering, and peak quality thresholds (Table 1). Statistical analysis (Section 2.6) identified features with distinct concentration patterns based on significant group differences, water level correlations, and coefficients of variation, yielding 176 prioritized features: 53 in August and 105 in February for ESI+, and 11 in August and 7 in February for ESI-, respectively.

Manual review excluded features with poor peak shape, implausible formula, or unusable fragmentation spectrum, resulting in 101 high-confidence features. Among these, database searches identified 55 ChemSpider matches and 39 mzCloud matches with some overlap. The list included 13 target compounds, of which eight have been described in our previous study [3]: 4-aminoantipyrine, azoxystrobin, carbamazepine, carbendazim, chlortoluron, metformin, metoprolol, and propamocarb; plus nicosulfuron, propyphenazone, sitagliptin, tetrabutylphosphonium, and venlafaxine. Three suspect compounds matched with our in-house library (1H-benzotriazole, 4-methyl-1H-benzotriazole, N-acetyl-4-aminoantipyrine). Forty-one of 101 features had no automated structural proposals.

After excluding targets and suspects, 85 unidentified features remained. The most plausible candidates were selected based on concentration trends, differential analysis (see [supplementary material](#) “Differential Analysis Results”), hierarchical clustering (see [supplementary material](#) “HCA Results”), and environmental plausibility, yielding 53 proposed structures for 34 features. Twenty-eight were commercially available; budgetary constraints limited purchases to 22 reference standards for 17 features (Table 2). Seven compounds were confirmed: ethyl centralite, N-desmethyltramadol, N,N'-

**Table 1**

Overview of the number of features retained after each individual filtering step.

	August		February		Sum
	POS	NEG	POS	NEG	
Total number of features	6318	5171	15,205	5679	32373
Not marked as background (Section 2.5)	2653	2136	8046	2319	15154
Within retention time window (Section 2.5)	2534	1896	7800	1936	14166
Peak rating $\geq 5$ (Section 2.5)	2030	1283	6274	1619	11206
MS <sup>2</sup> data and predicted composition available (Section 2.5)	1285	286	3429	700	5700
Applying statistical criteria (Section 2.6)	53	11	105	7	176
<b>Remaining after manual plausibility review</b>	<b>34</b>	<b>1</b>	<b>61</b>	<b>5</b>	<b>101</b>
Target compounds	4	0	9	0	13
In-house database matches (incl. target compounds)	5	0	11	0	16
<b>Unidentified features</b>	<b>29</b>	<b>1</b>	<b>50</b>	<b>5</b>	<b>85</b>
Online spectral database matches (mzCloud)	8	0	29	2	39
Online chemical structure database (ChemSpider)	20	0	31	4	55
No automated structural proposal	19	1	20	1	41
<b>After manually reviewing unidentified features</b>					
Plausible structures	15	0	35	3	53
Available as Reference Standard	9	0	19	0	28
Purchased as Reference Standard	5	0	17	0	22
<b>Confirmed via Reference Standard</b>	<b>1</b>	<b>0</b>	<b>6</b>	<b>0</b>	<b>7</b>

diphenylguanidine, O-desmethyltramadol, phenylethylmalonamide, tributylphosphine oxide, and triisopropanolamine.

#### 3.2. Identifications

Non-target analysis revealed seven previously unsuspected compounds in the tidal reach of the Elbe River. Below, we summarize their observed dynamics in regard to the studied tidal river section, their most relevant uses (as proxies for plausible sources), general environmental occurrence and behavior, and discuss why their presence matters for riverine water quality assessment.

##### 3.2.1. Phenylethylmalonamide (PEMA; 2-ethyl-2-phenylpropanediamide; CAS 7206-76-0)

This feature occurred constantly with low CV at both stations during August with pronounced negative water level correlation at SH. Peak areas were slightly higher in August than February. Cluster analysis grouped it with WWTP-derived compounds caffeine and carbamazepine. Structure elucidation suggested phenylethylmalonamide (PEMA) and pheneturide as candidates, and PEMA was confirmed by reference standard.

