From:	[redacted]
To:	Hampshire Water Project
Subject:	HWTWRP – Water Environment Hearing – new research papers
Date:	02 November 2026 22:24:37
Attachments:	Persistent pharmaceuticals and their transformation Products_ Oct_2026.pdf Accumulation of PFAS in reservoirs_Zhao-Feng Guo et al_2026.pdf

HWTWRP - WA010002 – Examination Process – Water Environment Hearing – XXX

Dear sir/ madam,
When speaking at the Water Environment Hearing on 12 November our community speakers will make reference to;

- The persistence of pharmaceuticals and their Transformation Products.
- The risk of persistent PFAS & other contaminants building up in the Havant Thicket Reservoir.

To substantiate these concerns, we have attached two recent research papers which confirm that the risks being raised by the community are valid and as a result require further assessment and modelling before informed judgements can be made about the impact of the HWTWRP.

1. Persistent pharmaceuticals and their transformation Products: From persistence mechanisms to AI-assisted integrated treatment for safe water reuse (Shomar & Domingo, 2026)

2. Asymmetrical contamination of anionic PFAS across global freshwater reservoirs (Guo et al, 2026)

The speakers do not anticipate asking for this research to be displayed at the hearing, but we felt that it was important to provide these papers as examples of research to substantiate the concerns being raised at the hearing.

Yours sincerely,

[redacted]

On behalf of Water Matters and other community representatives
PINS registration identification number is: [redacted]

Water Research 289 (2026) 124940

Contents lists available at ScienceDirect

Water Research

journal homepage: www.elsevier.com/locate/watres

Asymmetrical contamination of anionic PFAS across global freshwater reservoirs

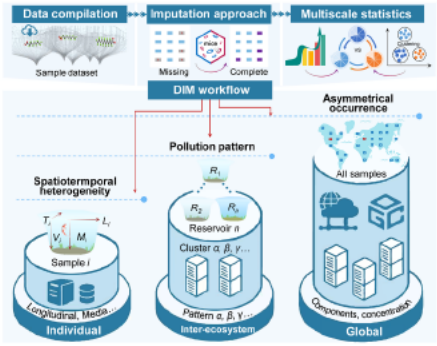
Zhao-Feng Guo [a], Mohamed Ateia [b,f], Edoardo Borgomeo [c], Wiebke J. Boeing [d], Daniel Malnes [e], Yu-Qin He [a], Dong Liu [a], Yao-Yang Xu [a,*]

[a] State Key Laboratory of Regional and Urban Ecology, Zhejiang Key Laboratory of Pollution Control for Port-Petrochemical Industry, Ningbo Observation and Research Station, Institute of Urban Environment, Chinese Academy of Sciences, Xiamen 361021, China
[b] Department of Chemical and Biomolecular Engineering, Rice University, Houston, TX 77005, USA
[c] Department of Engineering, University of Cambridge, Cambridge CB2 1PZ, United Kingdom
[d] Department of Fish, Wildlife & Conservation Ecology, New Mexico State University, Las Cruces, NM 88003, USA
[e] Helsinki Commiss HELCOM, Baltic Marine Environm Protect Commiss, Helsinki 00160, Finland
[f] AECOM, Dallas, TX 75240, USA

HIGHLIGHTS

- Global PFAS patterns in reservoirs were resolved using a new DIM workflow.
- Three contamination paradigms for PFAS in freshwater reservoirs were defined.
- PFAS partitioning was shaped by source types, hydrodynamics, and morphology.
- Short-chain PFAS dominance signals regulatory substitution and deposition.
- Encourage environmental data integration and consider scale dependence.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Per-and polyfluoroalkyl substances
Freshwater reservoirs
DIM workflow
Asymmetrical occurrence
Contamination paradigms

ABSTRACT

Freshwater reservoirs worldwide are increasingly threatened by contamination from anionic per- and polyfluoroalkyl substances (PFAS), yet the fragmented nature of existing data limits a comprehensive understanding of their distribution and sources. Here, we develop a workflow of Data compilation, Imputation approach, and Multiscale statistics (DIM) to synthesize and quantify anionic PFAS occurrence across spatial scales. By compiling sparse data from 813 samples across 74 reservoirs spanning five continents and applying a tested multiple imputation by chained equations-based method to construct an anionic PFAS concentration matrix, we identify three distinct contamination paradigms. Perfluorooctanoic acid (PFOA)-dominated paradigm typifies early-stage contamination linked to domestic and industrial discharges. PFOA and perfluorooctane sulfonate (PFOS)-co-dominated paradigm signals ongoing accumulation from mixed sources. Perfluorobutanoic acid (PFBA)-dominated paradigm reflects long-term buildup under partial abatement, driven by dry deposition, industrial inputs, and internal cycling. These paradigms reveal marked asymmetry in anionic PFAS contamination across global

* Corresponding author.
E-mail address: yyxu@iue.ac.cn (Y.-Y. Xu).

https://doi.org/10.1016/j.watres.2025.124940
Received 26 June 2025; Received in revised form 26 October 2025; Accepted 8 November 2025
Available online 10 November 2025
0043-1354/© 2025 Elsevier Ltd. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

reservoirs, shaped by source dominance and contamination history. The DIM workflow enables data robustness and integrative reliability, providing a transparent framework for scale-aware monitoring and developing tailored PFAS management strategies that reflect the spatial heterogeneity and data limitations of reservoir contamination worldwide.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are persistent environmental contaminants of global concern due to their adverse effects on ecosystems and human health (Rahman et al., 2014; Ateia and Scheringer, 2024; Tokranov et al., 2024). Their extensive use in industrial and consumer applications, combined with global production exceeding one million tons annually, has led to widespread environmental dissemination across the entire product lifecycle from manufacturing to disposal (Calafat et al., 2007; Evich et al., 2022; Scheringer, 2023). Among the numerous PFAS subclasses, anionic species, particularly perfluoroalkyl carboxylic acids and sulfonates, dominate environmental detection profiles, especially in aquatic ecosystems (Xiao et al., 2023), with long-chain PFAS ($\geq$ C7 perfluoroalkyl chains) drawing regulatory scrutiny due to their elevated toxicological profiles and bioaccumulative potential (Pelch et al., 2019; Ng et al., 2021; Arp et al., 2023).

Despite increasing regulatory and scientific interest, efforts to characterize anionic PFAS contamination remain hampered by fragmented and geographically uneven datasets, inconsistencies in analytical methodologies, and divergent monitoring frameworks (Johnson et al., 2020; Cordner et al., 2024). The sheer diversity of PFAS components (i.e., number of variables) further complicates integrative assessments, resulting in high-dimensional, sparse datasets that obscure meaningful ecological patterns and impede comparative analysis (Altman and Krzywinski, 2018). Moreover, overlooking key ecosystem-specific attributes, such as ecosystem typologies or spatial gradients, can obscure patterns and bias interpretations, limiting both mechanistic understanding and policy relevance of PFAS assessments.

Reservoirs are artificial lakes formed by impounding water with dams. They fulfill diverse human needs while representing critical interfaces between engineered and natural systems. Their construction has globally fragmented river networks, disrupted hydrological connectivity, and altered downstream material transport (Grill et al., 2019), leading to enclosed environments that are particularly prone to contaminant accumulation. At the same time, their role as drinking water sources and aquatic habitats makes reservoirs particularly vulnerable to pollution from anthropogenic activities within their catchments (Holzer et al., 2008; Janssen et al., 2020). Given this vulnerability, reservoirs also serve as model ecosystems whose structural and functional heterogeneity offers a unique opportunity to investigate contaminant behaviors across spatiotemporal and environmental dimensions, including longitudinal gradients (e.g., distance to dam), vertical stratification, and cross-media interactions (e.g., water, sediment, biota) (Zarfl et al., 2015; Maavara et al., 2020; Janssen et al., 2021). However, understanding PFAS behavior in such systems remains limited by mismatches between the spatial scales of contamination processes and the scales at which data are collected (Messager et al., 2016; Maavara et al., 2017; Spake et al., 2022).

Advances in data science and environmental monitoring have increased the availability of reservoir PFAS data; however, their effective integration remains constrained by challenges such as data heterogeneity, missing values, and structural inconsistencies. Addressing these barriers requires a framework capable of (i) harmonizing disparate datasets, (ii) minimizing imputation bias, and (iii) supporting multiscale inference. In this context, the structured integration and effective processing of raw data, tailored to the characteristics of the data and analytical requirements, are critical for data reuse, information transformation, and fostering innovation(Kosnik et al., 2022a).

Given the multi-component characteristics and data sparsity of reservoir PFAS, prioritizing dominant compounds offers a pragmatic solution to reduce dimensionality, mitigate data sparsity, and strengthen the reliability of subsequent analyses (Altman and Krzywinski, 2018). Among imputation strategies, Multiple imputation by chained equations (MICE) stands out for its robustness and flexibility, particularly in datasets with small to moderate sample sizes ($n < 30{,}000$), outperforming deep learning techniques such as Generative Adversarial Interpolation Networks in terms of stability and accuracy (Sun et al., 2023). Critically, MICE maintains the intrinsic statistical structure of the data without imposing strong parametric assumptions, making it a widely accepted tool across disciplines such as ecology, environmental science, and medicine (Nakagawa and Freckleton, 2008; Ellington et al., 2014; Chang et al., 2020). When applied within consistent spatial or methodological frameworks, this approach ensures coherence in the underlying distributions, thereby improving cross-study comparability and enhancing data reuse (Spake et al., 2021). This approach is essential to elucidate the spatiotemporal heterogeneity of PFAS and to unravel the causal relationships that are obscured across varying spatial and temporal scales (Kosnik et al., 2019).

Here, we develop a data-driven workflow of Data compilation, Imputation approach, and Multiscale statistics (DIM) to integrate fragmented PFAS datasets and elucidate contamination patterns across global freshwater reservoirs. We compiled 813 sample data from 74 reservoirs spanning five continents and employed MICE to construct a comprehensive PFAS concentration matrix. Through multiscale statistics, we addressed three questions: (i) What is the spatial occurrence of PFAS contamination from global to intra-reservoir scales? (ii) What are the dominant PFAS contamination paradigms and their potential sources? (iii) What knowledge gaps persist, and how can future research improve surveillance and mitigation? To assess the global representativeness of our dataset, we compared the key characteristics of the study reservoirs with those of freshwater systems in the HydroLAKES global inventory. Despite an uneven geographic distribution, the study reservoirs encompass wide gradients in catchment area, surface area, storage capacity, and mean depth (Fig. S1), capturing the broad variability observed in reservoir systems worldwide. The DIM framework thus provides a scalable strategy for synthesizing heterogeneous contaminant datasets and a foundation for global PFAS monitoring and management efforts.

2. Materials and methods

We constructed a DIM workflow for reservoir PFAS, which is divided into three segments: Data compilation (D, Fig. 1a), Imputation approach (I, Fig. 1b), and Multiscale statistics (M, Fig. 1c). We define 'Data compilation' as the process of literature screening, data extraction, and data sieving to obtain usable data and facilitate subsequent data analysis. 'Imputation approach' is a multiple imputation method, specifically selected to address the missing data in PFAS components, tailored to the underlying data structure and characteristics. 'Multiscale statistics' is a process of multivariate statistical analysis based on three different scales: global, reservoir level, and intra-reservoir to integrate existing research results and systematically understand PFAS pollution in reservoirs. This workflow enables robust synthesis and interpretation of heterogeneous and incomplete PFAS data.

2.1. Data compilation

Reservoir PFAS data were collected through a structured review of

peer-reviewed literature indexed in Web of Science and Scopus databases on June 5, 2024. The search strategy targeted articles with the terms: TITLE-ABS-KEY = ("reservoir" OR "dam") AND ("perfluorocarbons" OR "polyfluorinated" OR "perfluorinated" OR "perfluorochemicals" OR "polyfluoroalkyl" OR "perfluoroalkyl"). We retrieved and downloaded a total of 190 documents and added 5 more articles that we found in the reference sections of some of the original 190 documents. Inclusion criteria required direct quantification of PFAS concentrations in reservoirs. Studies that aggregated data across multiple reservoirs or time points were excluded to preserve spatiotemporal resolution. After removing duplicates and applying screening criteria, 43 studies were retained for data extraction (Fig. 1a).

From these, we compiled 813 samples representing 74 distinct reservoirs (Table S1). The dataset comprises three principal components: (i) quantified concentrations of individual components of PFAS; (ii) spatial-temporal sampling metadata (geographic coordinates, sampling depth, and collection date); and (iii) basic reservoir characteristics, including reservoir capacity, watershed catchment area, surface area, water level, mean depth and hydraulic residence time. Primary data were extracted through multimodal acquisition from textual content, tabular data, and graphical representations, with figure-based data digitized using GetData Graph Digitizer (v2.26) under quality control protocols. Geospatial coordinates for unspecified sampling locations were georeferenced using Google Earth™ based on schematic maps presented in source publications. Supplementary reservoir characteristics were cross-validated through triangulation with external

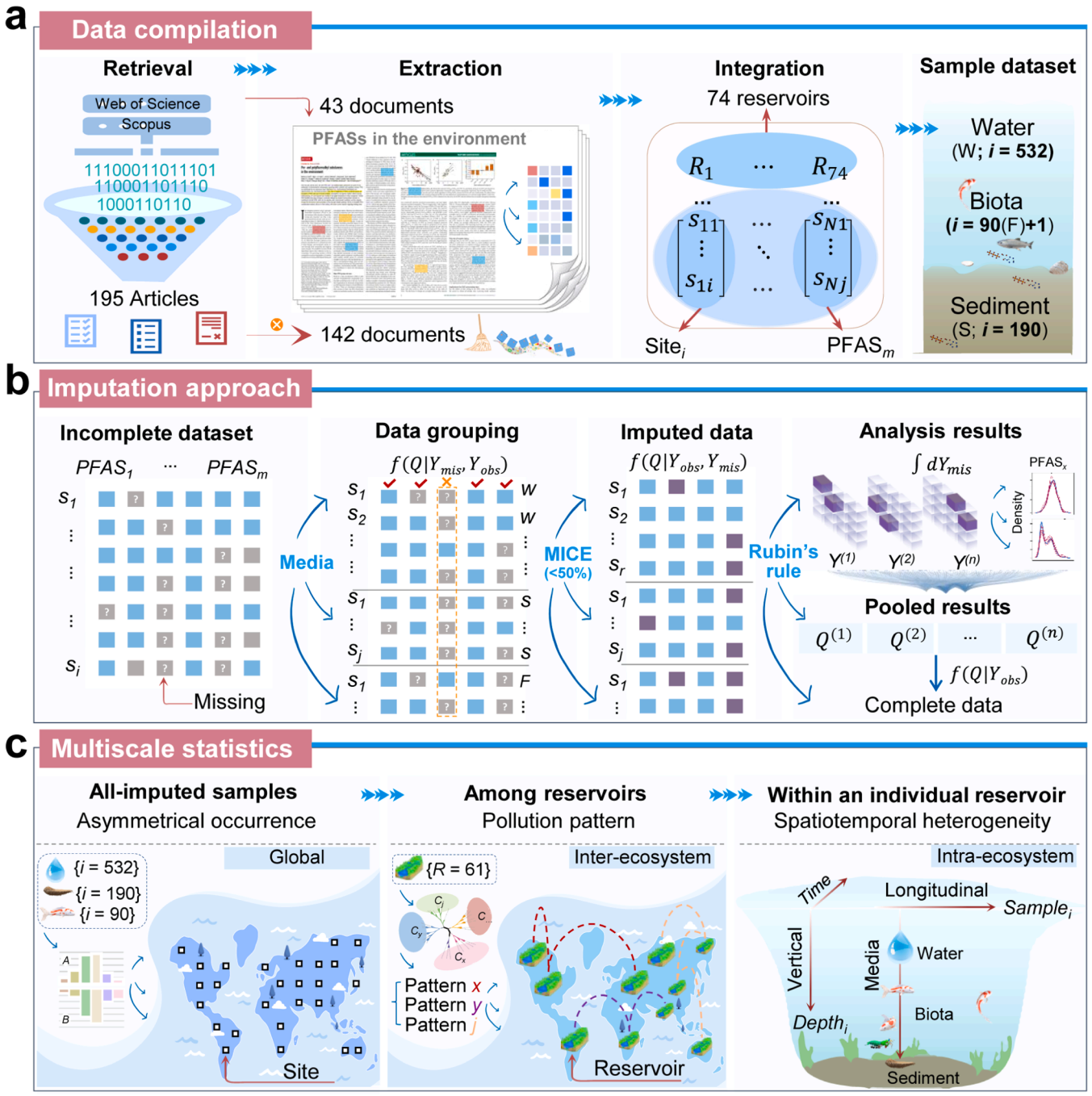


Fig. 1. The DIM workflow. (a) Data compilation; (b) Imputation approach; (c) Multiscale statistics. Some studies have investigated a variety of environmental media. Some of the reservoirs were investigated in different studies with different environmental media.

hydrological databases and secondary literature sources.

Analytical measurements of individual components of PFAS below instrument detection limits (LOD) were treated as left-censored data and assigned zero values. For interval-censored observations between LOD and limit of quantification (LOQ), concentrations were imputed as LOQ/2 following established environmental chemistry protocols. Samples extracted from 74 reservoirs were further classified by environmental media—water ($n = 481$ from 56 reservoirs), sediment ($n = 190$ from 13 reservoirs), fish tissue ($n = 90$ from 21 reservoirs), and invertebrate tissue ($n = 1$ from 1 reservoir). Most reservoirs were sampled across multiple environmental media. The reservoirs were located in/around 60 different cities, spanning five continents. The sampling sites were located in Asia (43 reservoirs), North America (13), Europe (10), Africa (5), and Oceania (3).

2.2. Imputation approach

Missing values in the compiled PFAS dataset were addressed using Multiple imputation by chained equations (MICE), a robust method suited to small or moderate-sized, multivariate environmental datasets with incomplete entries. Of the 30 detected PFAS components, 14 had missing rates below 50 % across matrices and were selected for imputation (Murray, 2018). These 14 PFAS represented compounds with detection frequencies exceeding 50 % across all reservoir datasets, ensuring that each was included as a target analyte in at least part of the compiled studies. Thus, missing entries among these components reflected random non-detects or unreported values rather than exclusion from analytical target lists.

MICE approach presupposes that the complete dataset P(Y|θ) is composed of randomly sampled observations from a multivariate distribution $Y(n \times f)$ encompassing f variables, wherein θ is an unknown parameter that governs the distribution of Y (van Buuren and Groothuis-Oudshoorn, 2011). The observed part of Y is Y^{obs}. With θ distribution known, data imputation is executed by sampling from the conditional distribution P(Y|θ) to address the missing values. The posterior distribution of θ is estimated via iterative Gibbs sampling (Eqs. (1), 2, 3, and 4):

$$\theta_1^{*(t)} \sim P\left(\theta_1 \middle| Y_1^{obs}, Y_2^{(t-1)}, \ldots, Y_p^{(t-1)}\right), \tag{1}$$

$$Y_1^{*(t)} \sim P\left(Y_1 \middle| Y_1^{obs}, Y_2^{(t-1)}, \ldots, Y_p^{(t-1)}, \theta_1^{*(t)}\right), \tag{2}$$

$$\theta_p^{*(t)} \sim P\left(\theta_p \middle| Y_p^{obs}, Y_1^{(t)}, \ldots, Y_{p-1}^{(t)}\right), \tag{3}$$

$$Y_p^{*(t)} \sim P\left(Y_p \middle| Y_p^{obs}, Y_1^{(t)}, \ldots, Y_p^{(t)}, \theta_p^{*(t)}\right), \tag{4}$$

Where $Y_j^{(t)} = \left(Y_j^{obs}, Y_j^{*(t)}\right)$ for the t cycle when the j time fills the variable.

To address each instance of missing data, imputations were performed, thereby generating $m = 100$ complete datasets. Each chain underwent 50 preliminary iterations before recording the imputation outcomes, thereby enhancing the reliability and convergence of the imputed chains. Following the multiple imputation procedure, the results from all imputed datasets were synthesized using Rubin's method, which integrates the uncertainty inherent in the imputations to provide comprehensive statistical estimates. The accuracy of the imputed estimates was assessed by evaluating the Monte Carlo Error (MCE) post-imputation, ensuring that the MCE was maintained below 10 % of the standard error of the estimates (Eqs. (5) and 6). This threshold confirms that the imputation introduces an error magnitude deemed acceptable relative to the variance of the estimates.

$$\overline{\alpha} = \sum_i^m \widehat{\alpha}_i \Big/ m, \tag{5}$$

$$MCE = \sqrt{Var(\widehat{\alpha}_j)/m}, \tag{6}$$

The convergence and stability of the MICE imputations were evaluated using MCE analysis (Text S1). All MCE values were below 10 % SE, confirming the reliability of the imputation results. The imputed dataset ($\sum_{14}$PFAS) was subsequently used for spatial visualization and pattern analysis across multiple environmental media and geographical scales (see Section 2.3).

2.3. Multiscale statistics

Spatial patterns and PFAS compositional profiles were examined across three analytical scales: global, inter-ecosystem, and intra-ecosystem (Fig. 1c). At the all-imputed sample level, ArcGIS was used to create maps to demonstrate global distribution of PFAS concentrations and their components. Inter-media comparisons of PFAS profiles (water, sediment, biota) were performed using chord diagrams.

To find patterns of PFAS contamination, PFAS components from different reservoir waters were clustered using Ward's method in agglomerative hierarchical clustering (Altman and Krzywinski, 2017). The similarity among water samples was quantified using the squared Euclidean distance, enabling the construction of a distance matrix that facilitated the subsequent computation of inter-sample similarity within matrix R (Eq. (7)). Matrix R encompasses concentrations of p PFAS components ($p = 14$) across n reservoirs. The similarity S_{jk} between samples y_{ni} and y_{nk} is quantified as per Eq. (8):

$$R_n = \begin{bmatrix} r_{11} & r_{12} & \cdots & r_{1p} \\ r_{21} & r_{22} & & r_{2p} \\ \vdots & \vdots & \ddots & \vdots \\ r_{n1} & r_{n2} & \cdots & r_{np} \end{bmatrix}, \tag{7}$$

$$S_{ik} = 1 \quad \frac{\sum_n |y_{ni} \quad y_{nk}|}{\sum_n (y_{ni} + y_{nk})}, \tag{8}$$

A Geodetector model was used to assess effects of geographical location, sampling depth, and reservoir characteristics (reservoir catchment area, surface water area, reservoir capacity, mean depth, and hydraulic residence time) on differences in PFAS concentration distributions among reservoirs and to evaluate interactions among these factors (Z.F. Guo et al., 2021). Calculating and comparing the q-value of each factor and the q-value of the two factors superimposed on each other, respectively, allows you to determine whether or not there is an interaction of the factors. The q-value was calculated as follows Eqn. (9):

$$q = 1 \quad \frac{\sum_{h=1}^{L} N_h \sigma_h^2}{N\sigma^2}, \tag{9}$$

Where $h = 1, \ldots, L$ represents the classifications of individual factors. N_h and N denote the number of classifications in class h and the total, respectively. σ_h^2 and σ^2 represent the variance of the PFAS distribution of class h and the total, respectively. A larger q-value indicates a greater explanatory power of the potential factor regarding the spatial differentiation of PFAS.

Within reservoirs, we used ANOVA or t-test to assess effects of stratified sampling, seasonal variation on PFAS concentrations, and diversity of PFAS components (Fig. 1c). The latter was used to test for variance in cases of heterogeneity of variance. Before quantifying distance-decay relationship, Mantel tests were used to assess correlation between PFAS compositional similarity (1-Bray-Curtis) and geographical distance. We used ANOSIM analysis (Analysis of Similarities) with the vegan package in R version 3.5.3 for testing the similarity of PFAS components between environmental media. A *p-value* of <0.05 was considered significant.