PEMA is the pharmacologically active metabolite of the anticonvulsant primidone but has no independent therapeutic use, making municipal wastewater the primary source to surface waters [27,28]. Field studies indicate PEMA is relatively persistent, showing poor biodegradability and negligible removal during bank filtration [29,30]. It has been detected throughout Berlin's urban water cycle at concentrations ranging from tens to several hundred ng/L in WWTP effluents, surface waters, and bank-filtered groundwater [31,32] but has rarely been identified in other surface waters. Despite its environmental persistence and presumed widespread occurrence as a metabolite of a common pharmaceutical, PEMA is not included in most monitoring programs. Available data are largely restricted to Central Europe, and both photolysis behavior and ecotoxicity thresholds remain unknown.

Table 2

Prioritized features with corresponding reference standards purchased for confirmation, including respective mass-to-charge ratios ( $m/z$ ) and retention times.

Detected		Reference Standard	CAS -RN	$m/z$		RT		Confirmed
Aug	Feb			Feature	RefStd	Feature	RefStd	
X		<b>phenylethylmalonamide</b>	<b>7206-76-0</b>	207.11268	207.11333	5.3	5.3	X
		pheneturide	90-49-3		207.11333		9.6	
X		NNK	64091-91-4	208.10803	208.10858	5.7	5.6	
X		cimaterol	54239-37-1	220.14426	220.14496	6.1	4.5	
X		estradiol valerate	979-32-8	357.24200	357.24295	19.6	NA	
X	X	<b>triisopropanolamine</b>	<b>122-20-3</b>	192.15942	192.15995	4.1	4.1	X
	X	3-aminosalicylic acid	570-23-0	171.07627	154.05040	4.3	NA	
		4-aminosalicylic acid	65-49-6		154.05040		1.6	
		mesalazine	89-57-6		154.05040		2.4	
X	X	<b>1,3-diphenylguanidine</b>	<b>102-06-7</b>	212.11809	212.11875	5.6	5.6	X
		vareniclin	249296-44-4		212.11875		4.8	
X	X	<b>N-desmethyltramadol</b>	<b>73806-55-0</b>	250.17995	250.18068	6.4	6.4	X
	X	<b>O-desmethyltramadol</b>	<b>80456-81-1</b>	250.17995	250.18068	5.1	5.1	X
	X	alprenolol	13655-52-2	250.17995	250.18068	4.8	8.7	
X	X	<b>tributylphosphine oxide</b>	<b>814-29-9</b>	219.18712	219.18775	14.7	14.6	X
X	X	<b>(ethyl) centralite</b>	<b>85-98-3</b>	269.16465	269.16537	16.1	16.0	X
		Michler's ketone	90-94-8		269.16537		15.3	
	X	isoniazid	54-85-3	120.05574	138.06671	5.7	4.3	
	X	pilocarpin	92-13-7	195.11283	209.12898	5.9	4.5	
	X	terazosin	63590-64-7	388.19967	388.19846	8.8	6.5	
	X	nicametate	3099-52-3	223.14394	223.14463	8.9	4.6	
	X	oxibendazole	20559-55-1	250.11838	250.11914	14.1	11.1	

### 3.2.2. Triisopropanolamine (TIPA; 1,1',1''-nitrioltri(2-propanol); CAS 122-20-3)

This feature exhibited relatively constant signals at both stations during both campaigns, with occasional outliers ( $n = 8$ , peak areas at least double the average) and strong negative water level correlations ( $R^2$  up to  $-0.86$ ). Average peak areas were tenfold higher in February. Field blanks contained relevant signals, likely from sampling equipment contamination, necessitating blank subtraction for accurate quantification. However, sample peak areas were at least fivefold higher than blanks levels, confirming environmental presence. Although not clustering with target compounds in HCA, conspicuous patterns and promising spectral matches with Triisopropanolamine (TIPA) prompted confirmation by reference standard.

TIPA is a tertiary alkanolamine widely used in cement, paper, plastic production, and cosmetics [33,34], implying both industrial and domestic pathways to wastewater. Previous studies report TIPA in WWTP effluents and surface waters at low ng/L concentrations [35–37]. While commonly found in effluents in the USA, China, and Central Europe, surface and estuarine water occurrence is sporadic. Environmental fate and ecotoxicity data remain incomplete.

### 3.2.3. N-desmethyltramadol (NDT; CAS 73806-55-0) and O-desmethyltramadol (ODT; CAS 80456-81-1)

Detected with similar abundances during both campaigns, this feature displayed transiently elevated peak areas with negative correlations ( $R^2 \leq -0.5$  on three days) at downstream station SH in February, suggesting temporarily increased inputs. Clustering with WWTP-related pharmaceuticals (carbamazepine, cetirizine, lamotrigine, O-desmethylvenlafaxine) pointed towards wastewater effluents as the source. Reference standards confirmed N-desmethyltramadol (NDT) and identified O-desmethyltramadol (ODT) as an isomeric peak, both were present in all samples. ODT was present in higher abundances in February and exhibited more pronounced intra-day variability.

NDT and ODT are primary metabolites of tramadol, with only ODT retaining pharmacological activity [38]. Emissions of both compounds are dominated by municipal wastewater and hospital discharges. ODT undergoes rapid photodegradation in surface waters while biotic degradation is slow with half-lives around 100 days [39,40]. Comparable degradation studies for NDT are lacking. Both metabolites are widely reported in WWTP effluents and wastewater impacted surface waters at concentrations similar to the parent compound tramadol,

ranging from low ng/L in rivers to  $\mu\text{g/L}$  in effluents [41,42]. Their occurrence across Africa, the Americas, Asia, and Europe highlights global relevance as emerging wastewater tracers.

### 3.2.4. Tributylphosphine oxide (TBPO; CAS 814-29-9)

Significant negative water level correlations ( $R^2 \leq -0.5$ ) at upstream station BU on five sampling days, combined with otherwise low variability and higher average peak areas compared to SH, distinguished this feature as likely originating from upstream sources. HCA placed it alongside metamitron-desamino (herbicide metabolite) and propylphenazone (anti-inflammatory drug). Tributylphosphine oxide (TBPO) was confirmed by reference standard.

TBPO is an organophosphorus compound used as catalyst and synergist in industrial or research applications [43,44], and potentially a transformation product of organophosphorus flame retardants or ionic liquids. Physicochemical properties and ecotoxicity predictions suggest environmental relevance [45]. Despite sparse application information, two environmental monitoring studies detected TBPO: along the Rhine and tributaries at low ng/L in 2 of 60 surface water samples at industrially influenced locations [46], and in a river impacted by major industrial manufacturing in Eastern China [45]. These detections and industrial use profile suggest specific manufacturing discharge sources. Its identification in the tidal Elbe warrants follow-up sampling near suspected point sources and inclusion in targeted screening lists.

### 3.2.5. Ethyl centralite (N,N'-diethylcarbanilide; 1,3-Diethyl-1,3-diphenylurea; CAS 85-98-3)

Temporal and spatial dynamics remarkably similar to the short-term point source entries of plant protection agents described previously [3] made this feature particularly noteworthy. During February, peak areas were similar at both stations initially, followed by distinct increases upstream at BU and two days later less pronounced downstream at SH. Days with rising peak areas partially showed strong negative water level correlations, consistent with tidally influenced transport. In August, the feature showed no strong water level correlations and abundance was higher at downstream station SH. HCA grouped it with fungicide cyproconazole and herbicide metabolites (desphenylchloridazon, methyl-desphenylchloridazon, terbuthylazine-desethyl). As plausible structure candidates, ethyl centralite and Michler's ketone were suggested, with ethyl centralite confirmed through reference standard.

Ethyl centralite is primarily used as stabilizer and burning-rate

moderator in smokeless propellants (gunpowder). Most environmental studies report its presence in soil and groundwater near military facilities [47,48], though [49] suggested alternative use as pesticide additive. Despite low water solubility and high  $\log K_{ow}$  limiting leaching potential [50], sporadic detections in German and Australian surface waters (<1 ng/L) and river sediments have been reported [49,51,52]. Given the absence of relevant military facilities nearby, the observed pattern likely points to application-related sources, potentially as pesticide additive.