3. Results and discussion

3.1. Global asymmetry of PFAS occurrence

PFAS are ubiquitously present in freshwater reservoirs worldwide, yet their reported environmental occurrence is not uniform. Analysis of 30 detected PFAS compounds across water, sediment, and fish tissues from 74 reservoirs reveals pronounced spatial and media-specific asymmetries (Fig. 2 and Table S1). Here, "asymmetrical contamination" denotes these unequal PFAS occurrence and composition across spatial scales and environmental media, reflecting differences in discharge sources, physicochemical properties, and persistence. While

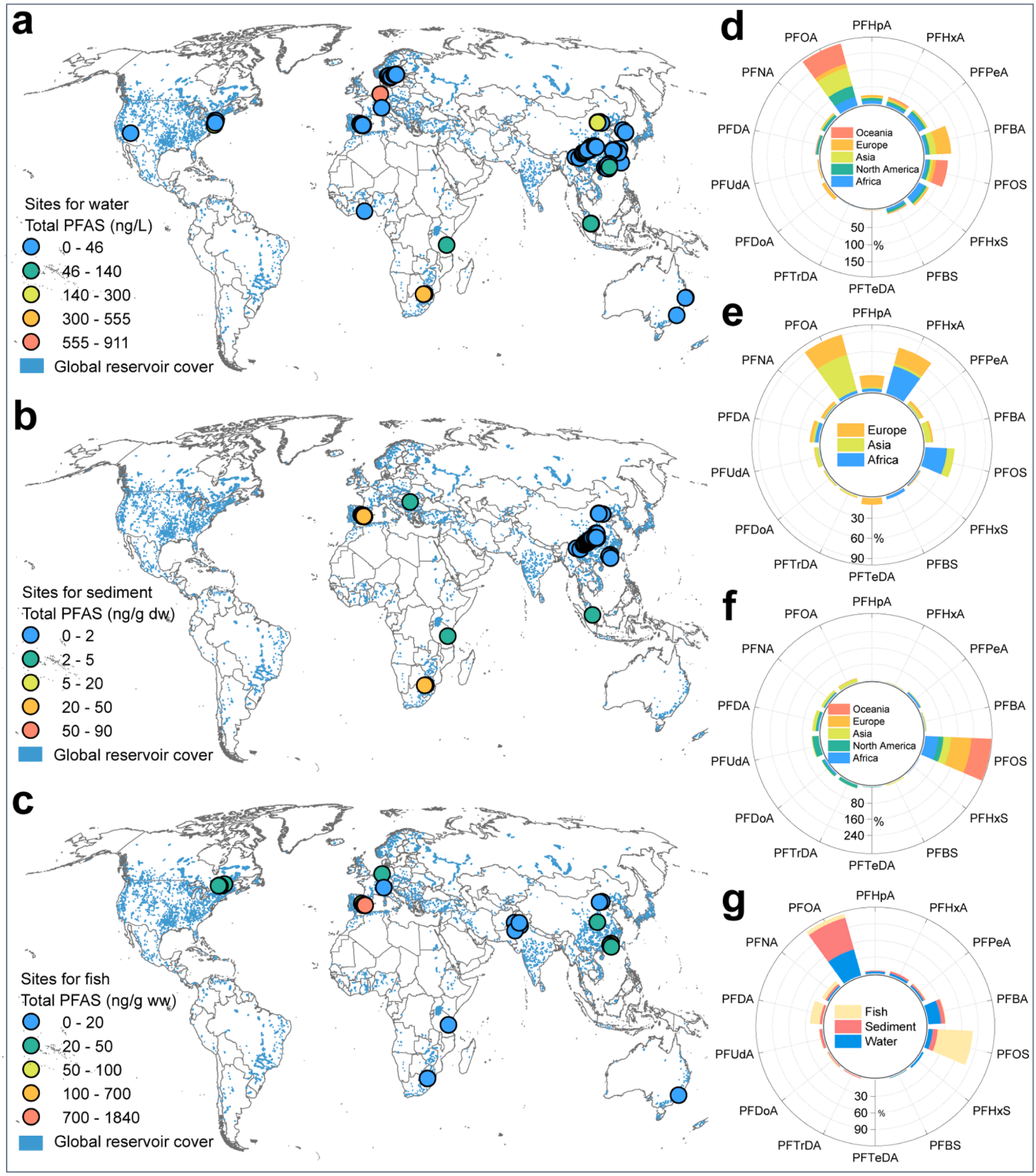


Fig. 2. Median concentrations (a, b, and c) of $\sum_{14}$PFAS. Percentage of individual PFAS components on each continent (d – in water, e – sediment, and f – fish) and all samples combined (g). Abbreviations of individual PFAS can be found in Table S1. All 14 PFAS compounds shown were target analytes in at least part of the compiled datasets; missing entries represent random non-detects or unreported values rather than exclusion from analytical target lists.

24, 25, and 24 PFAS were identified in water, sediments, and fish, respectively, their detection frequencies and dominant compound profiles varied markedly among continents and media. Reservoirs in Asia exhibited the highest PFAS detections, particularly in surface water, largely due to dense sampling coverage. In contrast, European studies emphasized sediment-associated PFAS, especially perfluoroalkyl carboxylic acids (PFCAs), whereas data from North America and Oceania lacked sediment-phase measurements. North American monitoring predominantly targeted PFAS bioaccumulation in fish, emphasizing long-chain compounds such as perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and perfluorooctane sulfonamide (FOSA).

Cross-continental differences were also evident in the cumulative concentrations of the 14 most frequently reported PFAS ($\sum_{14}$PFAS). African reservoir waters exhibited the highest burdens (234 ± 224 ng/L), with PFHxA and PFOS dominating sediment (44.8 ± 22.8 ng/g dry weight) (Fig. 2a and d). European fish tissues exhibited the greatest bioaccumulation (1.84×10^3 ng/g wet weight), one to three orders of magnitude higher than in other regions (Fig. 2c and f). These disparities reflect legacy discharges, regulatory actions, and regional variations in PFAS use and waste management.

A striking feature is the divergence in compound dominance across environmental compartments. PFOA was most prevalent in water (detection frequency: 92 %), contributing nearly half of the total concentrations. In sediments, PFOA remained dominant (75 % detection), alongside C4–C11 PFCAs (≥ 53 %). In fish, PFOS prevailed (89 %), followed by C8–C12 PFCAs (≥ 61 %) (Fig. 2*g* and Table S1). These patterns align with compound-specific physicochemical properties, particularly the enhanced hydrophobicity and bioaccumulative potential of long-chain PFCAs, which promote their persistence in biota relative to short-chain analogs (Calafat et al., 2019). Such compound-specific partitioning highlights the need to consider media-specific risk profiles as long-chain PFAS in fish pose heightened ecological and human health risks due to their persistence and trophic magnification (Joudan et al., 2020). Similar observations in aquatic plants and macroinvertebrates further underscore biological reservoirs as long-term PFAS sinks (Ahrens et al., 2009).

Despite global detection, PFAS monitoring remains regionally fragmented. Major geographic blind spots, such as South America and large parts of South and Southeast Asia, lack systematic surveillance, even as they host hundreds of large reservoirs and experience continued PFAS production and use (Lehner et al., 2011; Sonne et al., 2023). This disparity exacerbates ecological risk and regulatory uncertainty (Ruyle et al., 2025). Notably, Africa, while underrepresented in monitoring studies, revealed unexpectedly high contamination levels, suggesting underappreciated exposure risks in low- and middle-income countries. Expanding analytical coverage in these regions is essential for calibrating exposure thresholds and informing water safety.

Our synthesis delineates PFAS contamination in global reservoirs not as a uniform phenomenon, but as a series of paradigms shaped by chemical profiles, environmental media, and spatiotemporal dynamics. Reservoir waters, as primary recipients of PFAS inputs, offer real-time snapshots of environmental loading, while sediments and fish integrate temporal exposure and bioaccumulative effects. This multiscale integration delineates three paradigms (Fig. 4): (1) single, long-chain dominated paradigm (PFOA-dominated); (2) double, long-chain dominated paradigm (PFOA and PFOS-dominated); and (3) short-chain dominated paradigm (PFBA-dominated). These paradigms reflect varying contamination maturity, source dominance, and mitigation legacy, providing a conceptual framework for reservoir-scale risk assessment and regulatory prioritization.

3.2. PFOA-dominated paradigm

Reservoirs in the PFOA-dominated *paradigm* (Cluster *α*, $n = 26$), spanning five continents, exhibited moderate PFAS burdens in surface waters (median $\sum_{14}$PFAS = 13.3 ng/L), with PFOA accounting for 64 % of total concentrations (Fig. 3a–b). In sediments and fish, PFAS concentrations remained low (1.15 ng/g dw in sediments; 13.0 ng/g ww in fish) (Table S1). Nevertheless, PFOA, PFOS, and perfluoroundecanoic acid (PFUdA) dominated sediments, whereas PFOS and perfluorododecanoic acid (PFDoA) prevailed in fish, indicating selective partitioning and trophic uptake. Geospatial and seasonal variability jointly explained over 90 % of the variance in PFAS distributions (Geodetector q-value > 0.90, $p < 0.05$; Fig. 3c).

PFOA-dominated paradigm represents incipient PFAS pollution, characterized by intermediate levels of PFAS concentrations in water and limited sediments or fish accumulation (Fig. 4a). This compartmental asymmetry suggests that fish bioaccumulation is shaped not only by ambient water concentrations but also by biological traits such as feeding behavior and compound-specific bioavailability (Holzer et al., 2011). Long-chain PFCAs, including PFOA, are preferentially adsorbed into biota and sediments (Ahrens et al., 2019; Higgins and Luthy, 2006), reinforcing their persistence and relevance for long-term assessments (Syvitski et al., 2022; Trang et al., 2022).

This contamination pattern is primarily associated with anthropogenic discharges from domestic and industrial wastewater. Diagnostic PFAS ratios, such as PFHpA/PFOA (0.26–16), PFOA/PFNA (2–15), and PFOS/PFOA (>1), fall within established diagnostic ranges for surface water source tracing (Li et al., 2020). These ratios respectively indicate contributions from atmospheric deposition, industrial discharge, and PFOS point sources or precursor degradation, providing context for source differentiation. Over half of the reservoirs in this cluster exhibited PFOA/PFNA ratios between 2 and 15, consistent with mixed industrial and domestic wastewater inputs. The widespread use of PFOA in manufacturing consumer goods (Glüge et al., 2020), especially in eastern China, aligns with its prevalence in this cluster. In the absence of advanced treatment infrastructure, industrial discharges remain a critical vector for PFOA introduction into aquatic systems (Cookson and Detwiler, 2022).

Despite being in an initial contamination stage, reservoirs within this paradigm still require proactive management due to seasonal fluxes and hydrological conditions that modulate pollutant dynamics. PFAS concentrations tended to rise during reservoir impoundment when reduced flow enhanced contaminant retention and remobilized bank-stored pollutants (Zarfl and Dunn, 2022). Vertical and longitudinal gradients, as seen in small systems like Singapore's Marina Reservoir (Fig. S2), further reveal the importance of hydrodynamics and morphology. These findings suggest that even early-stage contamination demands temporal sensitivity in monitoring design and adaptive mitigation.

3.3. PFOA and PFOS-co-dominated paradigm

Reservoirs within the PFOA and PFOS-co-dominated paradigm (Cluster *β*, $n = 25$), predominantly located in Asia (85 %), exhibited co-dominance of PFOA (41 %) and PFOS (52 %) and the highest median $\sum_{14}$PFAS concentration (15.3 ± 27.1 ng/L, Fig. 3a–b). Sediments showed a median $\sum_{14}$PFAS concentration was 1.24 ng/g (dw), primarily with PFOA and PFOS, while fish showed a higher concentration level with PFOS (98 % of $\sum_{14}$PFAS) (Table S1). Catchment area emerged as the most influential predictor (q-value = 0.48), reflecting the importance of land-based sources such as industrial zones and urban runoff (Fig. 3c). PFAS load was significantly higher during flood periods compared to storage periods ($p < 0.05$, t-test), and an increasing interannual trend was observed ($p < 0.05$, t-test; Fig. S3). Spatially, smaller reservoirs such as Baoshan showed concentration increases toward the dam, reflecting morphology-driven transport, unlike larger reservoirs like Three Gorges (Fig. S4).

The paradigm indicates that reservoirs have historically accumulated and ongoing PFAS inputs (Fig. 4b). High frequencies and concentrations of PFOA and PFOS occur across all media, with water showing the greatest burden. Elevated PFAS levels in fish and sediments relative to

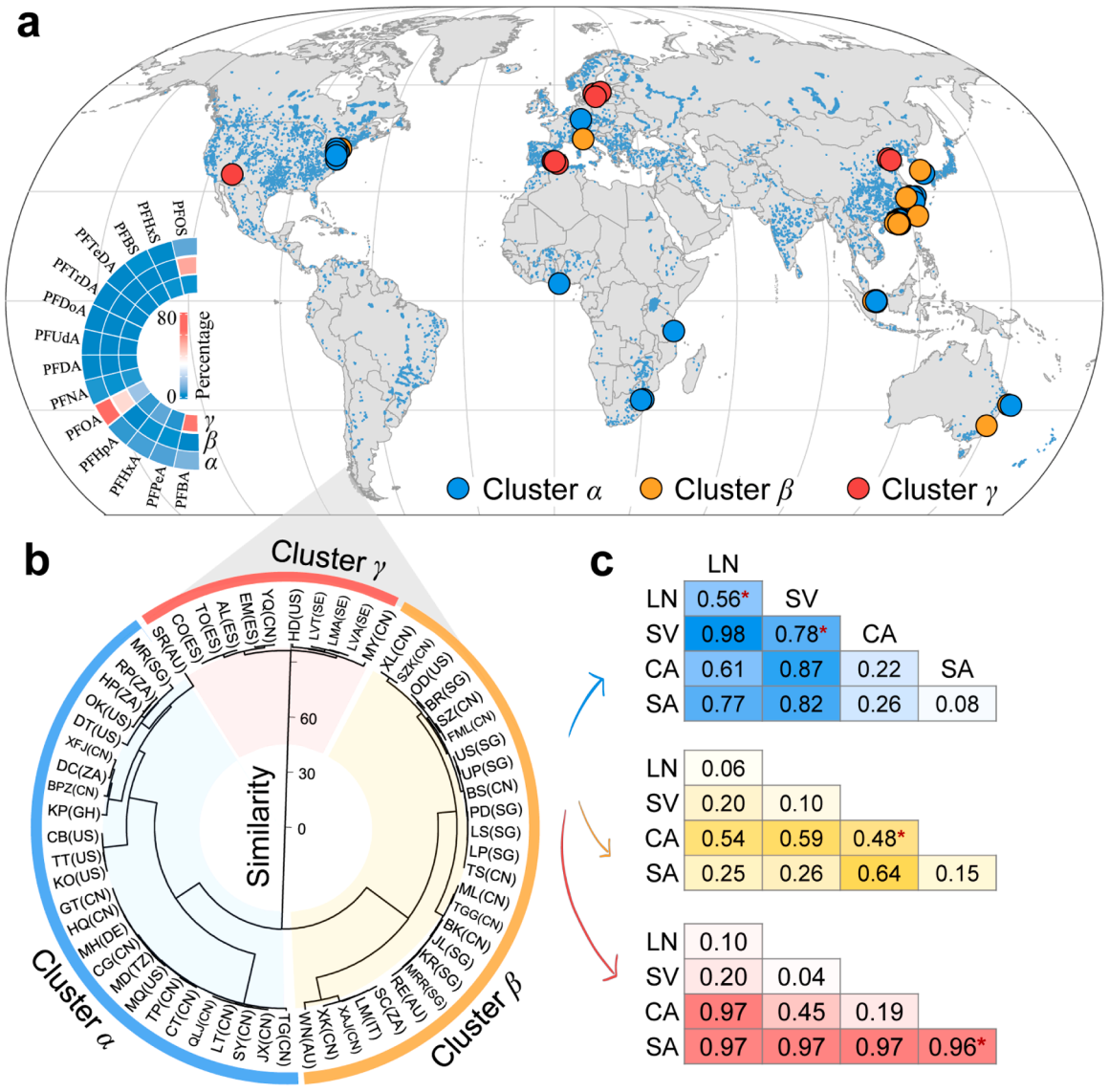


Fig. 3. Dendrogram and map of PFAS component similarity among reservoir water. (a) Heatmap indicates proportion of components to $\sum_{14}$PFAS concentration. (b) Cluster diagram shows the reservoir name (country located). Abbreviations of reservoir names can be found in Table S1. (c) The left triangular matrix shows values for interaction between pairs of factors. The values on diagonal line are driving forces of individual factors, and "*" indicates 5 % significance levels. Several potential factors exhibited no significant impact on distribution of PFAS concentrations across any of the three clusters and were therefore not included here. LN — Longitude, SV — Seasonal variation, CA — Catchment area, SA — Surface area. All 14 PFAS included were target analytes across the compiled datasets.

the PFOA-only dominated cluster reflect prolonged exposure and bioaccumulation, consistent with the sediment affinity of long-chained components such as C7-C10 PFSAs (Higgins et al., 2007).

Notably, 72 % of reservoirs in this cluster exhibited high PFOA/PFNA ratios and nearly one-third displayed PFOS/PFOA > 1, suggesting composite sources involving industrial effluents, precursor degradation, and surface runoff (Li et al., 2020; Ankley et al., 2021). These sites frequently receive inputs from metal plating and coating operations, where PFOS and PFOA remain key contaminants (Glüge et al., 2020). Elevated flood period concentrations further implicate stormwater-driven mobilization (Cousins et al., 2022; Kali et al., 2025). Detection of emerging PFAS substitutes underscores the evolving nature of chemical profiles under regulatory pressure (Glüge et al., 2022). The co-dominant paradigm thus represents a transitional and potentially expanding pollution phase, where regulatory and management efforts must contend not only with persistent legacy contaminants but also with newer analogs of uncertain ecological impact.

3.4. PFBA-dominated paradigm

Reservoirs within PFBA-dominated paradigm (Cluster γ, $n = 10$), primarily located in European and eastern China, illustrate a shift toward short-chain PFAS contamination, particularly PFBA, which constituted 62 % of anionic PFAS (median $\sum_{14}$PFAS = 8.00 ± 18.7 ng/L; Fig. 3a–b). These reservoirs harbored the highest PFAS burdens in sediments and fish, with biota dominated by perfluoropentanoic acid (PFPeA, 93 %), and sediments enriched in PFBA (54 %), perfluorodecanoic acid (PFDA, 16 %), and PFOS (12 %). In these reservoir PFAS, surface water area was the dominant driver (q-value = 0.96) (Fig. 3c). Reservoir capacity, hydraulic residence time, and sampling depth were not significant predictors in any cluster (Geodetector's factor detection, $p > 0.05$).

PFBA-dominated paradigm represents a late-stage contamination profile, shaped by both historical PFAS accumulation and evolving regulatory landscapes (Fig. 4c). Characterized by predominance of short-chain PFAS like PFBA in fish and sediments, these reservoirs show

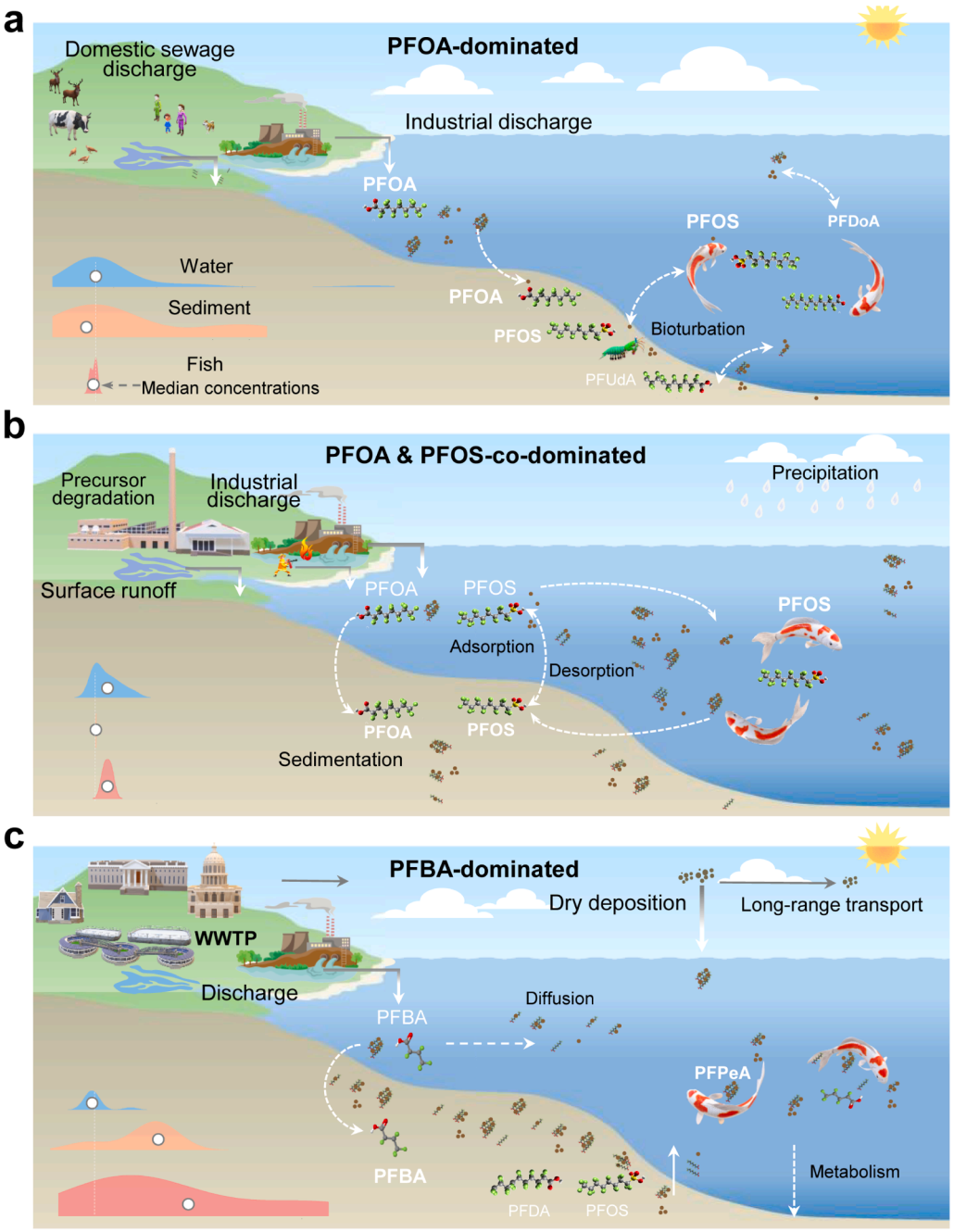


Fig. 4. Three contaminated paradigms and potential causes of reservoir PFAS concentrations. (a) PFOA-dominated, (b) PFOA and PFOS-dominated, and (c) PFBA-dominated contamination paradigm. The split violin plots show the distribution of $\sum_{14}$PFAS concentrations in each medium (top to bottom: water, sediment, and fish) of the reservoir. The circles represent median concentration of the corresponding distribution. Abbreviations of PFAS components can be found in Table S1.

the highest PFAS loads in biota despite low water concentrations, consistent with global increases in short-chain PFAS discharge via municipal wastewater (Cookson and Detwiler, 2022). Mainly located in economically developed regions such as Europe and eastern China, where restrictions on long-chain PFAS have driven their substitution with short-chain analogs (Lindim et al., 2016; Joudan and Lundgren, 2022), this shift has introduced challenges. Short-chain PFAS are highly mobile, persistent, prone to atmospheric deposition, and resist conventional treatment, leading to sediment accumulation and secondary pollution (Boyer et al., 2021; Neuwald et al., 2022). The absence of group-based regulation has allowed them to proliferate, while analytical constraints of TOF-based techniques may underestimate their environmental presence (Pan and Helbling, 2023; Hansen et al., 2024).

PFBA-dominated paradigm appears to be primarily influenced by dry deposition, industrial discharges, and secondary releases. Over 70 % exhibited PFHpA/PFOA ratios of 0.26–16, a diagnostic range consistent with atmospheric deposition signals (Li et al., 2020). In addition, PFAS pollution was higher during storage period than during flooding period (Fig. S3), indicating enrichment when deposition outweighs dilution. These observations, together with the chemical persistence and volatility of short-chain PFAS, suggest that atmospheric deposition represents an important, though not exclusive, contributor to PFBA loading (Bjornsdotter et al., 2022; Xia et al., 2024; Kali et al., 2025). Nevertheless, lacking concurrent atmospheric data, this inference remains

indicative, highlighting the need for integrated monitoring of atmospheric, hydrological, and sedimentary fluxes to better constrain source apportionment.

Compositional similarity between water and sediments suggests bidirectional exchanges, whereby sediments may gradually transition from sinks to secondary sources (Cooley et al., 2021). Field observations in Tokyo Bay demonstrated that short-chain PFAS such as PFBA and PFPeA persist in pore water and can be continuously released into the overlying water column (Ahrens et al., 2009). This sustained environmental availability, combined with the high solubility and moderate polarity of PFBA, favors uptake via gill diffusion and dietary exposure rather than lipid partitioning (Holzer et al., 2011; Liang et al., 2022). Although PFBA shows limited biomagnification, its persistence and continuous sediment–water exchange may lead to steady-state accumulation. Thus, PFBA bioaccumulation in fish likely reflects chronic environmental availability rather than trophic magnification, emphasizing the need to integrate bioaccumulation modeling into short-chain PFAS monitoring framework.