### 3.2.6. 1,3-Diphenylguanidine (DPG; CAS 102-06-7)

Opposing water level correlation patterns at the two stations, consistently positive at BU and negative at SH during August, provided indication of a primary source within Hamburg's metropolitan region. In February, abundances were approximately fivefold higher than August with less consistent correlation patterns, though significant negative correlations at SH again suggested local inputs upstream of SH. HCA grouped it with pharmaceuticals and metabolites commonly introduced via municipal wastewater (lidocaine, methocarbamol, N-formyl-4-aminoantipyrine, phenazone). Structure elucidation identified 1,3-diphenylguanidine (DPG) and varenicline as the most probable candidates, of which DPG was confirmed using a reference standard.

DPG is widely used as rubber vulcanization accelerator, primarily introduced through tire wear washed off during stormwater events, with minor inputs from elastomeric materials in infrastructure [53–55]. Observed concentrations range from hundreds of  $\mu\text{g/L}$  in urban stormwater to low  $\text{ng/L}$  in large rivers and rural waters [56]. Continental-scale surveys report widespread occurrence with median river concentrations of tens of  $\text{ng/L}$  [57,58]. WWTP removal of DPG is negligible, with some studies reporting negative removal efficiencies, suggesting in-plant formation [59]. August patterns point to major input from Hamburg's urban area. As no significant precipitation occurred during this period, WWTP effluent is the most likely source. February's variable patterns alongside minor rainfall events suggest additional diffuse contributions via stormwater runoff.

### 3.3. Tidal influence on pollutant distribution patterns

Table 3 summarizes key tidal and hydrological parameters derived from the water level records at both sampling stations (Fig. 2), providing a mechanistic basis for interpreting the observed contaminant patterns.

Despite a 3.2-fold difference in river discharge between campaigns, the mean tidal range changed only moderately from August to February. The tidal asymmetry (expressed as the flood-to-ebb duration ratio) shifted between August and February, with shorter, more intense flood phases and longer ebb phases under higher discharge conditions in February. This asymmetry was consistently less pronounced at SH, reflecting the influence of the wider, morphologically complex harbor area on tidal propagation. The tidal wave propagated from BU to SH (19 km) with a high-water lag of 37 min in August and 25 min in February, while the low-water lag was substantially longer in both campaigns, consistent with slower ebb drainage through the complex

**Table 3**  
Key tidal and hydrological parameters.

	August		February	
Average river discharge (Neu Darchau) [ $\text{m}^3/\text{s}$ ]	228		739	
Flood phase lag between SH and BU [min]	37		25	
Ebb phase lag between SH and BU [min]	57		52	
Flood wave propagation speed [km/h]	24		29	
	<b>BU</b>	<b>SH</b>	<b>BU</b>	<b>SH</b>
Mean tidal range [cm]	344	353	368	389
Flood duration [h]	5.2	5.6	4.9	5.4
Ebb duration [h]	7.2	6.9	7.5	7.1
Tidal time asymmetry (flood to ebb ratio)	0.72	0.81	0.65	0.76

channel geometry of the Hamburg port area.

Combining these hydrodynamic characteristics with the results of the present NTA study and the target screening reported in Schneider et al. [3], three general tidal transport archetypes can be distinguished. First, continuously emitted, persistent compounds such as carbamazepine and PEMA exhibited low intra-day variability and minimal water-level correlation. Tidal mixing distributes these compounds throughout the river system, while their environmental persistence renders them insensitive to the extended residence times caused by tidal oscillation. The most pronounced concentration differences for these compounds occurred between campaigns, with higher August concentrations resulting from reduced dilution at lower discharge. Second, episodically released compounds such as ethyl centralite and propamocarb displayed transient concentration peaks propagating from BU to SH with attenuation and temporal broadening. The asymmetric phase lag implies that contaminant plumes oscillate back and forth rather than simply traveling downstream, thereby repeatedly passing the monitoring stations before net discharge carries them seaward. This explains the recurring, tidally modulated peaks observed for these compounds, which conventional grab sampling would likely miss or misinterpret as multiple independent contamination events. Third, transformation-susceptible compounds such as O-desmethyltramadol and 4-aminoantipyrine [3] showed additional variability superimposed on the tidal signal. For these compounds, the extended residence time imposed by tidal oscillation enhances exposure to degradation processes, an effect particularly pronounced under low-discharge summer conditions, where reduced net downstream displacement coincides with elevated temperatures, increased sunlight exposure, and enhanced microbial activity.