3.5. Challenge of process diversity and workflow construction

Although our study delineates three dominant paradigms of PFAS contamination in reservoirs, they likely represent only part of a broader continuum of environmental processes. Distinct patterns observed across water, sediment, and biota underscore the need to examine PFAS behavior not only by concentrations (Fig. S5), but also by dynamic partitioning, transformation, and cross-media transfer (Kosnik et al., 2022b). Due to their unique physicochemical properties, PFAS deviate from traditional pollutant behavior, challenging existing conceptual models of aquatic contaminant cycling (Lohmann et al., 2020). Their sorption and transformation depend on compound-specific affinities, surface chemistry of adsorbents, and surrounding water chemistry such as pH and ionic strength (Wu et al., 2020).

The heterogeneity observed—across continents, reservoir morphologies, and within reservoirs—suggests that single-point, single-media sampling strategies are insufficient to capture the spatiotemporal complexity of PFAS contamination. For instance, small reservoirs displayed sharp concentration gradients from surface to dam, while seasonal shifts in flow regimes affected PFAS retention and remobilization. Hence, further monitoring should incorporate multi-point, stratified sampling across different media, including sediments, biota, and water (Z.F. Guo et al., 2021). Additionally, trophic transfer within aquatic food webs remains poorly characterized, despite its importance for assessing bioaccumulation and biomagnification of both legacy and emerging PFAS (Evich et al., 2022).

The DIM workflow further revealed methodological limitations: sparsity and inconsistent metadata, variable sampling depth and timing, and non-standardized reporting hampered integration. Most studies remain cross-sectional, offering snapshots rather than temporal trends (Muir and Miaz, 2021), while fluctuations in PFAS concentrations are increasingly driven by climate-sensitive processes such as flood pulses and dry deposition (Maavara et al., 2020). Although our dataset capture spans five continents (Fig. S1), global coverage remains geographically uneven—reservoirs from South America and Africa are particularly underrepresented. These disparities reflect monitoring capacity gaps rather than true absence of contamination, potentially constraining generalization of the three paradigms (Grunfeld et al., 2024). Nevertheless, the sampled reservoirs encompass wide gradients in catchment area, storage capacity, and morphometry, thus capturing key features of global reservoir systems. The DIM framework presented here—integrating data compilation, imputation, and multiscale analysis—provides a scalable foundation for future datasets as coverage expands, potentially revealing additional contamination paradigms under diverse climatic and socioeconomic contexts.

Despite the robustness of the MICE-based method, uncertainty is inherent when reconstructing incomplete datasets. Restricting imputation to PFAS species with <50 % missingness provided a balance between data completeness and reliability. Nevertheless, this criterion may have led to the underrepresentation of certain short-chain PFAS that are more variable or sporadically detected, potentially biasing the inferred compositional structure toward longer-chain compounds in regions where short-chain alternatives are increasingly dominant. While MICE preserves covariance structure among PFAS and environmental covariates, it remains a statistical approximation that is unable to fully capture compound-specific behaviors or episodic contamination events. Therefore, imputed results should be regarded as an optimized estimate rather than a substitute for empirical observations. Hybrid approaches combining probabilistic and process-based or Bayesian modeling could further constrain uncertainty and enhance ecological realism.

Bridging these knowledge gaps requires concerted international coordination and data sharing. The DIM framework is designed to facilitate such cross-scale integration by offering a transparent, modular approach to synthesize heterogeneous datasets and identify emergent patterns. As PFAS disperse globally through air, water, and trade (Fuller et al., 2022), localized or single-media studies cannot resolve their complex environmental pathways (Cousins et al., 2022). In response to this challenge, our initiative is to develop the DIM workflow to promote data integration, effectively bridging the data gap and fostering interdisciplinary (Nakagawa et al., 2020; Ateia et al., 2023). Beyond methodological improvements, effective PFAS governance demands institutional coordination at multiple levels. To achieve our goal, countries should adopt complementary roles and take joint actions in acquiring, managing, sharing, and utilizing data (Game et al., 2018; Alexander et al., 2019). Integrating toxicological platforms such as the PFAS-Tox database (Pelch et al., 2022) within environmental datasets would align research and regulatory efforts under the "One Health" paradigm, where human, ecological, and chemical risks are addressed in tandem (Bourne et al., 2022).

4. Conclusions

This study presents a global-scale assessment of PFAS contamination in freshwater reservoirs, integrating multi-media data from 74 sites using a DIM (Data integration–Imputation–Multiscale analysis) workflow. Unsupervised clustering identified three distinct contamination paradigms: PFOA-dominated, PFOA and PFOS co-dominated, and PFBA-dominated, which represent distinct stages of PFAS evolution shaped by historical usage, regulatory shifts, and environmental processes. The PFOA-dominated paradigm reflects early-stage, spatial and inter-media asymmetric contamination driven by hydrodynamics and limited legacy accumulation. The PFOA and PFOS co-dominated paradigm, primarily found in Asia, indicates persistent and expanding pollution under compound sources and hydrological extremes, characterized by elevated burdens in all compartments and emergence of substitute PFAS. The PFBA-dominated paradigm, mainly in Europe and eastern China, illustrates a regulatory transition toward short-chain PFAS prevalence with elevated sediment and biotic burdens linked to dry deposition and secondary release. Together, these paradigms reveal that PFAS contamination in reservoirs is shaped by a complex interplay of source diversity, hydrological processes, and compound-specific physicochemistry, challenging traditional pollutant models. The strong cross-media heterogeneity observed underscores the limitations of single-media or snapshot-style assessments. We therefore recommend multi-point, stratified, and cross-media sampling integrated within frameworks like DIM to better capture temporal and spatial dynamics and to enable robust global comparison.

Furthermore, the study highlights critical knowledge gaps, including inconsistent metadata reporting, temporal discontinuity, and limited biotic data, that hinder cross-study synthesis. Bridging these gaps requires coordinated international efforts in data sharing, methodological harmonization, and cross-sector collaboration under a One Health approach. The DIM workflow provides a scalable foundation for such

integration, enabling data-driven refinement of contamination paradigms as global coverage expands. Ultimately, effective PFAS governance demands multi-level institutional cooperation and adaptive regulatory frameworks capable of addressing both legacy compounds and emerging analogs across environmental, ecological, and human health dimensions.

CRediT authorship contribution statement

Zhao-Feng Guo: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Mohamed Ateia:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Formal analysis, Data curation, Conceptualization. **Edoardo Borgomeo:** Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Data curation, Conceptualization. **Wiebke J. Boeing:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Conceptualization. **Daniel Malnes:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Yu-Qin He:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Dong Liu:** Writing – review & editing, Writing – original draft, Visualization. **Yao-Yang Xu:** Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No.: 42307066; 32301334; 42021005), the Ningbo S&T project (2021-DST-004), and the Open Competition Mechanism to Select the Best Candidates Program (IUE-JBGS-202203). We are grateful to Prof. Shinichi Nakagawa for his insightful guidance on the development and application of data imputation approaches. We also acknowledge Prof. Naomi Altman and Dr. Andrea K. Tokranov, whose published work and correspondence provided valuable insight into the data analysis and understanding of PFAS contamination mechanisms. We appreciate the assistance of Dr. Cai Chen and Mr. Gang Luo with figure preparation. The views presented are those of the authors and do not necessarily reflect those of the NSFC, the Helsinki Commission, or the Contracting Parties to the Helsinki Convention.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.watres.2025.124940.

Data availability

I have shared the link to my data at the Attach File step

References

Ahrens, L., Benskin, J.P., Cousins, I.T., Crimi, M., Higgins, C.P., 2019. Themed issues on per- and polyfluoroalkyl substances. Environ. Sci.: Process. Impacts 21 (11), 1797–1802. https://doi.org/10.1039/c9em90047k.

Ahrens, L., Yamashita, N., Yeung, L.W.Y., Taniyasu, S., Horii, Y., Lam, P.K.S., Ebinghaus, R., 2009. Partitioning behavior of per- and polyfluoroalkyl compounds between pore water and sediment in two sediment cores from Tokyo Bay. Japan. Environ. Sci. Technol. 43, 6969–6975. https://doi.org/10.1021/es901213s.

Alexander, S.M., Jones, K., Bennett, N.J., Budden, A., Cox, M., Crosas, M., Game, E.T., Geary, J., Hardy, R.D., Johnson, J.T., Karcher, S., Motzer, N., Pittman, J., Randell, H., Silva, J.A., da Silva, P.P., Strasser, C., Strawhacker, C., Stuhl, A., Weber, N., 2019. Qualitative data sharing and synthesis for sustainability science. Nat. Sustain. 3 (2), 81–88. https://doi.org/10.1038/s41893-019-0434-8.

Altman, N., Krzywinski, M., 2017. Clustering. Nat. Methods 14 (6), 545–546. https://doi.org/10.1038/nmeth.4299.

Altman, N., Krzywinski, M., 2018. The curse(s) of dimensionality. Nat. Methods 15 (6), 399–400. https://doi.org/10.1038/s41592-018-0013-3.

Ankley, G.T., Cureton, P., Hoke, R.A., Houde, M., Kumar, A., Kurias, J., Lanno, R., McCarthy, C., Newsted, J., Salice, C.J., Sample, B.E., Sepulveda, M.S., Steevens, J., Valsecchi, S., 2021. Assessing the ecological risks of per- and polyfluoroalkyl substances: current state-of-the science and a proposed path forward. Environ. Toxicol. Chem. 40 (3), 564–605. https://doi.org/10.1002/etc.4869.

Arp, H.P.H., Aurich, D., Schymanski, E.L., Sims, K., Hale, S.E., 2023. Avoiding the next silent spring: our chemical past, present, and future. Environ. Sci. Technol. 57 (16), 6355–6359. https://doi.org/10.1021/acs.est.3c01735.

Ateia, M., Scheringer, M., 2024. From “forever chemicals” to fluorine-free alternatives. Science 1979 385 (6706), 256–258. https://doi.org/10.1126/science.ado5019.

Ateia, M., Sigmund, G., Bentel, M.J., Washington, J.W., Lai, A., Merrill, N.H., Wang, Z.Y., 2023. Integrated data-driven cross-disciplinary framework to prevent chemical water pollution. One Earth. 6 (8), 952–963. https://doi.org/10.1016/j.oneear.2023.07.001.

Bjornsdotter, M.K., Yeung, L.W.Y., Karrman, A., Jogsten, I.E., 2022. Mass balance of perfluoroalkyl acids, including trifluoroacetic acid, in a freshwater lake. Environ. Sci. Technol. 56 (1), 251–259. https://doi.org/10.1021/acs.est.1c04472.

Bourne, P.E., Bonazzi, V., Brand, A., Carroll, B., Foster, I., Guha, R.V., Hanisch, R., Keller, S.A., Kennedy, M.L., Kirkpatrick, C., Mons, B., Nusser, S.M., Stebbins, M., Strawn, G., Szalay, A., 2022. Playing catch-up in building an open research commons. Science 1979 377 (6603), 256–258. https://doi.org/10.1126/science.abo594.

Boyer, T.H., Ellis, A., Fang, Y., Schaefer, C.E., Higgins, C.P., Strathmann, T.J., 2021. Life cycle environmental impacts of regeneration options for anion exchange resin remediation of PFAS impacted water. Water. Res. 207, 117798. https://doi.org/10.1016/j.watres.2021.117798.

Calafat, A.M., Kato, K., Hubbard, K., Jia, T., Botelho, J.C., Wong, L.Y., 2019. Legacy and alternative per- and polyfluoroalkyl substances in the U.S. general population: paired serum-urine data from the 2013-2014 national health and nutrition examination survey. Environ. Int. 131, 105048. https://doi.org/10.1016/j.envint.2019.105048.

Calafat, A.M., Wong, L.Y., Kuklenyik, Z., Reidy, J.A., Needham, L.L., 2007. Polyfluoroalkyl chemicals in the U.S. population: data from the national health and nutrition examination survey (NHANES) 2003-2004 and comparisons with NHANES 1999-2000. Environ. Health Perspect. 115 (11), 1596–1602. https://doi.org/10.1289/ehp.10598.

Chang, C., Deng, Y., Jiang, X.Q., Long, Q., 2020. Multiple imputation for analysis of incomplete data in distributed health data networks. Nat. Commun. 11 (1), 5467. https://doi.org/10.1038/s41467-020-19270-2.

Cookson, E.S., Detwiler, R.L., 2022. Global patterns and temporal trends of perfluoroalkyl substances in municipal wastewater: a meta-analysis. Water. Res. 221, 118784. https://doi.org/10.1016/j.watres.2022.118784.

Cooley, S.W., Ryan, J.C., Smith, L.C., 2021. Human alteration of global surface water storage variability. Nature 591 (7848), 78–81. https://doi.org/10.1038/s41586-021-03262-3.

Cordner, A., Brown, P., Cousins, I.T., Scheringer, M., Martinon, L., Dagorn, G., Aubert, R., Hosea, L., Salvidge, R., Felke, C., Tausche, N., Drepper, D., Liva, G., Tudela, A., Delgado, A., Salvatore, D., Pilz, S., Horel, S., 2024. PFAS contamination in Europe: generating knowledge and mapping known and likely contamination with "expert-reviewed" journalism. Environ. Sci. Technol. 58 (15), 6616–6627. https://doi.org/10.1021/acs.est.3c09746.

Cousins, I.T., Johansson, J.H., Salter, M.E., Sha, B., Scheringer, M., 2022. Outside the safe operating space of a new planetary boundary for per- and polyfluoroalkyl substances (PFAS). Environ. Sci. Technol. 56 (16), 11172–11179. https://doi.org/10.1021/acs.est.2c02765.

Ellington, E.H., Bastille-Rousseau, G., Austin, C., Landolt, K.N., Pond, B.A., Rees, E.E., Robar, N., Murray, D.L., 2014. Using multiple imputation to estimate missing data in meta-regression. Methods Ecol. Evol. 6 (2), 153–163. https://doi.org/10.1111/2041-210x.12322.

Evich, M.G., Davis, M.J.B., McCord, J.P., Acrey, B., Awkerman, J.A., Knappe, D.R.U., Lindstrom, A.B., Speth, T.F., Tebes-Stevens, C., Strynar, M.J., Wang, Z., Weber, E.J., Henderson, W.M., Washington, J.W., 2022. Per- and polyfluoroalkyl substances in the environment. Science 1979 375 (6580), eabg9065. https://doi.org/10.1126/science.abg9065.

Fuller, R., Landrigan, P.J., Balakrishnan, K., Bathan, G., Bose-O'Reilly, S., Brauer, M., Caravanos, J., Chiles, T., Cohen, A., Corra, L., Cropper, M., Ferraro, G., Hanna, J., Hanrahan, D., Hu, H., Hunter, D., Janata, G., Kupka, R., Lanphear, B., Lichtveld, M., Martin, K., Mustapha, A., Sanchez-Triana, E., Sandilya, K., Schaefli, L., Shaw, J., Seddon, J., Suk, W., Tellez-Rojo, M.M., Yan, C., 2022. Pollution and health: a progress update. Lancet Planet. Health 6 (6), e535–e547. https://doi.org/10.1016/S2542-5196(22)00090-0.

Game, E.T., Tallis, H., Olander, L., Alexander, S.M., Busch, J., Cartwright, N., Kalies, E.L., Masuda, Y.J., Mupepele, A.C., Qiu, J., Rooney, A., Sills, E., Sutherland, W.J., 2018. Cross-discipline evidence principles for sustainability policy. Nat. Sustain. 1 (9), 452–454. https://doi.org/10.1038/s41893-018-0141-x.

Glüge, J., London, R., Cousins, I.T., DeWitt, J., Goldenman, G., Herzke, D., Lohmann, R., Miller, M., Ng, C.A., Patton, S., Trier, X., Wang, Z., Scheringer, M., 2022. Information

requirements under the essential-use concept: PFAS case studies. Environ. Sci. Technol. 56 (10), 6232–6242. https://doi.org/10.1021/acs.est.1c03732.
Glüge, J., Scheringer, M., Cousins, I.T., DeWitt, J.C., Goldenman, G., Herzke, D., Lohmann, R., Ng, C.A., Trier, X., Wang, Z., 2020. An overview of the uses of per- and polyfluoroalkyl substances (PFAS). Environ. Sci.: Process. Impacts 22 (12), 2345–2373. https://doi.org/10.1039/d0em00291g.
Grill, G., Lehner, B., Thieme, M., Geenen, B., Tickner, D., Antonelli, F., Babu, S., Borrelli, P., Cheng, L., Crochetiere, H., Ehalt Macedo, H., Filgueiras, R., Goichot, M., Higgins, J., Hogan, Z., Lip, B., McClain, M.E., Meng, J., Mulligan, M., Nilsson, C., Olden, J.D., Opperman, J.J., Petry, P., Reidy Liermann, C., Saenz, L., Salinas-Rodriguez, S., Schelle, P., Schmitt, R.J.P., Snider, J., Tan, F., Tockner, K., Valdujo, P. H., van Soesbergen, A., Zarfl, C., 2019. Mapping the world's free-flowing rivers. Nature 569 (7755), 215–221. https://doi.org/10.1038/s41586-019-1111-9.
Grunfeld, D.A., Gilbert, D., Hou, J., Jones, A.M., Lee, M.J., Kibbey, T.C.G., O'Carroll, D. M., 2024. Underestimated burden of per- and polyfluoroalkyl substances in global surface waters and groundwaters. Nat. Geosci. 17 (4), 340–346. https://doi.org/10.1038/s41561-024-01402-8.
Guo, Z.F., Boeing, W.J., Xu, Y.Y., Borgomeo, E., Mason, S.A., Zhu, Y.G., 2021a. Global meta-analysis of microplastic contamination in reservoirs with a novel framework. Water. Res. 207, 117828. https://doi.org/10.1016/j.watres.2021.117828.
Guo, Z.F., Boeing, W.J., Xu, Y.Y., Yan, C.Z., Faghihinia, M., Liu, D., 2021b. Revisiting seasonal dynamics of total nitrogen in reservoirs with a systematic framework for mining data from existing publications. Water. Res. 201, 117380. https://doi.org/10.1016/j.watres.2021.117380.
Hansen, S.F., Bunde, C.T.H., Roy, M.A., Tickner, J.A., Baun, A., 2024. Late lessons from early warnings on PFAS. Nat. Water 2 (12), 1157–1165. https://doi.org/10.1038/s44221-023-00168-4.
Higgins, C.P., Luthy, R.G., 2006. Sorption of perfluorinated surfactants on sediments. Environ. Sci. Technol. 40, 7251–7256. https://doi.org/10.1021/es061000n.
Higgins, C.P., McLeod, P.B., MacManus-Spencer, L.A., Luthy, R.G., 2007. Bioaccumulation of perfluorochemicals in sediments by the aquatic oligochaete lumbriculus variegatus. Environ. Sci. Technol. 41, 4600–4606. https://doi.org/10.1021/es062792o.
Holzer, J., Goen, T., Just, P., Reupert, R., Rauchfuss, K., Kraft, M., Muller, J., Wilhelm, M., 2011. Perfluorinated compounds in fish and blood of anglers at Lake Mohne, Sauerland area. Germany. Environ. Sci. Technol. 45 (19), 8046–8052. https://doi.org/10.1021/es104391z.
Holzer, J., Midasch, O., Rauchfuss, K., Kraft, M., Reupert, R., Angerer, J., Kleeschulte, P., Marschall, N., Wilhelm, M., 2008. Biomonitoring of perfluorinated compounds in children and adults exposed to perfluorooctanoate-contaminated drinking water. Environ. Health Perspect. 116 (5), 651–657. https://doi.org/10.1289/ehp.11064.
Janssen, A.B.G., Droppers, B., Kong, X., Teurlincx, S., Tong, Y., Kroeze, C., 2021. Characterizing 19 thousand Chinese lakes, ponds and reservoirs by morphometric, climate and sediment characteristics. Water. Res. 202, 117427. https://doi.org/10.1016/j.watres.2021.117427.
Janssen, A.B.G., Hilt, S., Kosten, S., de Klein, J.J.M., Paerl, H.W., Van de Waal, D.B., 2020. Shifting states, shifting services: linking regime shifts to changes in ecosystem services of shallow lakes. Freshw. Biol. 66, 1–12. https://doi.org/10.1111/fwb.13582.
Johnson, A.C., Jin, X.W., Nakada, N., Sumpter, J.P., 2020. Learning from the past and considering the future of chemicals in the environment. Science 1979 367, 384–387. https://doi.org/10.1126/science.aay6637.
Joudan, S., Liu, R.Z., D'eon, J.C., Mabury, S.A., 2020. Unique analytical considerations for laboratory studies identifying metabolic products of per- and polyfluoroalkyl substances (PFASs). Trends. Analyt. Chem. 124, 115431. https://doi.org/10.1016/j.trac.2019.02.032.
Joudan, S., Lundgren, R.J., 2022. Taking the "F" out of forever chemicals. Science 1979 377 (6608), 816–817. https://doi.org/10.1126/science.add1813.
Kali, S.E., Osterlund, H., Viklander, M., Blecken, G.T., 2025. Stormwater discharges affect PFAS occurrence, concentrations, and spatial distribution in water and bottom sediment of urban streams. Water. Res. 271, 122973. https://doi.org/10.1016/j.watres.2024.122973.
Kosnik, M.B., Hauschild, M.Z., Fantke, P., 2022a. Toward assessing absolute environmental sustainability of chemical pollution. Environ. Sci. Technol. 56 (8), 4776–4787. https://doi.org/10.1021/acs.est.1c06098.
Kosnik, M.B., Kephalopoulos, S., Munoz, A., Aurisano, N., Cusinato, A., Dimitroulopoulou, S., Slobodnik, J., De Mello, J., Zare Jeddi, M., Cascio, C., Ahrens, A., Bruinen de Bruin, Y., Lieck, L., Fantke, P., 2022b. Advancing exposure data analytics and repositories as part of the European exposure science strategy 2020-2030. Environ. Int. 170, 107610. https://doi.org/10.1016/j.envint.2022.107610.
Kosnik, M.B., Planchart, A., Marvel, S.W., Reif, D.M., Mattingly, C.J., 2019. Integration of curated and high-throughput screening data to elucidate environmental influences on disease pathways. Comput. Toxicol. 12, 100094. https://doi.org/10.1016/j.comtox.2019.100094.
Lehner, B., Liermann, C.R., Revenga, C., Vörösmarty, C., Fekete, B., Crouzet, P., Döll, P., Endejan, M., Frenken, K., Magome, J., Nilsson, C., Robertson, J.C., Rödel, R., Sindorf, N., Wisser, D., 2011. High-resolution mapping of the world's reservoirs and dams for sustainable river-flow management. Front. Ecol. Environ. 9 (9), 494–502. https://doi.org/10.1890/100125.
Li, J., Gao, Y., Xu, N., Li, B., An, R., Sun, W.L., Borthwick, A.G.L., Ni, J.R., 2020. Perfluoroalkyl substances in the Yangtze River: changing exposure and its implications after operation of the three Gorges Dam. Water. Res. 182, 115933. https://doi.org/10.1016/j.watres.2020.115933.
Liang, X.X., Yang, X.Y., Jiao, W.Q., Zhou, J., Zhu, L.Y., 2022. Simulation modelling the structure related bioaccumulation and biomagnification of per- and polyfluoroalkyl substances in aquatic food web. Sci. Total. Environ. 838 (VPart 3), 156397. https://doi.org/10.1016/j.scitotenv.2022.156397.
Lindim, C., van Gils, J., Cousins, I.T., 2016. Europe-wide estuarine export and surface water concentrations of PFOS and PFOA. Water. Res. 103, 124–132. https://doi.org/10.1016/j.watres.2016.07.024.
Lohmann, R., Cousins, I.T., DeWitt, J.C., Gluge, J., Goldenman, G., Herzke, D., Lindstrom, A.B., Miller, M.F., Ng, C.A., Patton, S., Scheringer, M., Trier, X., Wang, Z. Y., 2020. Are fluoropolymers really of low concern for human and environmental health and separate from other PFAS? Environ. Sci. Technol. 54 (20), 12820–12828. https://doi.org/10.1021/acs.est.0c03244.
Maavara, T., Chen, Q.W., Van Meter, K., Brown, L.E., Zhang, J.Y., Ni, J.R., Zarfl, C., 2020. River dam impacts on biogeochemical cycling. Nat. Rev. Earth. Environ. 1 (2), 103–116. https://doi.org/10.1038/s43017-019-0019-0.
Maavara, T., Lauerwald, R., Regnier, P., Van Cappellen, P., 2017. Global perturbation of organic carbon cycling by river damming. Nat. Commun. 8, 15347. https://doi.org/10.1038/ncomms15347.
Messager, M.L., Lehner, B., Grill, G., Nedeva, I., Schmitt, O., 2016. Estimating the volume and age of water stored in global lakes using a geo-statistical approach. Nat. Commun. 7, 13603. https://doi.org/10.1038/ncomms13603.
Muir, D., Miaz, L.T., 2021. Spatial and temporal trends of perfluoroalkyl substances in global ocean and coastal waters. Environ. Sci. Technol. 55 (14), 9527–9537. https://doi.org/10.1021/acs.est.0c08035.
Murray, J.S., 2018. Multiple imputation: a review of practical and theoretical findings. Stat. Sci. 33 (2), 142–159. https://doi.org/10.1214/18-sts644.
Nakagawa, S., Dunn, A.G., Lagisz, M., Bannach-Brown, A., Grames, E.M., Sanchez-Tojar, A., O'Dea, R.E., Noble, D.W.A., Westgate, M.J., Arnold, P.A., Barrow, S., Bethel, A., Cooper, E., Foo, Y.Z., Geange, S.R., Hennessy, E., Mapanga, W., Mengersen, K., Munera, C., Page, M.J., Welch, V., 2020. A new ecosystem for evidence synthesis. Nat. Ecol. Evol. 4 (4), 498–501. https://doi.org/10.1038/s41559-020-1153-2.
Nakagawa, S., Freckleton, R.P., 2008. Missing inaction: the dangers of ignoring missing data. Trends. Ecol. Evol. 23 (11), 592–596. https://doi.org/10.1016/j.tree.2008.06.014.
Neuwald, I.J., Hubner, D., Wiegand, H.L., Valkov, V., Borchers, U., Nodler, K., Scheurer, M., Hale, S.E., Arp, H.P.H., Zahn, D., 2022. Ultra-short-chain PFASs in the sources of German drinking water: prevalent, overlooked, difficult to remove, and unregulated. Environ. Sci. Technol. 56 (10), 6380–6390. https://doi.org/10.1021/acs.est.1c07949.
Ng, C., Cousins, I.T., DeWitt, J.C., Glüge, J., Goldenman, G., Herzke, D., Lohmann, R., Miller, M., Patton, S., Scheringer, M., Trier, X., Wang, Z.Y., 2021. Addressing urgent questions for PFAS in the 21st century. Environ. Sci. Technol. 55 (19), 12755–12765. https://doi.org/10.1021/acs.est.1c03386.
Pan, Y.T., Helbling, D.E., 2023. Revealing the factors resulting in incomplete recovery of perfluoroalkyl acids (PFAAs) when implementing the adsorbable and extractable organic fluorine methods. Water. Res. 244, 120497. https://doi.org/10.1016/j.watres.2023.120497.
Pelch, K.E., Reade, A., Kwiatkowski, C.F., Merced-Nieves, F.M., Cavalier, H., Schultz, K., Wolffe, T., Varshavsky, J., 2022. The PFAS-Tox Database: a systematic evidence map of health studies on 29 per- and polyfluoroalkyl substances. Environ. Int. 167, 107408. https://doi.org/10.1016/j.envint.2022.107408.
Pelch, K.E., Reade, A., Wolffe, T.A.M., Kwiatkowski, C.F., 2019. PFAS health effects database: protocol for a systematic evidence map. Environ. Int. 130, 104851. https://doi.org/10.1016/j.envint.2019.05.045.
Rahman, M.F., Peldszus, S., Anderson, W.B., 2014. Behaviour and fate of perfluoroalkyl and polyfluoroalkyl substances (PFASs) in drinking water treatment: a review. Water. Res. 50, 318–340. https://doi.org/10.1016/j.watres.2013.10.045.
Ruyle, B.J., Pennoyer, E.H., Vojta, S., Becanova, J., Islam, M., Webster, T.F., Heiger-Bernays, W., Lohmann, R., Westerhoff, P., Schaefer, C.E., Sunderland, E.M., 2025. High organofluorine concentrations in municipal wastewater affect downstream drinking water supplies for millions of Americans. Proc. Natl. Acad. Sci. U.S.A. 122 (3), e2417156122. https://doi.org/10.1073/pnas.2417156122.
Scheringer, M., 2023. Innovate beyond PFAS. Science (1979) 381 (6655), 251. https://doi.org/10.1126/science.adj7475.
Sonne, C., Bank, M.S., Jenssen, B.M., Cieseielski, T.M., Rinklebe, J., Lam, S.S., Hansen, M., Bossi, R., Gustavson, K., Dietz, R., 2023. PFAS pollution threatens ecosystems worldwide. Science (1979) 379 (6635), 887–888. https://doi.org/10.1126/science.adh0934.
Spake, R., Mori, A.S., Beckmann, M., Martin, P.A., Christie, A.P., Duguid, M.C., Doncaster, C.P., 2021. Implications of scale dependence for cross-study syntheses of biodiversity differences. Ecol. Lett. 24 (2), 374–390. https://doi.org/10.1111/ele.13641.
Spake, R., O'Dea, R.E., Nakagawa, S., Doncaster, C.P., Ryo, M., Callaghan, C.T., Bullock, J.M., 2022. Improving quantitative synthesis to achieve generality in ecology. Nat. Ecol. Evol. 6 (12), 1818–1828. https://doi.org/10.1038/s41559-022-01891-z.
Sun, Y., Li, J., Xu, Y., Zhang, T., Wang, X., 2023. Deep learning versus conventional methods for missing data imputation: a review and comparative study. Expert. Syst. Appl. 227, 120201. https://doi.org/10.1016/j.eswa.2023.120201.
Syvitski, J., Ángel, J.R., Saito, Y., Overeem, I., Vörösmarty, C.J., Wang, H.J., Olago, D., 2022. Earth's sediment cycle during the Anthropocene. Nat. Rev. Earth. Environ. 3 (3), 179–196. https://doi.org/10.1038/s43017-021-00253-w.
Tokranov, A.K., Ransom, K.M., Bexfield, L.M., Lindsey, B.D., Watson, E., Dupuy, D.I., Stackelberg, P.E., Fram, M.S., Voss, S.A., Kingsbury, J.A., Jurgens, B.C., Smalling, K. L., Bradley, P.M., 2024. Predictions of groundwater PFAS occurrence at drinking water supply depths in the United States. Science 1979 386 (6723), 748–755. https://doi.org/10.1126/science.ado6638.

Trang, B., Li, Y.L., Xue, X.S., Ateia, M., Houk, K.N., Dichtel, W.R., 2022. Low-temperature mineralization of perfluorocarboxylic acids. Science (1979) 377 (6608), 839–845. https://doi.org/10.1126/science.abm8868.

van Buuren, S., Groothuis-Oudshoorn, K., 2011. Mice: multivariate imputation by chained equations in R. J. Stat. Softw. 45 (3), 1–67. https://doi.org/10.18637/jss.v045.i03.

Wu, C.Y., Klemes, M.J., Trang, B., Dichtel, W.R., Helbling, D.E., 2020. Exploring the factors that influence the adsorption of anionic PFAS on conventional and emerging adsorbents in aquatic matrices. Water. Res. 182, 115950. https://doi.org/10.1016/j.watres.2020.115950.

Xia, C., Capozzi, S.L., Romanak, K.A., Lehman, D.C., Dove, A., Richardson, V., Greenberg, T., McGoldrick, D., Venier, M., 2024. The ins and outs of per- and polyfluoroalkyl substances in the Great Lakes: the role of atmospheric deposition. Environ. Sci. Technol. 58 (21), 9303–9313. https://doi.org/10.1021/acs.est.3c10098.

Xiao, F., Deng, B.L., Dionysiou, D., Karanfil, T., O'Shea, K., Roccaro, P., Xiong, Z.J., Zhao, D.Y., 2023. Cross-national challenges and strategies for PFAS regulatory compliance in water infrastructure. Nat. Water 1 (12), 1004–1015. https://doi.org/10.1038/s44221-023-00164-8.

Zarfl, C., Berlekamp, J., Tockner, K., Lumsdon, A.E., Tydecks, L., 2015. A global boom in hydropower dam construction. Aquat. Sci. 77, 161–170. https://doi.org/10.1007/s00027-014-0377-0.

Zarfl, C., Dunn, F.E., 2022. The delicate balance of river sediments. Science 1979 376, 1385–1386. https://doi.org/10.1126/science.abq6986.

Chemosphere 414 (2026) 145133

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

Review

Persistent pharmaceuticals and their transformation Products: From persistence mechanisms to AI-assisted integrated treatment for safe water reuse

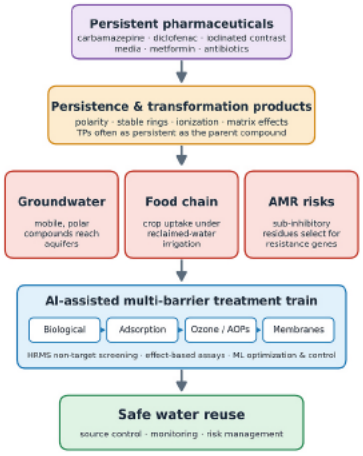
Basem Shomar [a], Jose L. Domingo [b,*]

[a] Interdisciplinary Research Center for Membranes and Water Security, King Fahd University of Petroleum & Minerals, Dhahran, 31261, Saudi Arabia
[b] Universitat Rovira i Virgili, Laboratory of Toxicology and Environmental, Health, School of Medicine, Sant Llorenç 21, 43201, Reus, Catalonia, Spain

HIGHLIGHTS

- Persistent pharmaceuticals evade conventional water and wastewater treatment systems.
- Multi-barrier treatment trains achieve >90% removal of recalcitrant pharmaceuticals.
- Transformation products often persist and may exceed parent compound toxicity.
- LC-MS/MS and HRMS are essential for tracing parent compounds and by-products.
- Integrated treatment and source control are critical for safe water reuse and SDG-6.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Persistent pharmaceuticals
Advanced oxidation processes
Integrated water treatment
Transformation products
Advanced reduction processes
Machine learning

ABSTRACT

This review examines the physicochemical mechanisms governing pharmaceutical persistence, the formation of transformation products (TPs), and the effectiveness and limitations of conventional and advanced treatment technologies for water reuse, focusing on carbamazepine, diclofenac, iodinated contrast media, metformin, and selected antibiotics, which persist through wastewater treatment. The review follows one chain of reasoning: persistence drivers determine which TPs form, which compartments and exposure pathways are reached, and which treatment barriers can act. Conventional activated sludge often provides incomplete removal, whereas integrated trains combining biological processes, adsorption, ozonation, UV/H_2O_2, membranes, and other advanced oxidation technologies can improve control, although energy demand, membrane fouling, residuals, and TP formation remain constraints. Pilot- and full-scale studies report average abatement of about 80% or more with ozonation or activated carbon, but behavior differs among compounds, and evidence for complete multi-barrier trains is limited. Unlike reviews addressing occurrence, individual technologies, or TPs separately,

* Corresponding author.
E-mail address: joseluis.domingo@urv.cat (J.L. Domingo).

https://doi.org/10.1016/j.chemosphere.2026.145133
Received 18 August 2026; Received in revised form 17 October 2026; Accepted 20 October 2026
Available online 24 October 2026
0045-6535/© 2026 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

this review links the drivers of persistence to the selection and sequencing of treatment barriers, and extends the assessment to groundwater migration, soil–plant and food-chain transfer, and antimicrobial-resistance pathways within a common water-reuse framework. This supports adaptive treatment design targeting parent compounds, TPs, and cross-compartment risks. HRMS, non-target screening, and AI/ML-assisted optimization support adaptive monitoring and control. However, identifying a TP does not demonstrate risk, so effect-based methods are needed, and AI/ML applications are mainly predictive and validated on small datasets. Safe and sustainable water reuse likely requires multi-barrier treatment, source control, continuous monitoring, TP assessment, and integrated risk management.

1. Introduction

Persistent contaminants in water are chemical substances that remain for long periods due to their resistance to photolytic, biological, and chemical degradation. These compounds exhibit high stability, long environmental half-lives, and the ability to bioaccumulate in organisms and biomagnify through food webs, leading to chronic ecological and health effects (Yu et al., 2024). They include persistent organic pollutants (POPs), per- and polyfluoroalkyl substances (PFAS), pharmaceuticals, and certain pesticides. These compounds are difficult to remove through conventional wastewater treatment processes. Persistent contaminants can be transported across great distances via water and air currents, resulting in their global distribution-even in remote regions such as the Arctic (UNEP, 2025).

Among persistent contaminants, pharmaceuticals warrant particular attention due to their extensive production, consumption, and biological activity. Approximately 4000 active pharmaceutical ingredients are used worldwide, with annual production reaching about 100,000 tonnes (Weber et al., 2016). Continuous inputs from excretion, disposal, and manufacturing, coupled with population ageing, are expected to further increase environmental releases (IFPMA, 2022). Pharmaceuticals and their transformation products have been detected in 71 countries, encompassing more than 600 substances (aus der Beek et al., 2016). A global survey of rivers in 104 countries found concentrations exceeding ecological safety thresholds or levels of concern for antimicrobial resistance at 25.7% of sampling sites (Wilkinson et al., 2022). Their impacts include wildlife mortality, pressures on fish populations, and the promotion of antimicrobial resistance (Oaks et al., 2004; Johnson and Sumpter, 2014; Kraemer et al., 2019). Although pharmaceuticals are not classical persistent organic pollutants under the Stockholm Convention framework (UNDP, 2024; UNEP, 2001), their continuous replenishment and incomplete removal during wastewater treatment justify their consideration in this review.

Recent reviews have substantially advanced understanding of pharmaceutical occurrence, environmental fate, treatment performance, and transformation products (Couto et al., 2019; Patel et al., 2019; Wada and Olawade, 2025), AOP-based removal (Kanakaraju et al., 2018, 2025), and applications of AI in water and wastewater treatment (Liu et al., 2025; Mathaba and Banza, 2023; Parsoya et al., 2026). However, these dimensions are still commonly addressed as relatively discrete components of the contamination problem. Therefore, the unresolved challenge is not simply to identify which pharmaceuticals persist or which technologies remove them, but to establish how compound-specific physicochemical and transformation mechanisms should determine the design and sequencing of treatment barriers across wastewater, reclaimed water, groundwater, and food-production pathways. The present review addresses this gap by developing a mechanistic driver-to-treatment-train perspective that connects persistence mechanisms with integrated treatment selection and AI-assisted optimization, while simultaneously considering cross-compartment transport, food-chain exposure, and antimicrobial-resistance risks.

Three observations support this perspective. First, pharmaceutical residues and co-selecting agents can promote antibiotic resistance in wastewater, making the fate of resistance genes as important as the removal of parent compounds (Sambaza and Naicker, 2023; Uluseker et al., 2021). Second, treatment processes frequently transform rather than eliminate pharmaceuticals, generating by-products that may equal or exceed the persistence or toxicity of the original molecules (Dong et al., 2024; Trognon et al., 2024). Third, no single technology achieves complete removal. Although ozonation and activated carbon can reduce micropollutant loads by around 80% or more, treatment efficiency varies substantially among compounds, highlighting the need for combined processes and transformation-product monitoring (Bourgin et al., 2018; Margot et al., 2013).

Based on this integrated perspective, the specific objectives of the current review were the following: 1) identify the key physicochemical drivers that confer persistence to pharmaceuticals in aquatic systems, 2) evaluate the efficacy of conventional and advanced treatment technologies in removing persistent pharmaceuticals, distinguishing parent-compound removal, degradation and mineralization and taking operating conditions into account, 3) discuss the formation and risks of transformation products (TPs) and antimicrobial resistance (AMR) linked to these contaminants, including the evidence from effect-based toxicity assessment, and 4) propose integrated, multi-barrier treatment frameworks and future research directions to mitigate their impact on water quality and public health, while separating evidence-supported findings from proposed directions, and critically appraise the evidence for AI/ML in pharmaceutical treatment, supporting global efforts toward sustainable water management and SDG 6.

The organizing axis of the review is the mechanism of persistence, and the review follows one chain of reasoning, summarized in Table 1. It begins with the molecular and physicochemical drivers that allow a pharmaceutical to pass through conventional treatment, and with the transformation products it leaves behind (Section 3). Because every later step depends on how reliably parent compounds and transformation products can be measured, the analytical constraints are then examined as a critical appraisal of what occurrence and removal data can and cannot show (Section 4). The review next follows persistent pharmaceuticals and their transformation products from release to transport, transformation, exposure and ecological or health consequence (Section 5). Treatment is evaluated against the same persistence drivers, so that each barrier is judged by whether it acts on the mechanism that causes persistence and by the transformation products, energy demand and residuals it generates (Section 6). These elements are finally combined into a multi-barrier design, in which AI/ML is considered as a decision-support tool for selecting and operating the barriers, and the evidence for it is appraised (Section 7). Remaining challenges and research gaps close the review (Sections 8 and 9). The central scientific questions are therefore: (Q1) which drivers make pharmaceuticals persist; (Q2) whether the disappearance of a parent compound means elimination; (Q3) where residues and transformation products go and what risks follow; (Q4) which barrier acts on which driver, and at what cost; and (Q5) how barriers should be sequenced for safe water reuse and where AI/ML can support that decision.

2. Search strategy and literature review methodology

To compile this narrative review, a comprehensive literature search was performed using scientific databases (PubMed, Scopus, Web of Science, and Google Scholar). The search strategy combined keywords

Table 1
Organization of the review: chain of reasoning, central questions, and the sections that address them.

Step in the chain	Central question	Sections	What is carried to the next step
Persistence drivers	Q1. Which molecular and physicochemical properties allow pharmaceuticals to pass through conventional treatment?	3.1, 3.2	A set of drivers and three patterns of behavior of the pharmaceutical groups
Transformation	Q2. Does disappearance of the parent compound mean elimination, and what do transformation products inherit from the parent?	3.3	Conversion must be distinguished from mineralization; transformation products are followed as targets in their own right
Evidence base	How reliably can parent compounds, transformation products and biological activity be measured?	4	Limits of target analysis; complementary roles of HRMS and effect-based methods
Fate, exposure and consequences	Q3. Where do residues and transformation products go, through which pathways are organisms and people exposed, and how strong is the evidence for each pathway?	5	Strength of evidence per pathway; treatment and monitoring objectives for discharge, irrigation and recharge
Barrier selectivity	Q4. Which treatment barrier acts on which driver, and with what transformation-product, energy and residual penalty?	6	Driver-to-barrier logic and the quantitative evidence on performance, transformation products and energy
Train design and decision support	Q5. How should barriers be sequenced for safe water reuse, and what can AI/ML contribute to selecting and operating them?	7	Multi-barrier train; evidence and limits of AI/ML
Risk mitigation and gaps	Which challenges and research gaps remain, and which measures complement treatment?	8, 9	Research gaps and priorities, including source control and monitoring

and Boolean operators to capture relevant studies on persistent pharmaceuticals in water treatment. Key search terms included: "persistent pharmaceuticals", "recalcitrant pharmaceuticals", "pharmaceuticals in wastewater", "advanced oxidation processes", "AOP", "ozonation", "UV/H_2O_2", "membrane bioreactor", "activated carbon", "adsorption", "transformation products", "pharmaceutical metabolites", "antimicrobial resistance", "endocrine disrupting compounds", "water reuse", "SDG 6″, and "emerging contaminants".

Original research articles, review papers, and book chapters about pharmaceuticals in water were included. These covered their presence, how they persist, treatment methods, and effects on the environment or health. By contrast, studies unrelated to water treatment, non-English publications, and non-peer-reviewed sources were excluded. The retrieved articles were screened by title and abstract, followed by full-text review. Relevant data were synthesized to structure the review along the driver-to-barrier chain described in the Introduction (Table 1), covering persistence drivers and transformation, analytical constraints, fate and exposure, removal strategies, integrated design, and future perspectives. Special emphasis was placed on recent advances (2020-2025) to ensure the review reflects current scientific and technological trends.

The initial literature search covered the period January 1, 2016, and was last updated on July 30, 2026. PubMed, Scopus, Web of Science and Google Scholar were the databases used for the search. After removal of duplicates, records were screened by title and abstract, and full texts were assessed. In response to the peer-review process, targeted supplementary searches were performed in September 2026 to retrieve pilot- and full-scale studies reporting operating conditions, transformation-product and toxicity data, energy and cost indicators, and applications of machine learning to pharmaceutical removal. For these questions, foundational studies, published before 2020, were included when they reported pilot- or full-scale data. When a quantity is not reported in the source, it is marked "n.r." in the tables and no value has been inferred.

The current review employs a narrative synthesis rather than a systematic review design. In contrast to systematic reviews that adhere to standardized frameworks such as Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), this work integrates and analyzes the available literature thematically to provide a comprehensive evaluation of pharmaceutical persistence mechanisms, treatment technologies, and associated environmental risks in aquatic systems. The narrative approach enables the inclusion of heterogeneous evidence (encompassing experimental investigations, field monitoring studies, and technological assessments) thereby accommodating the methodological diversity inherent in this research area. Considering the broad scope and exploratory character of the present review, application of PRISMA guidelines was not warranted. Because a narrative design does not allow a formal risk-of-bias assessment, the tables report the scale of each study (laboratory, pilot or full scale) so that readers can weigh the strength of the evidence. Results from different studies were compared by the persistence driver acting on each compound, the endpoint measured (parent-compound removal, degradation or mineralization), the scale of the study, and the water matrix, so that differences between studies could be interpreted and not only listed.

3. Mechanisms of pharmaceutical persistence: which pharmaceuticals persist and why

Within the wider group of persistent contaminants introduced in Section 1, pharmaceuticals are examined in this review because they are designed to be biologically active at low doses, are released continuously through excretion, disposal and manufacturing, and include compounds that pass through wastewater treatment, generate transformation products and select for antimicrobial resistance. This section first identifies the molecular and physicochemical drivers of persistence (Section 3.1), then shows how these drivers translate into the behavior of the main pharmaceutical groups in conventional wastewater treatment (Section 3.2), and finally examines how transformation extends or ends persistence (Section 3.3).

3.1. Physicochemical and molecular drivers of persistence

Fig. 1 shows the molecular and physicochemical drivers that make pharmaceuticals persistent in water and wastewater treatment: high polarity, which means that they pass through treatment processes without being effectively adsorbed; strong aromatic/fluorinated rings as they resist oxidation within the treatment processes; ionizable, where they remain dissolved and not captured by membranes; stable metabolites, where their derivatives are often more persistent than the parent compounds, and poor biodegradability, where microorganisms cannot metabolize them. These drivers are not independent. Structural stability (strong bonds and stabilized or halogenated ring systems) determines whether a compound is attacked by enzymes and oxidants; polarity and ionization determine whether it is retained by sorbents, sludge and membranes; and the water matrix and microbial context determine how much of the available oxidant or biological capacity actually reaches the compound. A compound that is persistent in one treatment step is therefore not necessarily persistent in another: carbamazepine, for example, passes through activated sludge with little removal but fell below the detection limit in full-scale ozonation (Hollender et al., 2009). This is why treatment has to be matched to the mechanism (Section 6).

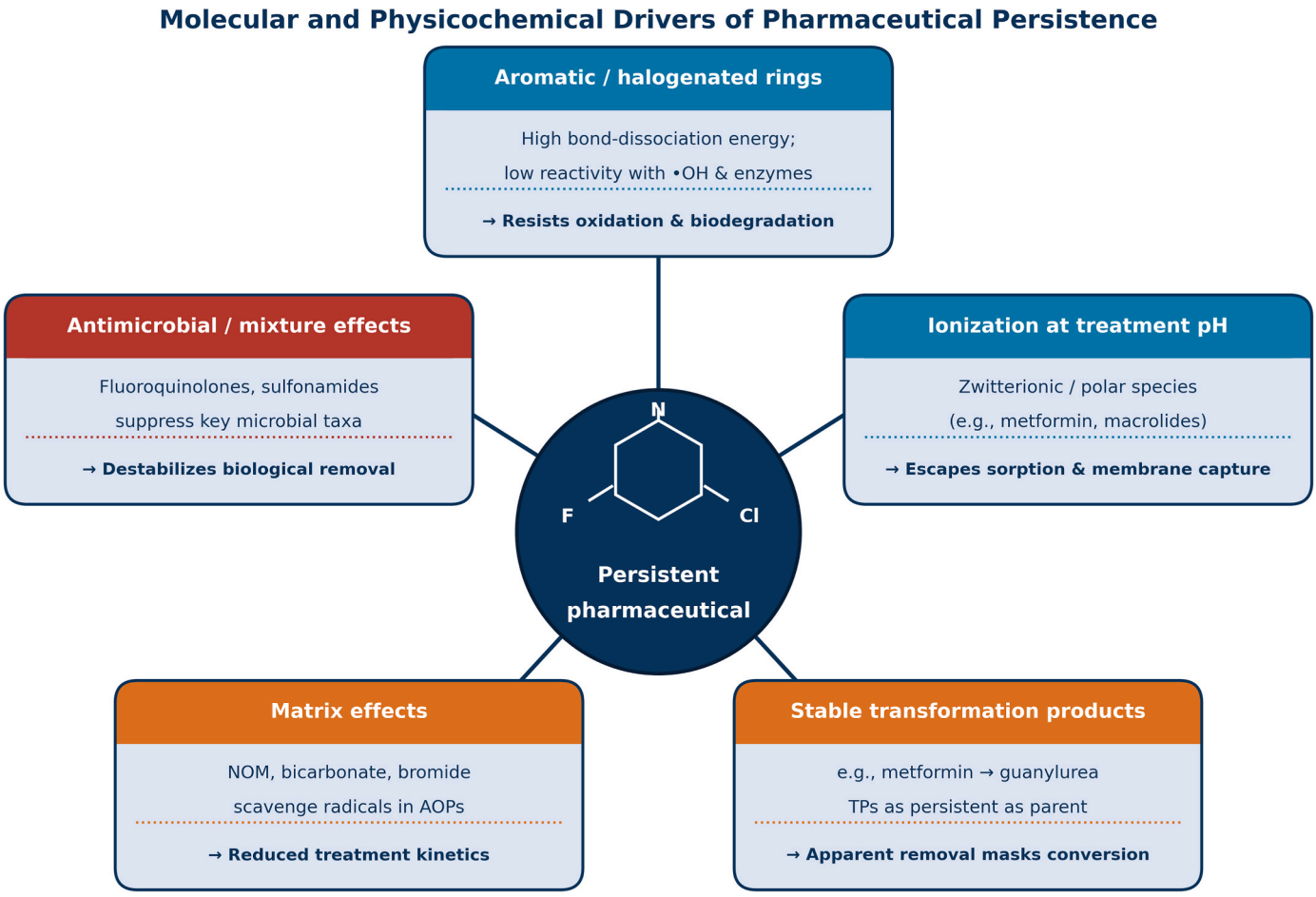


Fig. 1. Molecular and physicochemical drivers of pharmaceutical persistence in water and wastewater treatment. The central hub represents a generic persistent pharmaceutical; the surrounding panels summarize the main mechanisms (aromatic/halogenated rings, ionization at treatment pH, formation of stable transformation products, matrix effects, and antimicrobial/mixture effects) and their consequence for treatment performance.