Compound-specific physicochemical properties modulate these archetypes further. For highly water-soluble, polar compounds with low sorption affinity (e.g., PEMA, metformin), tidal oscillation primarily drives spatial redistribution in the dissolved phase. By contrast, compounds with higher sorption potential may interact with tidally driven sediment resuspension, a process potentially enhanced at SH, where more pronounced slack-water conditions are reflected in higher conductivity, TOC, and turbidity levels. A different concentration of suspended sediments at the two sampling stations may contribute to the spatial concentration gradients observed for less polar analytes such as tributylphosphine oxide, though quantifying this contribution would require complementary sediment sampling.

Principal component analysis confirmed that seasonal differences constitute the dominant source of variation in overall chemical composition, far exceeding the influence of sampling station or tidal phase (see [supplementary material "PCA Analysis"](#)).

## 4. Conclusions

This study demonstrates that spatiotemporal pattern-based non-target analysis can effectively identify unsuspected organic micro-pollutants in tidal rivers using accessible analytical methods and general statistical tools. By applying univariate statistical metrics and hierarchical cluster analysis to high-frequency HPLC-HRMS data from the tidal Elbe River, we identified seven compounds that are not part of any routine monitoring program. The entire workflow, from sample collection through compound identification, was implementable by a single analyst using standard regulatory monitoring equipment and general statistics, demonstrating that comprehensive chemical characterization of complex tidal systems is operationally feasible for regulatory monitoring laboratories without extensive personnel resources or specialized statistical expertise.

The seven compounds identified span pharmaceuticals and their metabolites, industrial and consumer product additives, and niche industrial or military chemicals. Their collective behavior in the tidal Elbe illustrates three recurrent themes critical for understanding contaminant dynamics in tidal rivers. First, PEMA and tramadol metabolites

demonstrate conservative transport of polar, persistent wastewater markers. These compounds maintain relatively stable daily and seasonal intensities, indicating continuous anthropogenic inputs. Elevated levels at the downstream station SH compared to upstream BU plus subtle negative tidal correlations at SH reveal relevant sources within Hamburg's metropolitan region. Second, episodic, source-proximal pulses from industrial activities, traffic-related inputs, or agricultural applications, exemplified by DPG, TBPO, and ethyl centralite, demonstrate that point sources near monitoring stations can create transient contamination events that conventional monitoring approaches would likely miss. Third, the behavior of O-desmethyltramadol illustrates how tidal oscillation can amplify environmental degradation by prolonging the exposure of susceptible compounds to photolysis and microbial processes. For compounds prone to sampling artifacts such as TIPA, robust field blank controls proved indispensable for accurate pattern recognition and interpretation. These compound-specific observations align with three general tidal transport archetypes (conservative mixing, episodic plume dispersion, and transformation-modulated transport) that emerge when the NTA results are integrated with the tidal hydrodynamic parameters recorded at both stations. While the relative contribution of tidal dynamics versus other factors cannot be fully disentangled with two discrete sampling campaigns, complete factorial attribution is not a prerequisite for exploiting these patterns for non-target identification. The tidally driven intra-day dynamics observed here are unique to tidal river systems, and recognizing the distinct transport archetypes they produce is essential for both interpreting monitoring data and designing effective non-target screening strategies in tidal environments.

A central finding of this work is that effective short-term pattern recognition in tidal rivers does not require sophisticated normalization procedures or advanced statistical methods. Our approach successfully identified compounds based on intra-day concentration patterns without internal standard normalization, as validated through parallel target analysis. While variability over multiple days proved too high for reliable pattern detection of subtle concentration shifts, intra-day data exhibited sufficient consistency for robust statistical analysis. This finding has important practical implications: monitoring programs focusing on long-term trends can straightforwardly be complemented with high-frequency sampling to capture highly relevant short-term dynamics within tidal rivers. The concentration patterns of compounds identified through NTA were not visually striking compared to the distinct tidal-related peaks observed for certain target analytes in our previous study. Nevertheless, the statistical framework successfully prioritized these features among thousands of detected signals, demonstrating that subtle but consistent patterns can be as environmentally relevant as dramatic concentration fluctuations. This reinforces the value of systematic statistical evaluation over subjective visual inspection of chromatographic data and compound patterns.