The key mechanistic reasons why pharmaceuticals persist through conventional water and wastewater treatment, with illustrative compounds (e.g., carbamazepine, venlafaxine, diclofenac, metformin/guanylurea, and iodinated contrast media) are next discussed. Firstly, intrinsic physicochemical stability and functionalization hinder biodegradation and oxidation. Electron-withdrawing groups (e.g., halogens on diclofenac, tricyclic/amide motifs in carbamazepine) increase bond dissociation energies, and reduce reactivity toward hydroxyl radicals and biocatalytic enzymes, leading to poor removal in activated sludge and modest susceptibility to advanced oxidation unless high oxidant exposures are applied (Nosek and Zhao, 2024; Trognon et al., 2024). Photostability or slow indirect photolysis further extends environmental half-lives, as shown for venlafaxine and other antidepressants (de Souza et al., 2022). Transformation often yields equally persistent or toxic transformation products (TPs) (e.g., diclofenac ozonation/UV TPs), complicating process optimization and risk assessment (Alharbi et al., 2022; Nosek and Zhao, 2024). Secondly, ionization behavior and speciation at treatment pH (6-8) reduce removal by sorption and membranes. Many pharmaceuticals are zwitterionic or highly polar cations/anions (e.g., metformin, macrolides), which limit hydrophobic partitioning to sludge and activated carbon, and enable passage through low-pressure membranes. For metformin, near-quantitative biotransformation to guanylurea occurs in WWTPs. The TP is similarly polar and persistent, so apparent "removal" reflects conversion rather than mineralization (Poursat et al., 2019). Iodinated contrast media are purposely designed to be highly water-soluble, sterically hindered, and biologically inert, yielding negligible sorption and biodegradation. Consequently, they pass through WWTPs and may form toxic iodinated disinfection by-products downstream (Zhang et al., 2023*b*; Yan et al., 2024). Thirdly, matrix effects in real waters suppress treatment kinetics. Natural organic matter (NOM), bicarbonate, and bromide scavenge radicals or shift AOP pathways; competitive adsorption with NOM reduces uptake on carbon and mineral sorbents, while short hydraulic/sludge retention times limit acclimation of specialist degraders. These effects collectively explain widely variable removals reported across facilities and seasons (Alfonso-Muniozguren et al., 2021; Shearer et al., 2022). Fourthly, antimicrobial activity and mixture effects inhibit biological processes. Fluoroquinolones and sulfonamides can suppress key microbial populations, slow nitrification, and alter community composition, reducing biotransformation capacity and promoting antibiotic resistance genes (ARGs), which further destabilizes removal performance (Uluseker et al., 2021; Rilstone et al., 2025). Finally, life-cycle and analytical blind spots perpetuate persistence. Many WWTP "removals" represent phase transfer (e.g., sorption to sludge) or conversion to unmonitored TPs. Downstream back-diffusion from biofilms/sediments and continuous inputs from hospitals and households maintain quasi-steady concentrations. Emerging multi-analyte HRMS surveys repeatedly uncover dozens of TPs for psychotropics and other classes, underscoring that apparent disappearance often masks transformation rather than mineralization (Wang et al., 2025). These transformation aspects are developed in Section 3.3, and the analytical blind spots in Section 4. These coupled factors explain why compounds such as carbamazepine, venlafaxine, sulfamethoxazole, and iodinated contrast media remain among the most persistent and frequently detected in

effluents and receiving waters, even where advanced treatment is deployed (Do et al., 2022; Yan et al., 2024).

Treatment design must match the mechanisms driving persistence. Ozone effectively removes reactive pharmaceuticals, whereas poorly reactive compounds require alternative processes; polar or ionized substances often evade sorption and show variable membrane retention; natural organic matter increases oxidant demand; and apparent removal may simply reflect transformation, necessitating polishing treatments and transformation-product monitoring (Bourgin et al., 2018; Gu et al., 2022; Hollender et al., 2009; Kabbani et al., 2021). This mechanism-to-barrier logic is developed in Section 6.1.

3.2. Groups of persistent pharmaceuticals and their behavior in conventional wastewater treatment

This section provides the compound-level basis for the rest of the review. It identifies which groups of pharmaceuticals repeatedly pass through wastewater treatment (Table 2), and how they behave in conventional and advanced processes (Table 3). Each group is read against the drivers established in Section 3.1, and the removal technologies are evaluated in Section 6.

Persistent pharmaceuticals can be categorized in nine groups (Table 2). The antiepileptic group represented by a common drug "carbamazepine" which is neutral, stable, and poorly biodegradable. In wastewater treatment plants, pharmaceuticals typically pass through conventionally activated sludge processes with little removal. Advanced processes (ozone/AOPs, electro-oxidation, high-dose PAC) can degrade it substantially (carbamazepine fell below the detection limit in full-scale ozonation of secondary effluent at a specific ozone dose of 0.47 g O_3 g ^{1} DOC; Hollender et al., 2009). Nonetheless, degradation efficiency depends on applied ozone dose and contact time. Complete mineralization is rarely achieved, and its byproducts/metabolites (e.g., CBZ-epoxide) may remain in water and sludge (Molnarova et al., 2023; Wada and Olawade, 2025). The NSAID group, represented by diclofenac, is known as a potent, persistent, and officially flagged in the EU Watch List because it evades standard treatment and drives measurable bioactivity via cyclooxygenase (COX) inhibition downstream (Simon et al., 2022). Diclofenac reacts quickly with ozone and falls below the detection limit in full-scale ozonation at 0.47 g O_3 g ^{1} DOC (Hollender et al., 2009). The specific ozone dose needed at a given plant depends on the effluent matrix (Bourgin et al., 2018), so removal is site-sensitive. The group of selected antibiotics of sulfamethoxazole (SMX) and trimethoprim (TMP) (antibiotics, co-prescribed) both show variable, often low removal in secondary treatment, and can persist in drinking-water systems. SMX remains detectable after distribution-system residence. Advanced oxidation may remove a major part of it. However, the process needs careful control (Rilstone et al., 2025; Wada and Olawade, 2025). The group of antidepressants represented by venlafaxine and O-desmethylvenlafaxine is frequently reported in water effluents because of high usage and biodegradation resistance. Adsorption in addition to the advanced oxidation process (AOP) "polishing" is typically required for meaningful control (Ahmed et al., 2025; Wada and Olawade, 2025). Metoprolol (a β-blocker) is often only partially removed in activated sludge, with residuals common in finished waters without advanced steps (Molnarova et al., 2023; Wada and Olawade, 2025). Iodinated X-ray contrast media (ICM: iopromide, iohexol, iopamidol) compounds are highly polar, mobile, and remarkably persistent. They pass through wastewater treatment plants (WWTPs) largely intact. Even where "biotransformation" occurs, yields are modest and by-products (including iodinated DBPs under chlorination) can be problematic. Complete mineralization of these compounds is hard (James et al., 2023; Zhang et al., 2023b). Finally, the antidiabetic group represented by metformin is abundant but is rapidly and repeatedly converted in WWTPs to guanylurea, which then persists ("dead-end" product in many systems). Emerging consortia capable of degrading metformin have been identified, but in practice, guanylurea,

Table 2
Persistent pharmaceutical groups and their physico-chemical persistence drivers.

Pharmaceuticals	Examples and properties	Physico-Chemical Persistence Drivers
Antiepileptics	Carbamazepine – the global benchmark for persistence • Extremely stable aromatic structure • Passes through activated sludge with little removal; abated by ozonation at a sufficient dose in full-scale plants (Section 3.2) • Detected in finished drinking water worldwide	Neutral polarity, high stability, low biodegradability, strong aromatic structure
Antibiotics	Sulfamethoxazole – poor biodegradation, requires high ozone doses for effective removal • Adsorbs strongly to sludge; recalcitrant to oxidation Azithromycin – high persistence and strong ecological impacts	Moderate hydrophilicity, polar functional groups, antimicrobial activity inhibits biomass
Antidepressants and Psychiatric Drugs	Venlafaxine • Very hydrophilic → not removed by activated carbon or membranes Fluoxetine (Prozac) • Strong partitioning to sludge but transforms into persistent metabolites	High water solubility, low Koc (poor sorption), resistant to biodegradation
Anti-inflammatories (NSAIDs)	Diclofenac – partially removed by ozonation but forms toxic byproducts Ibuprofen and naproxen – partially removed, but metabolites remain persistent	Weak acid (pKa ≈ 4.2), photosensitive but recalcitrant in dark, partial ionization limits sorption
β-blockers and cardiovascular drugs	Atenolol – hydrophilic, resistant to activated carbon Metoprolol – stable and moderately persistent in secondary effluent	Moderate polarity, low volatility, partial sorption, slow biodegradation
Hormones and endocrine disruptors	17α-ethinylestradiol (EE2) – extremely potent at ng/L concentrations Estrone (E1) – persistent metabolite, difficult to fully remove	Hydrophobicity, low biodegradability, stability, and strong adsorption tendencies
Antidiabetic drugs	Metformin – one of the most abundant emerging contaminants • Resistant to chlorination; degradation by ozonation requires high exposure • Converted to guanylurea in WWTPs; apparent removal reflects conversion, not mineralization (Section 3.3)	Highly polar cationic compound (metformin), guanylurea is even more persistent and hydrophilic
Contrast agents (X-ray, MRI agents)	Iodinated contrast media (ICMs) – the most recalcitrant class overall • Almost no removal in WWTPs • Highly stable benzene structures with iodine substituents Gadolinium-based MRI agents – remain intact through all treatment stages	High polarity, stability, low biodegradability, and mobility
Cytostatics	Extremely persistent, genotoxic, mutagenic	Very high toxicity, poor removal in WWTPs, special concern in hospital effluents

Table 3
Persistent pharmaceuticals and recommended removal strategies.

Persistent Pharmaceuticals	Recommended Removal Train (based on literature evidence)
Carbamazepine (antiepileptic)	Ozonation or UV/H_2O_2 AOP → Biologically Active Filtration (BAF) or GAC polishing; high-dose PAC as pre-adsorption
Diclofenac (NSAID)	Ozonation → GAC or biological sand filtration; membrane bioreactor (MBR) hybrid systems enhance biodegradation
Sulfamethoxazole/Trimethoprim (antibiotics)	UV/H_2O_2 AOP or electro-oxidation → BAF or constructed wetland for polishing; PAC adsorption possible but variable
Venlafaxine/O-desmethylvenlafaxine (antidepressants)	Ozone or UV-based AOPs → GAC or bio-GAC; integrated ozonation–MBR systems highly effective
Metoprolol (β-blocker)	Ozonation → GAC or ion-exchange resin; alternative: Fenton/photo-Fenton oxidation
Iopromide/Iohexol/Iopamidol (ICM)	UV/persulfate or electro-oxidation → Nanofiltration/Reverse Osmosis (RO) → BAF for residuals
Metformin → Guanylurea (antidiabetic + by-product)	Advanced oxidation (ozone, photocatalysis) → Bio-GAC for guanylurea degradation; anaerobic pretreatment may improve results

Note: The trains in this table are literature-based recommendations and are qualitative. Quantitative performance, with operating conditions and scale, is given in Table 5, while transformation-product and toxicity information is given in Table 6.

the main transformation product, predominates in water effluents (Li et al., 2023; Dong et al., 2024).

Cytostatic pharmaceuticals are an emerging group of highly persistent contaminants of particular concern because many exhibit genotoxic, mutagenic, and carcinogenic effects. Their molecular design confers high stability against biotransformation, so they are only weakly removed in conventional wastewater treatment processes and can pass through into receiving waters. Multiple monitoring studies have reported these compounds in hospital effluents and WWTP influents and effluents at concentrations typically in the ng/L to low μg/L range, with conventional treatment often achieving very limited removal (Castellano-Hinojosa et al., 2023; González-Burciaga et al., 2025).

The groups in Table 2 show three patterns of behavior in conventional treatment, which are more informative than the group labels themselves. In the first pattern the parent compound passes through largely unchanged because its structure resists both enzymes and oxidants and, in several cases, because it is also poorly sorbed: carbamazepine, venlafaxine, the iodinated contrast media, and the cytostatics, whose molecular design confers stability against biotransformation. In the second pattern the parent compound is converted but the product is itself persistent, so that apparent removal reflects conversion and not mineralization: metformin is converted to guanylurea, and carbamazepine yields by-products such as CBZ-epoxide that may remain in water and sludge. In the third pattern removal is partial and depends on the matrix and operating conditions, so that the same compound is removed to very different extents at different plants: this applies to sulfamethoxazole and trimethoprim, to metoprolol, and to diclofenac, for which the ozone dose needed at a given plant depends on the effluent matrix. These patterns have different implications for treatment, which are developed in Section 6.1: the first requires a barrier that either attacks the persistent structure or retains the compound; the second requires monitoring of transformation products in addition to parent-compound removal; and the third requires dose control and site-specific monitoring. Because the pattern, and not the pharmaceutical class, determines which barrier is needed, the compound-specific trains in Table 3 are read in this review as illustrations of these principles, and the quantitative evidence behind them is examined in Section 6.2.

3.3. Transformation products as part of the persistence problem

Persistence cannot be judged from the parent compound alone, because the disappearance of a parent molecule may be conversion and not elimination. The studies reviewed here show three recurring situations, which can be distinguished by what the transformation does to the structural feature that makes the parent persistent. In the first, the transformation leaves that feature unchanged. Metformin is converted almost quantitatively to guanylurea in wastewater treatment plants, and this product is similarly polar and persistent, so that it behaves as a dead-end product in many systems and predominates in effluents even though metformin-degrading consortia have been identified (Poursat et al., 2019; Li et al., 2023; Dong et al., 2024). In the second, the transformation is reversible or yields products whose persistence, mobility and toxicity can exceed those of the parent. Carbamazepine-N-glucuronide undergoes deconjugation during soil aquifer treatment and regenerates the parent compound (He et al., 2024), and some transformation products of carbamazepine show persistence, mobility and toxicity characteristics that may exceed those of carbamazepine itself (He et al., 2024; Trognon et al., 2024). In the third, oxidative treatment removes the parent but introduces new products, some of which may be as persistent or toxic as the parent: numerous transformation products have been reported for carbamazepine and diclofenac (Alharbi et al., 2022; Nosek and Zhao, 2024; Trognon et al., 2024), and the oxidation or chlorination of iodinated contrast media can give iodinated disinfection by-products (Yan et al., 2024; Zhang et al., 2023b). A contrasting case is reductive: in the laboratory, UV/sulfite treatment of iopamidol released iodine as iodide and gave products of lower toxicity (Gu et al., 2022), which suggests that what matters for the fate of a product is whether the reaction removes or retains the feature that made the parent problematic. This remains a laboratory observation for a single compound class.

Transformation products are therefore not only an additional issue arising after treatment but a continuation of the persistence problem. They are formed by the same reactions that are meant to remove the parent compound; they can be as polar and persistent as the parent or more so, as for guanylurea (Table 2), and less sorbable than the parent, as for the ozonation products that were sorbed less than their parents on fresh granular activated carbon (Bourgin et al., 2018); and only a few have been quantified, which limits any quantitative relationship between structure, transformation pathway, stability and toxicity. For this reason, transformation products are followed through the rest of the review as targets in their own right: in the environment (Section 5), in the analytical effort needed to find and quantify them (Section 4), and in their formation and abatement during treatment (Section 6.3).

4. Analytical basis and limits of the evidence on persistent pharmaceuticals and their transformation products

All the examined in the following sections (occurrence, fate, removal efficiency and transformation-product formation) is only as reliable as the analytical methods that produced it. Therefore, this section does not describe analytical instruments for their own sake. It identifies the analytical features that determine what can be concluded about persistence, exposure and treatment performance, and the limits that follow from them.

Detection and quantification of persistent pharmaceuticals in aquatic environments require highly sensitive, selective and robust instrumentation because these compounds are typically present at low ng-μg/L levels, in complex matrices, and often alongside transformation products or metabolites.

Sample preparation: Solid-phase extraction (SPE) is the standard for concentrating trace pharmaceuticals from large water volumes while reducing matrix interferences (Alqarni, 2024).

Separation techniques: High-performance liquid chromatography (HPLC) or ultra-performance liquid chromatography (UPLC) are the

dominant methods for separating pharmaceuticals prior to detection (Molnarova et al., 2023; Omotola and Olatunji, 2020). For more volatile or thermally stable compounds, gas chromatography (GC) coupled to MS has been applied, although LC-MS/MS has largely become the gold standard for pharmaceuticals due to their polarity and thermal lability (Alqarni, 2024).

Detection and quantification: Tandem mass spectrometry (MS/MS) connected to LC (LC-MS/MS) is the cornerstone instrument for trace pharmaceutical analysis because of its high selectivity, sensitivity and ability to identify compounds based on precursor/product ion transitions. More recently, direct injection LC-MS/MS (without extensive preconcentration) has been applied to monitor pharmaceuticals in wastewater and reuse streams, demonstrating the evolving instrumentation and methods (Domínguez-García et al., 2025). Ionization sources (electrospray, atmospheric-pressure chemical ionization) and high-resolution mass spectrometry (HRMS) are increasingly used for non-target screening of pharmaceuticals and transformation products.

Data reliability and quality assurance: Accurate quantification requires internal standards (often isotopically labeled compounds), calibration curves, limits of detection/quantification (LODs/LOQs) and control of matrix effects. Alqarni (2024) note that matrix suppression/enhancement remains a persistent challenge in water and wastewater analytics. HRMS combined with suspect and non-target screening has advanced the detection of pharmaceuticals in environmental samples by identifying unknown transformation products without relying on reference standards. TOF and Orbitrap analyzers deliver high mass accuracy (typically <5 ppm) to support molecular formula assignment, and integration with MS/MS fragmentation data and retention time modeling aids in elucidating structures of novel compounds. These methods prove especially useful for evaluating effluents after advanced treatments, where oxidation yields diverse and unpredictable transformation products (Castaño-Ortiz et al., 2024).

Three consequences of these methods bear directly on the interpretation of the studies in the following sections. First, targeted LC-MS/MS quantifies a predefined list of compounds, so that removal efficiencies calculated from parent-compound concentrations cannot distinguish mineralization from conversion to unmonitored transformation products or from transfer to sludge or to a concentrate stream, which is why apparent removal can mask transformation (Section 3.1). Second, matrix suppression or enhancement (Alqarni, 2024) and differences between laboratories are potential sources of variation, in addition to treatment conditions, when removal efficiencies for the same compound differ among studies, and the need for inter-laboratory-comparable methods has been noted (Wu et al., 2024). Third, concentrations are reported at ng L^{-1} to µg L^{-1} levels, so that the limit of quantification determines which compounds and which transformation products can be followed at all, and a removal efficiency computed against a value at the limit of quantification is a lower bound and not an exact figure.

Suspect and non-target HRMS workflows propose candidate structures for transformation products. They have been evaluated as an alternative to target analysis across environmental compartments (Castaño-Ortiz et al., 2024). However, identification shows only that a structure is present. It does not establish the concentration (unless reference standards or a semi-quantification approach are used) or the biological activity. Effect-based methods address the second question by measuring the combined biological effect of a sample, including mixtures, without identifying the causative compounds. They are discussed together with transformation-product toxicity in Section 6.3.

Three levels of evidence can therefore be distinguished: target quantification of parent compounds and of the few transformation products for which standards exist; HRMS identification of candidate structures; and effect-based measurement of biological activity. Most of the removal data in this review rest on the first level, whereas conclusions on transformation products and toxicity rest on a smaller number of quantified products (for example, seven ozonation products at one plant; Bourgin et al., 2018) and on bioassay studies (Section 6.3). The consequence for the interpretation of this review is that parent-compound removal is not taken as evidence of reduced risk.

5. Environmental fate, exposure pathways and consequences of persistent pharmaceuticals

Having established which pharmaceuticals persist and why (Section 3) and how reliably this can be measured (Section 4), this section follows them from wastewater effluent into receiving surface waters (Section 5.1), groundwater (Section 5.2) and the food chain (Section 5.3), and then to the ecological (Section 5.4) and human-health consequences (Section 5.5). The sequence follows the stages through which a risk is formed: release of the parent compound and its metabolites with effluent, biosolids or manure; transport and transformation in the compartment reached; exposure of organisms and people through water, food or resistance determinants; and the resulting ecological or health consequence. Because the compartments are connected, with infiltration from irrigation and recharge reaching groundwater, groundwater discharging to surface water as baseflow, and return flows replenishing irrigation sources, each pathway is discussed once, in the compartment where it first becomes dominant, and is cross-referenced elsewhere. Hydrological, climatic and societal conditions are described here because they control the concentrations and exposure that treatment has to address: flow regime and dilution, evapoconcentration in dry periods, population ageing and the resulting consumption of medicines (IFPMA, 2022), the extent of wastewater reuse, and the capital and skills available to small utilities (Jani and Kumari, 2024). In turn, the consequences for treatment ambition are discussed in Sections 5.6 and 8.

5.1. Release and behavior in surface waters: the role of hydrology and sediments

Persistent pharmaceuticals (antibiotics, antidepressants, hormones, antiepileptics) move from WWTP effluent to rivers and floodplains, where chronic low-dose exposure alters organismal behavior, endocrine function and reproduction. Population-level effects and community shifts have been reported for fish and invertebrates (Kock et al., 2023; WHO, 2012). High baseflows and storm events spread residues widely, while combined sewer overflows create acute pulses that coincide with sensitive life stages (OECD, 2019). Biofilms and sediments act as long-term reservoirs, sustaining benthic exposure and trophic transfer to higher consumers. Mixture effects with nutrients, metals and PFAS increase risk beyond single-compound assessments (Ashfield et al., 2025; Khan et al., 2020). Continuous sub-MIC antibiotic exposures select for antimicrobial-resistance genes (ARGs) in biofilms and sediments, enhancing horizontal gene transfer and creating riverine AMR hotspots (Ashfield et al., 2025; OECD, 2019).

Elevated ionic strength and temperature can alter sorption/partitioning, increasing persistence of neutral and ionizable pharmaceuticals and promoting sediment entrapment with episodic remobilization during flash floods (Mosharaf et al., 2025). In endorheic or groundwater-dependent basins, limited dilution and extensive wastewater reuse elevate steady-state concentrations in canals, wadis, and recharge basins, while evapoconcentration during dry periods further amplifies contaminant loads and contact times in aquatic refugia (Khan et al., 2020; Mateo-Sagasta et al., 2022).

Taken together, the studies in this section show that exposure in surface waters is controlled by two kinds of factors that act independently. The hydrological context (dilution, baseflow and storm pulses, evapoconcentration) sets the concentration and timing of exposure, and the sorption behavior of the compound (Section 3.1) determines whether it remains dissolved or accumulates in biofilms and sediments that later act as secondary sources. This separation explains why the same effluent can have different ecological consequences in different basins, and why treatment objectives need to be set with the receiving hydrology in mind.

5.2. Movement of persistent pharmaceuticals to groundwater systems

Persistent pharmaceuticals can indeed migrate to shallow groundwater under certain hydrogeological, chemical, and land-use conditions. This mobility depends on a combination of persistence, aqueous solubility, low sorption affinity, and subsurface transport mechanisms. Persistent pharmaceuticals that resist biodegradation and persist in the aqueous phase are more likely to infiltrate soils during irrigation, recharge events, or effluent disposal operations (Kolpin et al., 2002). In permeable soils with low organic matter and minimal sorption potential (e.g., sandy substrates in arid regions), contaminants travel quickly beneath infiltration basins or recharge ponds (Chia et al., 2025). Moreover, pharmaceuticals applied via treated wastewater reuse, a growing trend in water-scarce regions, raise recharge risk if buffer zones or pre-treatment barriers are inadequate (Mosharaf et al., 2025). Recent investigations using isotopically labeled compounds have revealed that carbamazepine metabolites, particularly carbamazepine-N-glucuronide, undergo deconjugation during soil aquifer treatment, regenerating the parent compound and increasing groundwater contamination beyond what influent concentrations would predict (He et al., 2024). This deconjugation dynamic represents a significant challenge for managed aquifer recharge systems and highlights the need for monitoring both parent compounds and conjugated metabolites.

Transport to shallow aquifers occurs through unsaturated zone leaching, preferential flow paths, and rapid percolation in fractured rock or coarse media. Pharmaceuticals with high water solubility (e.g., sulfonamides, certain beta-lactams) and low partitioning to organic carbon are more mobile (Couto et al., 2019). Arid environments present accelerated infiltration of treated effluents during episodic recharge events, with less competition from microbial degradation, supporting deeper penetration (Wang et al., 2025). Conversely, wet regions may attenuate pharmaceuticals via greater soil sorption and microbial activity, although high recharge volumes can overwhelm attenuation capacity (Dibyanshu and Scheytt, 2025). In endorheic or groundwater-dependent basins, bank filtration and managed aquifer recharge (MAR) schemes risk breakthrough of highly mobile, polar pharmaceuticals (e.g., carbamazepine, metformin), challenging attenuation capacity (Khan et al., 2020; Mateo-Sagasta et al., 2022).

Field studies documented pharmaceuticals such as carbamazepine and diclofenac in shallow groundwater beneath urban recharge zones (Wada and Olawade, 2025). In Spain, Biel-Maeso et al. (2018) detected traces of sulfonamides and trimethoprim in soils irrigated with reclaimed wastewater, with potential for vertical migration under certain conditions. Laboratory column tests show that when infiltration rates exceed certain thresholds, attenuation declines sharply and compounds bypass soil retention layers (Couto et al., 2019).

Groundwater contamination by persistent pharmaceuticals poses risks to human health via potable water supply and to ecosystems via baseflow discharge into surface water. It complicates aquifer recovery efforts in water-scarce regions and increases treatment costs at end-use. Monitoring and establishing subsurface attenuation models are urgently needed to assess long-term impacts and design effective barriers.

In summary, mobility to groundwater is greatest for persistent, polar and weakly sorbing compounds in permeable, low-organic soils and under high infiltration, and it can be underestimated when conjugated metabolites that deconjugate in the subsurface are not monitored (He et al., 2024). These observations support applying more stringent treatment and monitoring to reclaimed water intended for infiltration or irrigation, and they motivate the monitoring of both parent compounds and metabolites.

5.3. Fate and transport of persistent pharmaceuticals in the food chain

Persistent pharmaceuticals (e.g., carbamazepine, diclofenac, fluoroquinolones, SSRIs) enter agro-aquatic systems primarily via wastewater effluent, reclaimed-water irrigation, sludge/manure application, aquaculture inputs, and combined sewer overflows. In surface waters, numerous compounds persist in dissolved form because of their polarity and weak sorption potential (low to moderate log K_{ow}), allowing them to travel downstream and be assimilated by primary producers and biofilms. In contrast, less polar contaminants tend to associate with sediments and benthic organic matter, forming long-term reservoirs that sustain benthic exposure (Boxall et al., 2012; Wilkinson et al., 2022). Plant uptake is well established: field and lysimeter studies show root absorption and xylem transport of recalcitrant pharmaceuticals (notably carbamazepine) with metabolite formation in edible tissues, especially under reclaimed-water irrigation and in sandy, low-organic soils (Malchi et al., 2014). Reclaimed-water irrigation also creates pathways to soils, pollinators and terrestrial food webs, and manure and aquaculture intensification add veterinary pharmaceuticals (Mosharaf et al., 2025; OECD, 2019). In terrestrial food chains, sludge-amended soils can transfer antibiotics and other drugs to forage crops and invertebrates, with residues detected in grazers and their products (Li et al., 2020). Quantitative structure-activity relationship (QSAR) modeling has revealed that certain pharmaceutical metabolites exhibit higher developmental toxicity than parent compounds, complicating risk assessment. For example, carbamazepine transformation products demonstrate persistence, mobility, and toxicity (PMT) characteristics that may exceed those of carbamazepine itself (He et al., 2024; Trognon et al., 2024).

Aquatic trophic transfer is compound- and tissue-specific. Classical biomagnification is often limited for polar pharmaceuticals. Nevertheless, biomagnification by protein binding and tissue sequestration (e.g., in fish brain, liver) can occur despite low logKow, while pseudo-biomagnification can arise in food webs exposed to continuous effluent inputs (Rilstone et al., 2025). Top predators can be at risk when compounds are both bioactive and poorly metabolized (Oaks et al., 2004). Sublethal effects (endocrine disruption, behavioral alteration, and immune modulation) have been reported at environmentally realistic concentrations, with consequences for feeding, predator avoidance, and reproduction, thereby altering energy flow and community structure (Boxall et al., 2012). In arid environments, intensive wastewater reuse enhances contaminant transfer through soil-plant pathways. Limited recharge events and low soil organic carbon reduce attenuation capacity, facilitating contaminant migration into shallow groundwater and return flows that subsequently replenish irrigation sources (Wilkinson et al., 2022). Across compartments, transformation to active metabolites, conjugation/deconjugation cycles, and photolysis by-products complicate risk assessment because metabolites can retain bioactivity and move differently through food webs (Rilstone et al., 2025). The formation and persistence of such products are discussed in Section 3.3. Overall, persistence, continuous inputs, edible-crop uptake, tissue-specific accumulation, and mixture effects combine to sustain exposure across trophic levels, highlighting the need for source control, advanced treatment, and food-chain-aware monitoring.

Plant uptake of persistent pharmaceuticals is well documented under reclaimed-water irrigation, whereas biomagnification in aquatic food webs is compound- and tissue-specific and generally limited for polar compounds. Therefore, the evidence is strongest for the irrigation pathway, which links wastewater treatment performance directly to food safety, and weaker for trophic transfer in aquatic systems.

5.4. Ecological consequences

Across surface waters, groundwater-fed baseflow and irrigated soils (Sections 5.1–5.3), the cross-cutting ecological risks of persistent pharmaceuticals include the following (i) endocrine disruption (e.g., ethinylestradiol): causing feminization and recruitment failure; (ii) behavioural and fitness changes from psychoactives (e.g., fluoxetine) reducing predator avoidance and reproductive success; (iii) selection for AMR with ecosystem-wide externalities; (iv) multi-stressor interactions under warming, hypoxia and salinity that amplify effects; and (v) legacy

storage in sediments with long recovery times once inputs are reduced (Ashfield et al., 2025; Kock et al., 2023; WHO, 2012). Laboratory and field studies have shown that pharmaceutical mixtures at environmentally realistic concentrations alter predator-prey interactions, reproductive timing, and stress responses across multiple trophic levels, with cascade effects on ecosystem function and resilience (Aich et al., 2024; Soriano et al., 2024). Managing these risks requires source control, advanced treatment, reuse governance, and monitoring that integrates flow regimes, sediment compartments and AMR endpoints.

5.5. Potential human health risks of persistent pharmaceuticals in water

Human exposure arises through three routes that follow directly from the pathways above: drinking water drawn from surface or groundwater sources that receive effluent or recharge (Sections 5.1 and 5.2), food produced on land irrigated with reclaimed water (Section 5.3), and the spread of antimicrobial resistance through water and the food chain. Risk is the product of hazard and exposure: the hazard comes from the biological activity that pharmaceuticals are designed to have at low doses, whereas the exposure is set by concentration, duration and pathway. At the ng L^{-1} to low μg L^{-1} levels typical of water, the exposure term is small for acute effects and uncertain for chronic, mixture-related effects, which is why the pathways below are described in terms of mechanism and strength of evidence.

Persistent pharmaceuticals (antibiotics, hormones, anticonvulsants, antidepressants, antineoplastics, and others) are now detected from ng/L to low μg/L in surface, ground, and occasionally finished waters worldwide (aus der Beek et al., 2016; Wilkinson et al., 2022). At these trace levels, acute toxicity for the general population is typically low. However, several scientifically credible risk pathways remain.

- **Endocrine disruption:** Synthetic estrogens (e.g., 17α-ethinylestradiol) and other hormonally active agents have picogram-to-nanogram potency and can alter endocrine signaling. While epidemiological evidence for human effects via drinking water is limited, margins of exposure are narrow for sensitive life stages (fetal, infant), warranting precaution (Johnson and Sumpter, 2014; WHO, 2012).
- **Antimicrobial resistance (AMR):** Sub-inhibitory antibiotic residues and co-selecting agents (biocides, metals) can enrich resistance genes and resistant bacteria in aquatic microbiomes, increasing the probability of human exposure through water or the food chain (Kraemer et al., 2019; OECD, 2019). AMR is a population-level health risk with substantial morbidity and cost implications.
- **Genotoxic and cytotoxic agents:** Antineoplastic drugs (e.g., cyclophosphamide), some anticonvulsants, and transformation products show genotoxic/oxidative-stress mechanisms. Although concentrations in drinking water are usually far below therapeutic doses, chronic low-dose and mixture effects remain insufficiently characterized (Boxall et al., 2012; Patel et al., 2019).
- **Neuroactive and psychoactive pharmaceuticals:** Compounds targeting the central nervous system (e.g., carbamazepine) are highly persistent and bioactive. Experimental studies suggest potential impacts on neuroendocrine and developmental endpoints, with particular concern for prenatal and early-life exposures (aus der Beek et al., 2016; Wilkinson et al., 2022). Epidemiological studies of prenatal and early-life exposure to mixtures of psychoactive pharmaceuticals at environmental concentrations remain limited, so this is a research gap and not an established risk (Aich et al., 2024).
- **Mixtures and transformation products:** Individuals are exposed to complex mixtures of parent drugs and metabolites/oxidation products whose combined effects may be additive or synergistic. Toxicological data for many by-products are sparse (Boxall et al., 2012; OECD, 2019).
- **Equity and susceptibility:** Vulnerable groups such as pregnant women, infants (higher water intake per body mass), patients with renal/hepatic impairment, and those relying on impacted sources may face comparatively higher risks (WHO, 2012).

At the trace concentrations typical of drinking water, acute toxicity is unlikely. The credible concerns are chronic, mixture-related and pathway-specific (endocrine effects, antimicrobial resistance), and for neurodevelopmental effects the evidence remains a research gap and not an established risk. These conclusions do not change the treatment objective, but they affect which endpoints should be monitored (effect-based tools, resistance genes) and why transformation products with sparse toxicity data have to be considered.

5.6. Synthesis: exposure pathways, strength of evidence and implications for treatment objectives

Comparing the pathways shows that the strength of evidence differs among them, and that the differences follow the mechanisms discussed in Section 3. In surface waters, exposure is controlled by hydrology as much as by the compound (Section 5.1). Mobility to groundwater is greatest for persistent, polar and weakly sorbing compounds in permeable, low-organic soils and under high infiltration, and it is underestimated when conjugated metabolites that deconjugate in the subsurface are not monitored (Section 5.2). Plant uptake under reclaimed-water irrigation is well documented, whereas biomagnification in aquatic food webs is compound- and tissue-specific and generally limited for polar compounds, so that the evidence is strongest for the irrigation pathway (Section 5.3). For human health, acute toxicity at the trace concentrations typical of water is unlikely; the credible concerns are chronic, mixture-related and pathway-specific (endocrine effects, antimicrobial resistance), and for neurodevelopmental effects the evidence is a research gap (Section 5.5). Two conclusions follow for the rest of the review. First, the reuse destinations that connect directly to the most strongly documented pathways, namely irrigation and infiltration or recharge, set the most demanding requirements on treatment performance and monitoring, including monitoring of conjugates and transformation products and not only of parent compounds. Second, because the endpoints of greatest concern are chronic and mixture-related, treatment performance cannot be judged by parent-compound removal alone, and effect-based and resistance-gene endpoints have to be part of the evaluation (Sections 6.3 and 8).

6. Treatment: matching barriers to persistence mechanisms

Treatment is evaluated against the persistence drivers identified in Section 3. For each barrier, the questions asked are whether it acts on the mechanism that makes the compound persistent, what it achieves in terms of parent-compound removal, degradation and mineralization, and what it generates in terms of transformation products, residual streams and energy and resource demand.

6.1. From persistence drivers to barrier selection

Table 4 links each persistence driver to the evidence on treatment performance and to its implication for the selection of barriers. Three generalizations emerge from its rows. First, the reactivity of a compound toward the oxidant, and not its pharmaceutical class, determines whether oxidation is effective: compounds with electron-rich moieties (carbamazepine, diclofenac and sulfamethoxazole) fell below detection limits at 0.47 g O_3 g $^{-1}$ DOC in full-scale ozonation, whereas iodinated X-ray contrast media and some triazine herbicides, which react slowly with ozone (second-order rate constants below 10^2 M^{-1} s^{-1}), persisted to a large extent (Hollender et al., 2009). Second, retention by sorption and membranes is governed by polarity, charge and size, so that compounds that are poorly reactive toward ozone are often also poorly sorbed, as for iodinated contrast media. For these compounds a different

Table 4
Link between persistence drivers and treatment-train selection.

Persistence driver (Section 3.33.1)	Illustrative compounds	Consequence for treatment (evidence; scale)	Implication for treatment-train selection	Key sources
Stable aromatic or halogenated structure; low reactivity toward oxidants and enzymes	Carbamazepine, diclofenac	Little removal in activated sludge (Section 3.2). Compounds with electron-rich moieties reacted quickly with ozone: carbamazepine, diclofenac and sulfamethoxazole fell below detection limits at 0.47 g O_3 g ^{1} DOC (full scale).	Oxidation (ozone or radical AOP) is effective, with the dose set per unit DOC; a polishing step is then needed for transformation products.	Hollender et al. (2009); Bourgin et al. (2018)
Low reactivity with ozone	Iodinated X-ray contrast media; some triazine herbicides	Persisted to a large extent in full-scale ozonation (second-order rate constants below 10^{2} M ^{1} s ^{1}). Oxidation can lead to iodinated by-products.	Consider reductive deiodination (ARP such as UV/sulfite: iopamidol degraded within about 2.5 min at pH 9 in the laboratory, with up to about 98% of iodine released as iodide and lower product toxicity) or membrane retention. ARP evidence is laboratory-scale only.	Gu et al. (2022); Hollender et al. (2009); Zhang et al. (2023b)
High polarity or ionization (limited sorption)	Metformin, venlafaxine, iodinated contrast media, macrolides	Poor retention by activated carbon and low-pressure membranes (Section 3.1). In nanofiltration, charged diclofenac was rejected at 90–99% versus 65–77% for neutral carbamazepine (bench scale). In a full-scale groundwater plant, NF/RO rejected more than 85% of almost all pharmaceuticals, with lower retention of some (acetaminophen 44.8–73%).	Charge- and size-based membranes retain many polar compounds but produce a concentrate that contains them (several hundred ng L ^{1} in the brine) and requires management; sorption alone is unreliable for polar cationic or zwitterionic compounds.	Kabbani et al. (2021); Radjenović et al. (2008)
Matrix effects (NOM, bicarbonate, bromide)	All oxidation-based steps	Scavenging raises the oxidant demand and bromide leads to bromate. At full scale doses are expressed per unit DOC; at 0.55 g O_3 g ^{1} DOC, bromate stayed at or below 5 μg L ^{1} and NDMA at or below 30 ng L ^{1}. Humic acid inhibited UV/sulfite in the laboratory.	Size the oxidant dose to the DOC and monitor bromate; lower the DOC before oxidation where feasible, as in the sequence of Section 7.1.	Bourgin et al. (2018); Gu et al. (2022); Hollender et al. (2009)
Stable or more persistent transformation products (conversion instead of mineralization)	Metformin to guanylurea; ozonation products (N-oxides)	Seven quantified ozonation products were stable in biological post-treatment and were sorbed on fresh GAC less than their parents; in the laboratory, DOC removal can be much lower than parent conversion (about 40% for carbamazepine).	Do not equate parent removal with risk reduction: add transformation-product monitoring and effect-based endpoints, and combine with polishing (sand filtration, BAC/GAC).	Bourgin et al. (2018); Jelic et al. (2013); Poursat et al. (2019)
Antimicrobial activity and mixture effects	Fluoroquinolones, sulfonamides	Suppression of key microbial populations and selection of resistance genes can lower biological removal (Section 3.1).	Biological treatment should not be the only barrier for antibiotics; combine with oxidation or adsorption and monitor resistance genes. No quantitative treatment-train data on resistance genes were compiled in this review.	Sambaza and Naicker (2023); Uluseker et al. (2021)

type of barrier has to be considered, namely reductive deiodination or membrane retention; the reductive route has so far been demonstrated only in the laboratory (Gu et al., 2022), and membranes produce a concentrate that contains the retained compounds (Radjenović et al., 2008). Third, the water matrix modulates all oxidation- and sorption-based steps: dissolved organic carbon, bicarbonate and bromide raise the oxidant demand or lead to by-products, so that oxidant doses are expressed per unit of DOC and bromate and N-nitrosodimethylamine have to be monitored (Bourgin et al., 2018; Hollender et al., 2009). Persistent transformation products add a requirement that applies to every barrier: parent-compound removal must not be equated with risk reduction (Section 6.3). Section 3.2 and Table 3 give compound-specific illustrations of these rules, and Sections 6.2 to 6.4 examine the quantitative evidence.

6.2. *Removal of persistent pharmaceuticals from water and wastewater*

Removing persistent pharmaceuticals from water and wastewater poses a growing challenge in environmental engineering. These compounds resist degradation due to their chemical stability, low concentrations, trace-level biological activity, poor response to conventional treatments, and potential to form transformation products (TPs) of unknown toxicity (Chaber-Jarlachowicz et al., 2025; Kanakaraju et al., 2018). Conventional biological wastewater treatment systems (e.g., activated sludge, CAS) are frequently unable to sufficiently remove many pharmaceuticals—studies report residual concentrations in effluents often in the ng-μg/L range, and removal efficiencies sometimes falling below 20% for compounds such as carbamazepine and fluoxetine, although removal rates vary considerably (20-70%) depending on compound properties and operating conditions (Chaber-Jarlachowicz et al., 2025; Inarmal and Moodley, 2024). Table 3 summarizes the treatment technologies used to remove each group from wastewater.

The current review distinguishes three treatment endpoints: parent-compound removal, degradation, and mineralization, which often do not coincide. Pharmaceuticals can be transformed without full mineralization, generating persistent or toxic by-products, while membrane processes may simply transfer contaminants to a concentrate stream rather than eliminate them (Escher et al., 2009; Jelic et al., 2013; Radjenović et al., 2008). Table 5 summarizes study scale, operating conditions, and endpoints.

One of the most promising routes involves advanced treatment trains combining adsorption, advanced oxidation processes (AOPs), membrane separation and biological polishing. Adsorption onto activated carbon (granular or powdered) remains a staple: inexpensive carbonaceous adsorbents and engineered materials such as biochars/bioadsorbents offer practical removal of a wide range of pharmaceuticals and TPs (Munuhe et al., 2025; Shearer et al., 2022). Evidence for individual barriers is summarized in Table 5. Ozonation, activated carbon, and membrane technologies can substantially reduce pharmaceutical contamination, although removal varies among compounds and treatment mechanisms (Bourgin et al., 2018; Hollender et al., 2009; Kabbani et al., 2021; Margot et al., 2013; Radjenović et al., 2008). AOPs, including ozonation, UV/H_2O_2, photo-Fenton, sonolysis and electrochemical oxidation, have gained traction for their ability to transform pharmaceuticals and convert them into more biodegradable forms,

Table 5
Operating conditions, scale and results of selected studies on the removal of pharmaceuticals and micropollutants. "n.r.": not reported in the source examined.

Process	Scale and matrix	Oxidant, sorbent or membrane conditions	Initial concentration/pH/time	Endpoint	Result	Source
Ozonation + sand filtration	Full scale; municipal WWTP, secondary effluent	0.47 g O_3 g ^{1} DOC; medium dose about 0.6 g O_3 g ^{1} DOC	pH 7 for rate constants only	Parent removal (220 micropollutants); NDMA, bromate	Sulfamethoxazole, diclofenac, carbamazepine below detection limit at 0.47; atenolol and benzotriazole above 85% at about 0.6; some X-ray contrast media and triazines persisted to a large extent; NDMA at or below 14 ng L ^{1}, bromate below 10 μg L ^{1}; mineralization n.r.	Hollender et al. (2009)
Ozonation + biological post-treatment (sand filter, moving bed, fixed bed) or GAC	Full scale; WWTP of 105,000 PE	0.35–0.97 g O_3 g ^{1} DOC tested, 0.55 recommended; fresh GAC filter up to 50,000 bed volumes	n.r.	Parent removal (12 indicators; 550 substances); DOC, AOC, TSS; TPs	At 0.55: at least 80% average abatement of 12 indicators, above 79% average for 550 substances; sand filtration best biological post-treatment; fresh GAC added 20–89% (27,000 bed volumes); seven ozonation TPs not abated biologically	Bourgin et al. (2018)
Ozone + sand filtration vs PAC + UF or sand filtration	Large-scale pilots, more than 1 year; municipal WWTP, Lausanne	Ozone 5.7 mg L ^{1} (average); PAC 10–20 mg L ^{1}	n.r.	Parent removal (more than 70 substances); toxicity	Both above 80% on average vs raw wastewater; PAC–UF gave the strongest toxicity decrease and disinfection but higher cost	Margot et al. (2013)
Nanofiltration/ reverse osmosis	Full scale; drinking-water plant, groundwater	Membrane type, pressure and pH	Feed (ng L ^{1}): diclofenac 60.2–219.4; carbamazepine 8.7–166.5	Parent rejection	Above 85% for almost all compounds; acetaminophen 44.8–73%, gemfibrozil 50–70%, mefenamic acid 30–50%; brine contains several hundred ng L ^{1}	Radjenović et al. (2008)
Nanofiltration	Bench scale; synthetic solutions at pharmaceutical-industry concentrations	One commercial NF membrane; NaCl and temperature varied	n.r.	Parent rejection	Diclofenac 90–99%; ibuprofen 85–96% (rises with salt); carbamazepine 65–77% (falls with salt and temperature)	Kabbani et al. (2021)
UV/sulfite (advanced reduction)	Laboratory; iopamidol	Sulfite dose and UV intensity varied; pH 9 best	time about 2.5 min for near-complete degradation	Parent degradation; deiodination; toxicity	k_{obs} 2.08 min ^{1} (about 4 times UV alone); about 98% of iodine as iodide; product toxicity significantly lower; humic acid inhibitory	Gu et al. (2022)
TiO_2/UV/ultrasound	Laboratory; demineralized water, groundwater, effluent	UV-A or simulated solar light; ultrasound	n.r.	Parent conversion; DOC removal; acute toxicity	DOC removal about 40% in pure water, lower than carbamazepine conversion; acute toxicity increased	Jelic et al. (2013)
Ozonation + biological sand filtration with bioassays	Full scale; municipal WWTP	n.r.	n.r.	Estrogenicity; non-specific and reactive toxicity	Estrogenicity: 95% secondary, 86% ozonation, 99.5% overall; ozone modifies but does not fully mineralize, leaving residual toxicity for some endpoints	Escher et al. (2009)
Ozone, PAC or GAC upgrades (13 plants)	Full scale; Swiss municipal WWTPs (6 ozone, 5 PAC, 2 GAC)	Plant-specific	n.r.	Annual average elimination	75–90% (the 80% aim mostly achieved)	VSA (2025)

although complete mineralization is seldom reached at practical doses (Kanakaraju et al., 2018). However, the formation of undesirable TPs (sometimes more toxic than parent compounds) remains a concern and highlights the need for downstream biological or adsorptive polishing. Hybrid systems that integrate adsorption and AOPs (e.g., electrochemical + GAC) have shown synergies in reducing persistent micropollutants (Munuhe et al., 2025).