The findings from this study carry several important implications for water quality monitoring in tidal rivers and similar dynamic aquatic systems:

- High-frequency sampling (one composite sample per hour) captures tidal-specific dynamics that conventional approaches miss. Ebb-exclusive, monthly or weekly sampling strategies systematically under-represent episodic inputs, especially from industrial discharges, traffic-related sources, and agricultural activities. Tidal rivers require sampling designs that account for ebb and flood cycles, and concurrent water level recording enables mechanistic interpretation of the resulting concentration patterns.
- Multi-station sampling strategies enable approximate source localization without extensive spatial surveys. Two strategically placed monitoring locations can distinguish between upstream, located in between, and downstream pollution sources through pattern comparison. For instance, opposing correlation patterns at different stations, as recorded for DPG, indicate sources located between monitoring points.

- Intra-day pattern analysis provides robust results without internal standard normalization. For monitoring programs with stable instrumentation, batch-wise statistical evaluation of high-frequency data can identify concentration patterns reliably without extensive internal standard corrections. This simplification reduces analytical overhead, data processing complexity, and most importantly risk of erroneous data correction.
- Pattern-based feature prioritization using general statistics can effectively identify relevant unknowns. Hierarchical cluster analysis combined with simple correlation and variance metrics successfully prioritized environmentally relevant features from thousands of detected signals. Advanced chemometric methods or machine learning may offer incremental improvements and a more comprehensive evaluation, but are not prerequisites for successful application of NTA in tidal river systems.
- Quality control must address sampling artifacts and low-intensity features. Field blank monitoring is critical when working with compounds that may leach from sampling equipment or appear as background contamination. Automated quality flags for mis-integrated peaks, particularly at low signal intensities, would substantially improve confidence in pattern recognition for near-detection-limit features.
- Transferable frameworks benefit global tidal river monitoring. The statistical methods and sampling strategies developed for the Elbe River are directly applicable to other tidal systems worldwide. Major tidal rivers such as the Thames, Seine, St. Lawrence, and numerous tropical estuaries face similar challenges in characterizing pollutant dynamics and would benefit from pattern-based NTA approaches.

The transferability of this approach to other tidal river systems represents perhaps its greatest value. By demonstrating that comprehensive chemical characterization can be achieved with standard equipment and software, and basic data evaluation tools, this work provides a replicable template for regulatory agencies and research institutions globally. Furthermore, the increasing accessibility of digital tools, most notably generative artificial intelligence and large language models, is democratizing data analysis capabilities that were previously restricted to specialists. Researchers and regulatory agencies without extensive statistical or programming expertise can now implement sophisticated workflows using freely available resources, fundamentally expanding the feasibility of comprehensive chemical monitoring. Future efforts should focus on integrating NTA into routine monitoring programs, developing standardized quality control procedures, and expanding analyte libraries to include the emerging contaminants identified through pattern-based discovery. As tidal rivers worldwide face increasing anthropogenic pressures from urbanization, industrialization, and agricultural intensification, accessible monitoring tools become ever more critical for protecting these vital ecosystems and the human populations depending on them.

### Environmental Implication

Tidal rivers worldwide face increasing contamination pressures yet remain poorly understood. This study reveals that conventional tidal-river monitoring systematically misses contamination events where contaminant concentrations oscillate with tidal cycles. We identified and characterized seven micropollutants, several of which have rarely been reported in any surface waters. The pattern-based discovery approach distinguishes diffuse versus point-source pollution, enabling targeted mitigation strategies. Importantly, the accessible workflow enables comprehensive hazard surveillance in resource-limited settings. Given that major tidal rivers globally support billions of people, improved assessment of substance dynamics in tidal river systems is critical for protecting human and environmental health.

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## CRediT authorship contribution statement

**Jörn Logemann:** Writing – review & editing, Validation, Supervision, Funding acquisition, Conceptualization. **Klaus Kümmerer:** Supervision, Project administration, Conceptualization. **Michael Radke:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization. **Jonas Richard Leonhard Schneider:** Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

## Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used Claude (Anthropic) and ChatGPT (OpenAI) in order to develop the R-code for statistical analysis as well as to improve the language of this work. After using these tools, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jhazmat.2026.142000.

## Data availability

Data will be made available on request.

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