Advanced reduction processes (ARPs) offer a complementary approach to oxidation by generating reducing species that effectively degrade poorly oxidizable compounds, including iodinated X-ray contrast media (Hollender et al., 2009; Yan et al., 2024; Zhang et al., 2023*b*). Laboratory studies showed rapid and near-complete degradation of iopamidol, substantial deiodination, and reduced toxicity of transformation products, although performance was inhibited by humic substances (Gu et al., 2022). Nevertheless, evidence remains limited to laboratory scale, and no pilot- or full-scale studies on pharmaceutical mixtures have been identified (Gu et al., 2022; Zhang et al., 2023*b*).

Tertiary polishing via biologically active carbon (BAC) filtration, constructed wetlands and microalgae systems also provide sustainable finishing steps for micropollutant removal. Microalgae, for example, have demonstrated 30-70% removal of selected pharmaceuticals through bioaccumulation/adsorption and metabolic degradation (Gupta et al., 2024). These biological processes are low-energy and can complement aggressive upstream treatments by handling residual concentrations.

Finally, to address persistent pharmaceuticals in water and wastewater, treatment schemes must evolve beyond conventional biological systems (Fig. 2). Multi-barrier trains that integrate adsorption, membranes, AOPs and biological polishing are the most promising option for reliably controlling these micropollutants, although complete trains have rarely been evaluated end-to-end (Section 7.1). However, success depends on vigilant monitoring of both parent compounds and TPs, and on tailoring treatment to local effluent chemistry.

Overall, biological treatment alone is often insufficient, whereas ozonation and activated carbon typically achieve >80% removal, although performance varies among compounds and treatment conditions. Membrane processes retain rather than destroy pharmaceuticals and generate concentrate streams, and comparisons among technologies

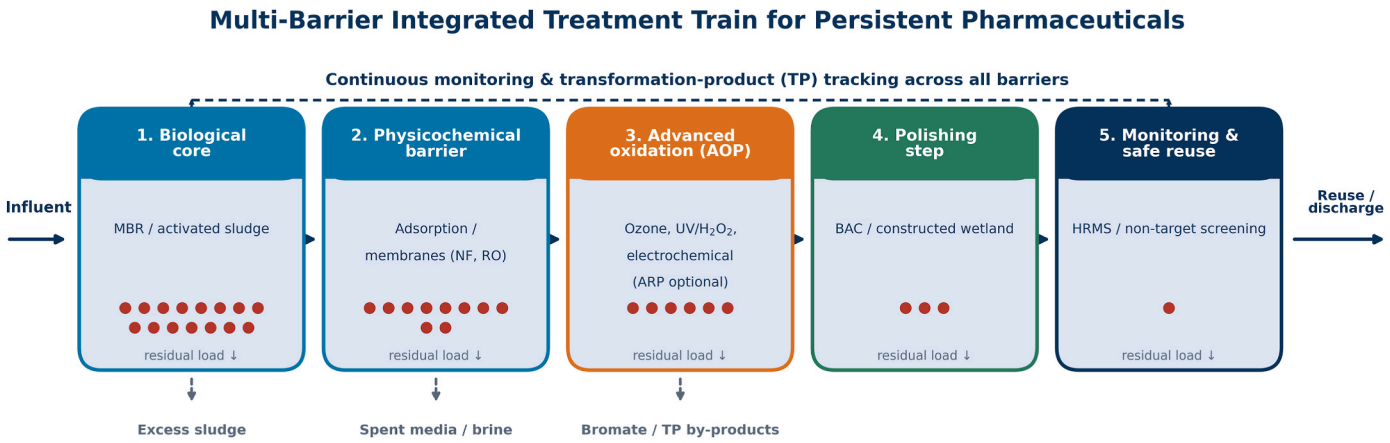


Fig. 2. Multi-barrier integrated treatment train for the removal of persistent pharmaceuticals, showing the sequential unit operations (biological core, physicochemical barrier, advanced oxidation, polishing, monitoring/reuse), decreasing residual pollutant load, associated residual streams, and continuous monitoring and transformation-product (TP) tracking across the train. ARP, advanced reduction process, is shown as an optional element for compounds that react poorly with ozone.

are constrained by differences in study design and scale (Table 5). Because parent-compound removal does not necessarily reduce risk, transformation products and toxicity must also be considered.

Comparing the studies in Table 5 shows why technologies of the same type give different results, and which of the differences are systematic. The first source of difference is dose normalization and matrix. The full-scale ozonation studies express the oxidant dose per unit of dissolved organic carbon (0.47 g O_3 g ^{1} DOC in Hollender et al., 2009; 0.55 g O_3 g ^{1} DOC recommended in Bourgin et al., 2018), whereas the pilot comparison of ozone and powdered activated carbon reports average doses in mg L ^{1} (ozone 5.7 mg L ^{1}; PAC 10–20 mg L ^{1}; Margot et al., 2013). A dose per unit DOC allows the oxidant dose to be scaled to the matrix, which absolute doses do not, and this is one reason why removals reported for the same compound at different plants are not directly comparable. The second source is charge and size in membrane retention. In bench-scale nanofiltration, charged diclofenac was rejected at 90–99%, against 65–77% for neutral carbamazepine, and carbamazepine rejection fell with increasing salt concentration and temperature whereas ibuprofen rejection rose with salt (Kabbani et al., 2021); the full-scale nanofiltration/reverse osmosis plant treating groundwater rejected more than 85% of almost all compounds but less of some, such as acetaminophen (44.8–73%), and its brine contained several hundred ng L ^{1} of pharmaceuticals (Radjenović et al., 2008). Membrane retention therefore depends on the compound and on the water matrix, and it relocates the compounds to a concentrate instead of destroying them. The third source is the endpoint. In the Lausanne pilots, ozone and PAC both achieved more than 80% average removal, but PAC combined with ultrafiltration gave the strongest decrease in toxicity and in disinfection, at a higher cost (Margot et al., 2013); full-scale ozonation decreased estrogenicity by 86% (99.5% overall) but left residual toxicity for some endpoints (Escher et al., 2009); and in the laboratory, photocatalytic treatment of carbamazepine with ultrasound converted the parent to a greater extent than it removed DOC (about 40%) and increased acute toxicity (Jelic et al., 2013). Parent-compound removal, mineralization and toxicity are therefore distinct endpoints, and a technology can rank differently depending on which one is used (Section 6.3). The fourth source is the scale of the evidence: reductive treatment with UV/sulfite has only laboratory evidence (Gu et al., 2022), whereas ozonation and activated carbon have full-scale evidence (Hollender et al., 2009; Bourgin et al., 2018; VSA, 2025), so that part of the apparent ranking of technologies reflects the scale at which they have been tested and not only how well they perform.

The principle that emerges is that each barrier is selective. Ozone and other radical-based oxidation act on electron-rich, oxidant-reactive structures; activated carbon acts on compounds that are sufficiently sorbable; charge- and size-based membranes retain many polar and charged compounds; reduction acts on halogen-rich structures that resist oxidation; and biological polishing acts on biodegradable intermediates. None of these covers all the persistence drivers of Section 3.1, which is the mechanistic reason for combining barriers (Section 7.1) and not only a matter of achieving a higher overall removal.

6.3. *Transformation products formed during treatment: formation, persistence and toxicity*

Section 3.3 showed that transformation can extend persistence; this section examines the transformation products formed by treatment processes. Parent-compound removal does not necessarily reduce risk because treatment can generate transformation products (TPs) that remain persistent or toxic. Numerous TPs have been reported for pharmaceuticals such as carbamazepine and diclofenac, and HRMS studies continue to identify additional products (Alharbi et al., 2022; Nosek and Zhao, 2024; Trognon et al., 2024; Wang et al., 2025). Full-scale ozonation studies show that some TPs persist through post-treatment, although biological filtration and activated carbon can reduce certain by-products (Bourgin et al., 2018; Hollender et al., 2009). Bioassays indicate that advanced treatments generally reduce toxicity but may also generate toxic TPs, highlighting the need to combine chemical monitoring with effect-based methods (Escher et al., 2009; Jelic et al., 2013; Völker et al., 2019). Some TPs may be more persistent, mobile, or toxic than their parent compounds (He et al., 2024; Trognon et al., 2024). Overall, parent-compound removal should be complemented by TP monitoring, TOC/DOC measurements, and effect-based endpoints (Bourgin et al., 2018; Escher et al., 2009).

The studies in Table 6 show that the outcome for a product depends on which part of the parent structure the treatment attacks and on what the downstream barrier can do with the product. Oxidation with ozone attacks reactive moieties, and the products can be stable and less sorbable than the parent. In the full-scale ozonation of a micropollutant mixture, seven primary products (chlorothiazide and six N-oxides) were not abated biologically and were sorbed less than their parents on fresh granular activated carbon; bromate was stable, whereas N-nitrosodimethylamine (NDMA) was abated by 41–83% in biological post-treatment (Bourgin et al., 2018), and NDMA was likewise removed by biological sand filtration at the earlier full-scale plant (Hollender et al., 2009). Reduction by UV/sulfite released iodine from iopamidol as iodide (up to about 98% of the iodine), and the 15 transformation intermediates showed significantly lower toxicity (Gu et al., 2022). Photocatalysis with ultrasound converted carbamazepine without comparable mineralization and increased acute toxicity (Jelic et al.,

Table 6
Transformation products and by-products of persistent pharmaceuticals: process, persistence and toxicity evidence. "n.r.": not reported in the source examined.

Parent compound or mixture	Process (scale)	Main TPs or by-products	Persistence and fate	Toxicity evidence	Source
Metformin	Biological treatment in WWTPs	Guanylurea	Polar; persists as a dead-end product in many systems; apparent removal reflects conversion	Co-occurrence and toxicity reviewed by Dong et al. (2024); not detailed here	Dong et al. (2024); Li et al. (2023); Poursat et al. (2019)
Carbamazepine	Oxidative treatments (review); photocatalysis (laboratory)	135 TPs reported, including CBZ-epoxide	Only a few TPs quantified; some TPs show persistence, mobility and toxicity characteristics that may exceed those of the parent	Acute toxicity increased during TiO_2/UV/ultrasound treatment (laboratory)	He et al. (2024); Jelic et al. (2013); Molnarova et al. (2023); Trognon et al. (2024)
Diclofenac	Ozonation and photolysis (laboratory)	New TPs identified; TPs reviewed	TPs may be as persistent or toxic as the parent	Toxicity implications reviewed by Nosek and Zhao (2024)	Alharbi et al. (2022); Nosek and Zhao (2024)
Micropollutant mixture (12 indicators; 550 substances)	Ozonation (0.55 g O_3 g ^{1} DOC) + post-treatments (full scale)	Seven primary TPs (chlorothiazide, six N-oxides); bromate; NDMA	TPs stable, not abated biologically; sorbed less than parents on fresh GAC; bromate stable; NDMA abated 41–83%	Biological post-treatment required to avoid ecotoxicological effects of biodegradable TPs and by-products (bromate at or below 5 μg L ^{1}; NDMA at or below 30 ng L ^{1})	Bourgin et al. (2018)
220 micropollutants	Ozonation + sand filtration (full scale)	NDMA; bromate	NDMA removed by biological sand filtration	n.r.	Hollender et al. (2009)
Iopamidol	UV/sulfite (laboratory, pH 9)	15 transformation intermediates; iodide	Up to about 98% of iodine released as iodide	Toxicity of degradation products significantly lower	Gu et al. (2022)
Iodinated contrast media	Oxidation, chlorination	Iodinated disinfection by-products	Can be problematic	n.r.	Zhang et al. (2023b); Yan et al. (2024)
Wastewater effluent (bioassay battery)	Full-scale ozonation + sand filtration	TPs (not identified in the bioassay study)	Not fully mineralized by ozone	Estrogenicity 86% decrease by ozonation, 99.5% overall; residual toxicity for some endpoints	Escher et al. (2009); Völker et al. (2019)

2013). Biological treatment in wastewater treatment plants converts metformin to guanylurea, which persists (Section 3.3). The fate of a product thus depends on three things: the reaction that formed it, the degree of mineralization, and whether a downstream step (sand filtration, biologically active carbon or granular activated carbon) can act on it.

Toxicity data are the weakest link. Bioassays indicate that advanced treatments generally reduce toxicity but may also generate toxic products, which is why chemical monitoring has to be combined with effect-based methods (Escher et al., 2009; Jelic et al., 2013; Völker et al., 2019). Effect-based methods measure the combined biological effect of a sample, including mixtures, without identifying the causative compounds (Section 4); chemical identification and effect-based measurement are therefore complementary, because the first shows what is present and the second whether it matters. For several products the toxicity evidence is taken from reviews and was not examined in detail here, or was not reported in the sources examined (Table 6).

Three generalizable points follow. First, persistence of a product is associated with conversion without mineralization: guanylurea and the seven ozonation products were stable, and in the laboratory DOC removal was lower than parent conversion (about 40% for carbamazepine; Jelic et al., 2013). Second, the fate of a product depends on the downstream barrier: NDMA and biodegradable intermediates are abated biologically, whereas the stable ozonation products were not, and they therefore require other barriers or monitoring. Third, toxicity cannot be inferred from the identity of the parent or from the extent of its conversion, and requires effect-based confirmation; only a few products have been quantified (for example, seven ozonation products at one plant), and toxicity data are sparse (Section 5.5).

6.4. Energy demand, resource consumption and cost of advanced treatment

Advanced treatments such as ozonation, PAC and GAC achieve substantial micropollutant removal with moderate energy and cost requirements, typically around 0.02-0.1 kWh m ^{3} and CHF 0.07-0.27 m^{-3}, although performance, resource consumption and costs are highly site-specific (Hollender et al., 2009). Life-cycle assessments indicate trade-offs among technologies, with activated-carbon production contributing substantially to overall energy demand (Mousel et al., 2017). Comparable quantitative data for membranes, UV-based AOPs and ARPs remain limited, and membrane treatment also generates pharmaceutical-containing brines requiring further management (Radjenović et al., 2008). Table 7 summarizes the available evidence.

Taken together, the indicators show that the choice among ozone, PAC and GAC is not decided by cost or energy alone. Electricity use at the plant is higher for ozonation (2–4 times that of PAC or GAC, excluding delivery heads), but the cumulative energy of the adsorption steps becomes higher once activated-carbon production is included (Mousel et al., 2017). The Swiss plants showed no systematic cost difference among the technologies (VSA, 2025), and greenhouse-gas emissions depend on the carbon source, being 1–4 kg CO_2-eq PE ^{1} a ^{1} for ozone against 6–23 for activated carbon from fossil sources and 3–7 for biogenic carbon (VSA, 2025). The choice therefore rests on the compound-specific performance discussed in Section 6.1 and on site conditions, and not on a general ranking. For membranes, UV-based AOPs and ARPs, comparable quantitative data are lacking, which limits the comparison with the barriers needed for compounds that ozone and activated carbon handle poorly.

7. Integrated multi-barrier design and AI-assisted decision support

This section assembles the evidence of Sections 3 to 6 into a design. The multi-barrier train follows from the persistence drivers and from the selectivity of each barrier (Section 6.1), and AI/ML is considered as a tool for the decisions that the design requires: which barrier a compound needs, how much oxidant or sorbent is required, and when.

7.1. Integrated system for removal of persistent pharmaceuticals in water

Persistent pharmaceuticals in water and wastewater pose increasing treatment challenges due to their low biodegradability, chemical stability, and the generation of transformation products (TPs) with residual toxicity (Kanakaraju et al., 2018). Conventional secondary biological treatment systems frequently fail to remove such compounds to

Table 7
Energy, reagent and cost indicators reported for advanced treatment. "n.r.": not reported in the source examined.

Technology	Indicator	Value	Scale and context	Source
Post-ozonation + sand filtration	Additional energy requirement	About 0.035 kWh m^{-3} (12% of a typical medium-sized nutrient-removal plant)	Full scale; 0.47 g O_3 g^{-1} DOC; 5 g DOC m^{-3}	Hollender et al. (2009)
Ozone, PAC, GAC (13 plants)	Electricity; primary energy	0.02–0.1 kWh m^{-3} (2–9 kWh PE $^{-1}$ a^{-1}); 0.1–0.8 kWh m^{-3}	Swiss municipal WWTPs (6 ozone, 5 PAC, 2 GAC); ozone tends to have higher electricity use	VSA (2025)
Ozone, PAC, GAC (13 plants)	Reagent consumption	Oxygen for ozonation 10–55 mg L^{-1}; activated carbon 5–20 mg L^{-1}	As above	VSA (2025)
Ozone, PAC, GAC (13 plants)	Operating cost; total cost incl. capital	CHF 0.02–0.09 m^{-3}; CHF 0.07–0.27 m^{-3}	As above; no systematic cost difference among technologies; regression or mean values not recommended	VSA (2025)
Ozone, PAC, GAC (13 plants)	Greenhouse gases	Ozone 1–4 kg CO_2-eq PE $^{-1}$ a^{-1}; AC from fossil sources 6–23; biogenic 3–7	As above; reactivation and biogenic carbon lower the footprint	VSA (2025)
Ozone vs PAC or GAC	Relative energy at the WWTP	Ozonation 2–4 times higher than PAC or GAC (excluding delivery heads)	Ten large-scale WWTPs; cumulative energy of adsorption steps higher once AC production is included	Mousel et al. (2017)
Ozone vs PAC (pilot)	Reagent dose	Ozone 5.7 mg L^{-1}; PAC 10–20 mg L^{-1}	Pilots at Lausanne WWTP; PAC–UF higher cost	Margot et al. (2013)
NF/RO	Energy; cost; concentrate	Energy and cost n.r.; brine with several hundred ng L^{-1} of pharmaceuticals	Full-scale groundwater plant	Radjenović et al. (2008)
UV/sulfite (ARP)	Energy; cost	n.r. (laboratory study only)	Laboratory	Gu et al. (2022)

acceptable levels, prompting the need for multi-barrier, integrated treatment trains. For example, the review by Shearer et al. (2022) highlighted that removal efficiencies for many macrolide antibiotics and biguanides remained below 50% in standard treatment plants.

The order of the barriers follows from the selectivities summarized in Section 6.1 and not from convention. The biological stage removes the biodegradable fraction and lowers the organic load that consumes oxidant; the physicochemical barrier removes compounds that are sorbable or retained and, where feasible, lowers the DOC before oxidation, as in the sequence of Table 4; the oxidation step acts on ozone- or radical-reactive structures; and the final polishing step acts on the biodegradable intermediates and by-products formed by oxidation.

A well-designed integrated system begins with a biological backbone (e.g., activated sludge, membrane bioreactor) to remove bulk organics and improve biodegradability of the influent. Membrane bioreactor (MBR) units provide better solids separation and longer sludge retention time, enhancing slow-growing microbial populations capable of degrading certain micropollutants. Integrated systems that combine MBR with adsorbents are increasingly reported (Ashfield et al., 2025).

Next, a physicochemical barrier such as adsorption on powdered activated carbon (PAC), granular activated carbon (GAC), or membrane filtration (nanofiltration, reverse osmosis) is introduced to capture recalcitrant compounds and reduce loading to downstream advanced units. Mansouri et al. (2021) showed that adsorption followed by oxidation significantly improved removal of pharmaceuticals. Following this, an advanced oxidation process (AOP) is integrated (such as ozonation, UV/H_2O_2, Fenton/photo-Fenton, or electrochemical oxidation) to break down persistent molecules and their TPs. These oxidizing barriers convert recalcitrant pharmaceuticals into more biodegradable intermediates or fully mineralize them. Kanakaraju et al. (2025) reviewed recent AOP developments for pharmaceuticals, stressing the need for downstream polishing to handle oxidation by-products.

After AOP treatment, a biologically active carbon (BAC) filter or a constructed wetland or other nature-based polishing step is crucial to remove remaining biodegradation intermediates, residual organics, and ensure ecotoxicological safety. Evidence for complete multi-barrier treatment trains remains limited. Pilot- and full-scale studies show that ozonation, activated carbon, and related treatment sequences can achieve average pharmaceutical removal rates of approximately 75-90%, with additional benefits from GAC polishing (Bourgin et al., 2018; Margot et al., 2013; VSA, 2025). However, no study has evaluated all components of the proposed treatment train simultaneously at pilot or full scale. Consequently, removal rates above 90% should be considered an expected outcome for readily oxidizable or sorbable compounds rather than a demonstrated performance, while poorly reactive compounds, including some X-ray contrast media, may persist (Bourgin et al., 2018).

Operationally, the system must include side stream treatment loops for high-load hospital or industrial effluents, and real-time monitoring of pharmaceuticals, TPs and toxicity to avoid unintended by-product emission. Integration also requires design attention to energy/OPEX, membrane fouling (in MBR/membrane steps), bromate formation (in ozonation), adsorbent regeneration and sludge management (Shearer et al., 2022).

Finally, a robust integrated system for removing persistent pharmaceuticals comprises (Fig. 2).

1. A biological core (MBR or activated sludge) to remove organics and improve biodegradability.
2. A physicochemical barrier (adsorption or membranes) to capture recalcitrant compounds.
3. An advanced oxidation process (AOP) to degrade persistent molecules and TPs.
4. A polishing step (BAC, constructed wetland, nature-based) to remove residuals and mitigate toxicity.
5. Monitoring and side stream treatment loops for streams with high pharmaceutical loads.

This holistic train addresses the limitations of single-process treatments, is expected to provide high removal of many pharmaceuticals (a target of $\geq$90% for readily oxidizable or sorbable compounds, not yet demonstrated for the complete train) and to limit transformation-product emissions, and supports water reuse goals under frameworks such as the UN SDG 6. Implementation challenges remain (cost, footprint, by-product control) but the literature increasingly supports the sequential/hybrid model as a promising pathway.

Read against the drivers of Section 3.1, each element of the train has a defined role (Fig. 2). The biological core handles the biodegradable fraction; adsorption and membranes act on compounds that are sorbable or retained according to their polarity, charge and size; oxidation acts on ozone- or radical-reactive structures, with reduction (ARP) as an optional step for halogen-rich structures that react poorly with ozone; polishing acts on the intermediates and by-products formed by oxidation; and monitoring, including transformation-product tracking and effect-based endpoints, covers the analytical blind spots of Section 4. Resistance genes also require monitoring, although no quantitative treatment-train data on them were compiled in this review (Table 4). No single barrier covers all the drivers, which is the mechanistic reason for the multi-barrier concept; the open question, addressed in the next section, is how to select and set the barriers for a given effluent.

The multi-barrier concept is supported by consistent evidence for its individual components but has not been demonstrated end-to-end; its

performance depends on compound-specific chemistry, matrix and dose, and its added value lies in covering the weaknesses of each barrier (Table 4). Section 7.2 examines how AI/ML could support the operation of such a train and what evidence exists.

7.2. Artificial intelligence and machine learning as decision support for pharmaceutical treatment: evidence and limitations

AI/ML enters the framework at the point where the mechanistic information of Sections 3 and 6 must be turned into decisions for a specific effluent. Artificial intelligence (AI) and machine learning (ML) have emerged as promising tools for optimizing integrated treatment systems. Published studies address mainly four tasks: predicting oxidant exposure and micropollutant abatement during ozonation, predicting removal in treatment plants from molecular structure, predicting adsorption capacity, and optimizing process operation. Examples with their input variables, data sets and validation are summarized below and in Table 8. These digital tools, combined with online sensors and automated control systems, are intended to enable adaptive treatment that responds to influent variability while minimizing energy consumption and chemical usage (Fig. 3). However, the practical implementation of AI/ML in water treatment remains at early stages, and therefore, further validation under real-world conditions is needed before these approaches become standard practice.

AI/ML has been applied to predict ozonation performance, pharmaceutical removal, adsorption efficiency, and contaminant fate using algorithms such as random forests, support-vector machines, gradient boosting, XGBoost, and neural networks (Cha et al., 2021; Choi et al., 2025; Cordero Solano et al., 2025; Zhang et al., 2023*a*). Additional applications include contaminant screening and wastewater-treatment optimization (Sgariboldi et al., 2025; Wang et al., 2026), while several reviews provide broader overviews of the field (Liu et al., 2025; Mathaba and Banza, 2023; Parsoya et al., 2026).

The studies summarized in Table 8 can be mapped onto the decisions of the driver-to-barrier framework. Models that predict removal from molecular structure address the driver end of the chain, because they indicate which compounds are likely to pass through a given treatment (Choi et al., 2025; Cordero Solano et al., 2025). Their scope is, however, limited: the models of Cordero Solano et al. (2025) were developed for conventional activated-sludge plants without advanced treatment, and the classification of Choi et al. (2025) rests on two full-scale facilities. Models of oxidant exposure and micropollutant abatement support the setting of the ozone dose, which is the control variable of the oxidation barrier (Cha et al., 2021), but the data set was small (60 samples at one ozone dose). Models of adsorption capacity support the choice and operation of the sorption barrier (Zhang et al., 2023a), but were built from laboratory data compiled from ten papers for one antibiotic. What is missing is the link between these predictions and the two outcomes that matter most for reuse: the formation and toxicity of transformation products, and the sequencing of several barriers. None of the four studies in Table 8 predicts transformation-product formation or toxicity, optimizes the sequence of barriers, or has been tested in closed-loop control of a pharmaceutical treatment train.

Three roles can therefore be distinguished, of which only the first two have some support. In pre-screening, structure-based predictions can flag compounds that are likely to pass through conventional treatment and need an advanced barrier. In dose control, predicted oxidant exposure based on water-quality inputs such as pH, alkalinity, DOC and fluorescence data can support the setting of the ozone dose (Cha et al., 2021), and the combination with online sensors is the intended basis of adaptive control (Fig. 3). In configuration screening, models could be used to compare train configurations against several objectives, such as removal, energy and chemical use (Fig. 3), but this role is conceptual and has not been demonstrated. Each role needs larger harmonized data sets that include transformation products and toxicity, and external validation across plants.

In summary, the evidence supports the use of AI/ML to predict oxidant exposure, adsorption and removal, and to focus experimental effort. However, it does not yet support claims of optimized or autonomous operation of pharmaceutical treatment trains. This is the reason for describing the approach in the title as AI-assisted. Accordingly, AI/ML is presented in this review as a decision-support component of the framework and not as a demonstrated means of optimization.

8. Remaining challenges for risk mitigation in removing persistent pharmaceuticals from water in the coming decades

Removing persistent pharmaceuticals from water bodies at scale will stay hard and expensive for reasons rooted in chemistry, biology, and systems constraints. Several critical reasons are next summarized, each

Table 8
Examples of AI/ML applications relevant to pharmaceutical removal: algorithms, inputs, data, validation and limitations. "n.r.": not reported in the source examined.

Application	Algorithm(s)	Input variables	Data	Validation	Reported outcome	Limitation/scale	Source
Oxidant exposure and micropollutant abatement in ozonation	Random forest (four model variants)	pH, alkalinity, DOC, fluorescence excitation–emission matrices	60 natural-water and wastewater-effluent samples; ozone dose 2.5 mg L^{-1}	Regression performance and Akaike information criterion compared across variants	High-resolution fluorescence data improved accuracy; useable to predict abatement and optimize the ozone dose	Small data set; one ozone dose; laboratory-determined exposures	Cha et al. (2021)
Removal of micropollutants in conventional WWTPs from molecular structure	More than 40 models; random forest best	Molecular structure representations (best performance: MACCS substructure fingerprints)	More than 1000 chemicals; more than 50 plants; open data set	Nested cross-validation	Best predictions with fingerprints and random forest; compounds with highly variable removal across plants impaired training	Conventional activated-sludge plants; no advanced treatment	Cordero Solano et al. (2025)
PPCP removal through reuse treatment trains	Support-vector machine, logistic regression, random forest	Abraham descriptors and log K_{ow}	149 PPCPs; two full-scale facilities	Classification accuracy of models	Support-vector machine most accurate (79.1%)	Two facilities; classification, not concentration	Choi et al. (2025)
Tetracycline adsorption on biochar	Random forest, gradient boosting, XGBoost, artificial neural network	Biochar properties and adsorption conditions	295 data sets from ten papers; 22 biochars	Comparison of four algorithms (details n.r. in the abstract)	Models developed to predict uptake and identify driving factors; web interface proposed	Literature-compiled laboratory data; one antibiotic	Zhang et al. (2023a)

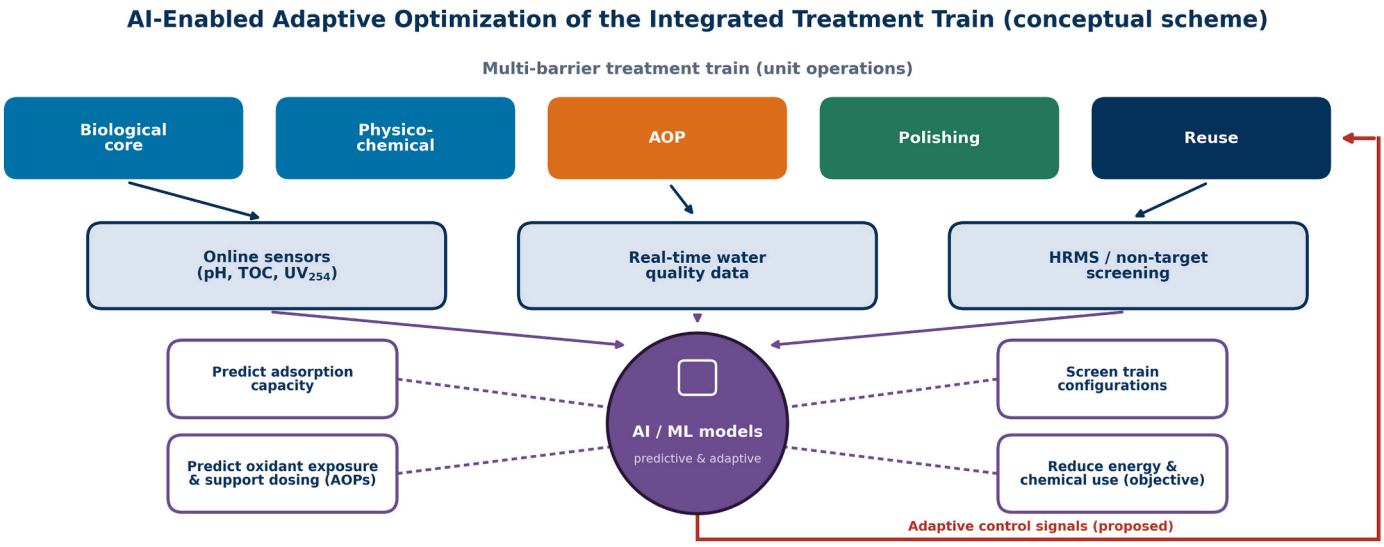


Fig. 3. AI-enabled adaptive optimization of the integrated treatment train. Online sensors, real-time water-quality data, and HRMS/non-target screening feed predictive AI/ML models, which can be used to predict adsorption capacity, support oxidant dosing, screen train configurations and reduce energy and chemical use. The scheme is conceptual: the components have been demonstrated separately (Table 8), but their integration into closed-loop control of a pharmaceutical treatment train has not been demonstrated in the studies reviewed.

corresponding to a stage of the framework in Table 1.

a) **The ultra-low and variable mixtures of persistent pharmaceuticals:** Water utilities face ng/L-µg/L cocktails spanning acids, bases, zwitterions, and chiral drugs with seasonally shifting loads from hospitals, households, and industry. Treatment trains tuned for one class (e.g., NSAIDs) underperform for others (e.g., psychiatric drugs), so "one-size" designs fail (Muambo et al., 2024).

b) **The transformation products and by-products of persistent pharmaceuticals:** Advanced oxidation (ozone, UV/H_2O_2) can degrade targets, although mineralization is seldom complete, and often yields dozens of transformation products with uncertain toxicity; brominated by-products (e.g., bromate) rise where bromide is present, forcing tighter control of dose, pH, and contact time. Tighter bromate control may increase operating costs (Morrison et al., 2023). In a full-scale evaluation, bromate stayed at or below 5 µg L^{1} and N-nitrosodimethylamine at or below 30 ng L^{1} at the recommended ozone dose (Bourgin et al., 2018).

c) **Antimicrobial resistance (AMR):** Sub-inhibitory antibiotic residues, co-selectors (metals, biocides), and dense microbial communities in sewers/WWTPs foster ARG proliferation. Upgrading plants to suppress ARGs (not just parent molecules) will require multi-barrier strategies and continuous monitoring (Sambaza and Naicker, 2023).

d) **Energy, footprints, and residuals:** Advanced polishing treatments such as ozonation/advanced oxidation processes (AOPs), nanofiltration/reverse osmosis, and high-dose granular activated carbon (GAC), impose substantial energy demands, media consumption, and chemical usage. Membrane-based systems produce concentrated brines laden with pharmaceuticals and by-products, while inland disposal of these residuals creates ongoing economic and environmental challenges (Satyam and Patra, 2025). Quantitative indicators for ozone, PAC and GAC are given in Section 6.4 (Table 7).

e) **Laboratory, analytics and oversight:** Regulations increasingly demand evidence for thousands of molecules, but non-target screening, suspect screening, and effect-based tools are still maturing for routine compliance. Utilities will need higher-throughput, inter-laboratory-comparable methods to avoid "unknown unknowns" (Wu et al., 2024).

f) **Climate and demographics:** Hotter, drier climates concentrate effluents in rivers; water reuse expands direct human exposure; aging populations increase pharmaceutical consumption—together raising influent loads and persistence pressure on plants (IFPMA, 2022). Hydrological and climatic influences are described in Section 5.1.

g) **Operational realities of water treatment facilities:** GAC exhaustion accelerates with NOM spikes; ion-exchange resins foul; AOP performance swings with alkalinity and scavengers; membranes face scaling/fouling trade-offs. Long-term O&M (media changeouts, cleaning, waste handling) will dominate lifecycle cost (Liu et al., 2023).

h) **Equity and implementation gaps:** Small and resource-constrained utilities lack capital and skilled staff for advanced trains, widening disparities in protection unless policy and funding close the gap (Jani and Kumari, 2024). As water reuse and resource recovery from wastewater gain prominence in circular economy frameworks, pharmaceutical contamination presents a fundamental barrier. Treated effluent and biosolids intended for agricultural reuse must meet stringent quality standards, yet many persistent pharmaceuticals and their metabolites remain at levels that could affect crop uptake, soil microbiomes, and food safety (Mosharaf et al., 2025). Developing integrated treatment trains that achieve safe resource recovery alongside complete destruction of persistent contaminants marks a key frontier in sustainable water management.

i) **Ecological risk persistence:** Even after treatment, low-level residues alter aquatic behavior, reproduction, and community dynamic sustaining pressure for ever-lower discharge limits and continuous upgrades (Aich et al., 2024). Advanced oxidation and other treatment processes can generate transformation products that are more mobile, more toxic, or more persistent than parent compounds. Short-chain PFAS products, N-nitrosamine derivatives from amine-containing pharmaceuticals, and halogenated by-products from chlorination all require expanded monitoring and assessment frameworks (González Fernández et al., 2025; Morrison et al., 2023).

These challenges are of different kinds: chemical (a, b, i), biological (c), engineering and economic (d, g, h), analytical and regulatory (e), and contextual (f, h). Only some of them are supported by quantitative evidence, namely energy, reagent and cost indicators (Table 7) and bromate and N-nitrosodimethylamine levels in full-scale ozonation. The others are reasoned from the literature and should be read as risks to be managed, not as measured outcomes. These challenges correspond to the stages of the framework: persistence and transformation (a, b, i;

Sections 3 and 6.3), antimicrobial resistance (c; Sections 5.1 and 5.5), treatment performance and cost (d, g; Sections 6.2 and 6.4), analytics (e; Section 4), and context and implementation (f, h; Section 5.1 and this section).

9. Conclusions

By linking the physicochemical drivers of pharmaceutical persistence to treatment-train design, and by extending this analysis across groundwater migration, food-chain transfer, and antimicrobial-resistance pathways within a framework in which AI/ML acts as decision support, this review offers an integrated perspective not provided by recent single-focus reviews on occurrence, treatment technologies, or transformation products alone. The review has followed one chain of reasoning, from the persistence drivers (Section 3) and the reliability of the evidence (Section 4) through exposure pathways (Section 5) and the selectivity of treatment barriers (Section 6) to train design and decision support (Section 7), and its conclusions are organized along this chain. It highlights that persistent pharmaceuticals remain an important environmental concern due to their chemical stability, polarity, and resistance to biodegradation and oxidation (Section 3.1). Compounds such as carbamazepine, diclofenac, metformin, and iodinated contrast media persist through conventional wastewater treatments, in some cases forming transformation products that are as persistent as the parent compound (for example guanylurea, Section 3.3).

Evidence shows that many pharmaceuticals are poorly removed by conventional treatment, whereas ozonation and PAC-based processes typically achieve >80% removal, although performance is compound-specific (Table 5, Section 6.2). Apparent removal can reflect transformation or transfer rather than elimination, and some transformation products remain persistent or toxic (Table 6, Section 6.3). Bioassays indicate that post-treatment can reduce residual toxicity, while AI/ML has shown potential for predicting treatment performance but not yet for demonstrated closed-loop control of pharmaceutical removal (Table 8, Section 7.2).

Analytical advances, particularly LC-MS/MS and HRMS, have improved detection and understanding of these substances at trace levels, revealing widespread environmental occurrence and persistence. These advances do not by themselves establish risk, which requires effect-based confirmation (Sections 4 and 6.3). The major findings emphasize that single treatment technologies are insufficient to achieve complete removal or mineralization. Instead, multi-barrier, integrated systems combining biological, physicochemical, and advanced oxidation processes (AOPs) are the most promising option. Evidence for complete trains is limited. the pilot- and full-scale data available concern parts of the train (Table 5). Despite technological advances, significant barriers remain, including elevated operational and energy costs, susceptibility to fouling, and the generation of harmful oxidation by-products such as bromate. For ozone, PAC and GAC at Swiss municipal plants, electricity use was 0.02–0.1 kWh m^{-3} and total annual costs including capital were CHF 0.07–0.27 m^{-3} (VSA, 2025).

The main remaining research gaps are the following: (1) Pilot- or full-scale evaluation of complete multi-barrier trains for defined pharmaceutical mixtures, with operating conditions, TOC/DOC and toxicity endpoints reported. (2) Quantification of transformation products (only a few have been quantified, for example seven ozonation products at one plant) together with effect-based confirmation of their toxicity. (3) Comparable energy, reagent and cost data for membranes, AOPs and ARPs, since indicators exist mainly for ozone, PAC and GAC at Swiss plants. (4) For AI/ML, larger harmonized and open datasets, external validation across plants, extension to transformation products and toxicity, and demonstrations of closed-loop control. (5) Better evidence on the fate of antimicrobial-resistance determinants and of pharmaceutical residues in groundwater and crops under realistic reuse conditions.

The following directions are proposals derived from these gaps and are not yet supported by demonstrated performance. The path forward in addressing pharmaceutical contamination requires a multifaceted approach. Future studies should prioritize the optimization of hybrid treatment systems tailored for real-world applications, particularly those involving complex matrices. There is also a critical need to advance the development of energy-efficient oxidation catalysts and to explore the integration of nature-based solutions, such as constructed wetlands and algal polishing, to ensure sustainable and resilient operations.

To align with circular economy principles, treatment systems should evolve beyond mere contaminant removal. They should be designed to facilitate safe water reuse, nutrient recovery, and energy generation, thereby preserving the intrinsic value of resources. This would require advances in selective separation technologies capable of extracting high-value components like phosphorus, nitrogen, and metals, while simultaneously degrading persistent organic pollutants. Furthermore, the integration of advanced analytical tools with effect-based monitoring frameworks will be pivotal in tracking the formation of transformation products and understanding the dynamics of antimicrobial resistance. On the policy front, there is an urgent need for frameworks that empower resource-constrained utilities by providing scalable, modular treatment solutions and standardized analytical protocols.

Complementing these efforts, source control strategies should be strengthened. This includes adopting green pharmacy principles to design safer pharmaceuticals, implementing take-back programs for unused medications, and deploying point-of-entry treatment systems at high-load sources, such as hospitals and pharmaceutical manufacturing plants. Together, these measures can form a robust response to the challenges posed by pharmaceutical contamination.

Addressing persistent pharmaceuticals may require a shift, from end-of-pipe treatment to holistic source control, advanced treatment integration, and continuous risk-based monitoring, to protect water security and achieve global sustainability goals under SDG 6.

CRediT authorship contribution statement

Basem Shomar: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Jose L. Domingo:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this article, the authors used Claude Sonnet 5 (Anthropic) to assist in the conceptual design and visual presentation of Figs. 1–3. The authors reviewed, verified, and edited all AI-assisted content and take full responsibility for the accuracy, originality, and integrity of the article. In the revised version, the authors additionally used Claude Sonnet 5.5 (Anthropic) to verify bibliographic details against publicly accessible records, to draft revised text and tables from the verified sources, and to regenerate Figs. 1–3 at higher resolution. The authors checked all added content against the cited sources and take full responsibility for it.

Funding

This work did not receive any financial support from any entity.

Declaration of competing interest

XX 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.

Data availability

This is a Review article. Therefore, no original data are included. Information was collected from a search in scientific databases

References

Ahmed, H.R., Ghafoor, D., Agha, N., Muhamad, G., Husamadin, P., Ali, T., 2025. Advanced strategies for the removal of venlafaxine from aqueous environments: a critical review of adsorption and advanced oxidation pathways. RSC Adv. 15, 38889–38905. https://doi.org/10.1039/D5RA06996C.

Aich, U., Polverino, G., Parast, F., Melo, G., Tan, H., Howells, J., Nosrati, R., Wong, B., 2024. Long-term effects of widespread pharmaceutical pollution on trade-offs between behavioural, life-history and reproductive traits in fish. J. Anim. Ecol. 94, 340–355. https://doi.org/10.1111/1365-2656.14152.

Alfonso-Muniozguren, P., Serna-Galvis, E., Bussemaker, M., Torres-Palma, R., Lee, J., 2021. A review on pharmaceuticals removal from waters by single and combined biological, membrane filtration and ultrasound systems. Ultrason. Sonochem. 76, 105656. https://doi.org/10.1016/j.ultsonch.2021.105656.

Alharbi, S., Ansari, A., Nghiem, L., Price, W., 2022. New transformation products from ozonation and photolysis of diclofenac in the aqueous phase. Process Saf. Environ. Prot. 157, 106–114. https://doi.org/10.1016/j.psep.2021.10.050.

Alqarni, A.M., 2024. Analytical methods for the determination of pharmaceuticals and personal care products in solid and liquid environmental matrices: a review. Molecules 29 (16), 3900. https://doi.org/10.3390/molecules29163900.

Ashfield, N., Li, J., Bouzas-Monroy, A., Boxall, A., 2025. Silent side effects: pharmaceuticals as contaminants of emerging concern. Annu. Rev. Environ. Resour. 50, 273–301. https://doi.org/10.1146/annurev-environ-111523-101837.

aus der Beek, T., Weber, F.-A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., Küster, A., 2016. Pharmaceuticals in the environment-global occurrences and perspectives. Environ. Toxicol. Chem. 35, 823–835. https://doi.org/10.1002/etc.3339.

Biel-Maeso, M., Corada-Fernández, C., Lara-Martín, P., 2018. Monitoring the occurrence of pharmaceuticals in soils irrigated with reclaimed wastewater. Environmental Pollution 235, 312–321. https://doi.org/10.1016/j.envpol.2017.12.085.

Bourgin, M., Beck, B., Boehler, M., Borowska, E., Fleiner, J., Salhi, E., Teichler, R., von Gunten, U., Siegrist, H., McArdell, C.S., 2018. Evaluation of a full-scale wastewater treatment plant upgraded with ozonation and biological post-treatments: abatement of micropollutants, formation of transformation products and oxidation by-products. Water Res. 129, 486–498. https://doi.org/10.1016/j.watres.2017.10.036.

Boxall, A.B.A., Rudd, M.A., Brooks, B.W., Caldwell, D.J., Choi, K., et al., 2012. Pharmaceuticals and personal care products in the environment: what are the big questions? Environ. Health Perspect. 120 (9), 1221–1229. https://doi.org/10.1289/ehp.110447.

Castaño-Ortiz, J.M., Gago-Ferrero, P., Barceló, D., Rodríguez-Mozaz, S., Gil-Solsona, R., 2024. HRMS-based suspect screening of pharmaceuticals and their transformation products in multiple environmental compartments: an alternative to target analysis? J Hazard Mater 465, 132974. https://doi.org/10.1016/j.jhazmat.2023.132974.

Castellano-Hinojosa, A., Gallardo-Altamirano, M.J., González-López, J., González-Martínez, A., 2023. Anticancer drugs in wastewater and natural environments: a review on their occurrence, environmental persistence, treatment, and ecological risks. J. Hazard Mater. 447, 130818. https://doi.org/10.1016/j.jhazmat.2023.130818.

Cha, D., Park, S., Kim, M.S., Kim, T., Hong, S.W., Cho, K.H., Lee, C., 2021. Prediction of oxidant exposures and micropollutant abatement during ozonation using a machine learning method. Environ. Sci. Technol. 55 (1), 709–718. https://doi.org/10.1021/acs.est.0c05836.

Chaber-Jarlachowicz, P., Gworek, B., Kalinowski, R., 2025. Removal efficiency of pharmaceuticals during the wastewater treatment process: emission and environmental risk assessment. PLoS One 20 (9), e0331211. https://doi.org/10.1371/journal.pone.0331211.

Chia, R., Lee, J.-Y., Ssekimpi, D., Amanze, C., Cha, J., 2025. Pharmaceuticals in soil and groundwater: analytical methods, sources, and mitigation techniques. Sci. Total Environ. 999, 180317. https://doi.org/10.1016/j.scitotenv.2025.180317.

Choi, J.M., Manthapuri, V., Keenum, I., Brown, C.L., Xia, K., Chen, C., Vikesland, P.J., Blair, M.F., Bott, C., Pruden, A., Zhang, L., 2025. A machine learning framework to predict PPCP removal through various wastewater and water reuse treatment trains. Environ. Sci. Water Res. Technol. 11 (2), 481–493. https://doi.org/10.1039/D4EW00892H.

Cordero Solano, J.A., Hafner, J., McLachlan, M.S., Singer, H., Fenner, K., 2025. Predicting micropollutant removal in wastewater treatment based on molecular structure: benchmark data and models. Environ. Sci. Technol. 59 (41), 22020–22028. https://doi.org/10.1021/acs.est.5c09314.

Couto, C., Lange, L., Amaral, M., 2019. Occurrence, fate and removal of pharmaceutically active compounds (PhACs) in water and wastewater treatment plants-A review. J. Water Proc. Eng. 32, 100927. https://doi.org/10.1016/j.jwpe.2019.100927.

de Souza, L., Sanches-Neto, F., Junior, G.M.Y., Ramos, B., Lastre-Acosta, A.M., Carvalho-Silva, V.H., Teixeira, A.C.S.C., 2022. Photochemical environmental persistence of venlafaxine in an urban water reservoir: a combined experimental and computational investigation. Process Saf. Environ. Prot. 166, 478–490. https://doi.org/10.1016/j.psep.2022.08.049.

Dibyanshu, D., Scheytt, T., 2025. Emerging contaminants: assessing the release of pharmaceuticals via managed aquifer recharge. Environ. Sci. Pollut. Res. 32, 14452–14464. https://doi.org/10.1007/s11356-025-36536-8.

Do, J.-M., Yeo, H.-T., Do, G.-S., Hong, J.W., Yoon, H.-S., 2022. Enhancement of carbamazepine removal rate using Tetradesmus obliquus KNUA061 and NaOCl and utilization of the resulting biomass. Front. Energy Res. 10, 1004613. https://doi.org/10.3389/fenrg.2022.1004613.

Domínguez-García, P., Tchantchane, C., Artigues, M., Cuadros, J., Gómez-Canela, C., 2025. Application of direct injection LC–MS/MS for pharmaceutical monitoring in wastewater and reclaimed water from the 14 wastewater treatment plants in Costa Brava (Catalonia, Spain). Appl. Water Sci. 15, 287. https://doi.org/10.1007/s13201-025-02615-x.

Dong, L., Li, S., Huang, J., Li, W.-J., Ali, M., 2024. Co-occurrence, toxicity, and biotransformation pathways of metformin and its intermediate product guanylurea: current state and future prospects for enhanced biodegradation strategy. Sci. Total Environ. 921, 171108. https://doi.org/10.1016/j.scitotenv.2024.171108.

Escher, B.I., Bramaz, N., Ort, C., 2009. JEM Spotlight: monitoring the treatment efficiency of a full scale ozonation on a sewage treatment plant with a mode-of-action based test battery. J. Environ. Monit. 11 (10), 1836–1846. https://doi.org/10.1039/b907093a.

González-Burciaga, L.A., Silerio-Vázquez, F.d.J., Antileo, C., Rosales-Castro, M., Núñez-Núñez, C.M., Proal-Nájera, J.B., 2025. A review on cytotoxic antibiotics: occurrence in water matrices, degradation by advanced oxidation processes, and By-Product Formation. Water 17 (5), 628. https://doi.org/10.3390/w17050628.

González Fernández, L.A., Medellín Castillo, N.A., Sánchez Polo, M., Vilasó-Cadre, J.E., Reyes-Domínguez, I.A., de León-Martínez, L.D., 2025. Emerging strategies for the photoassisted removal of PFAS from water: from fundamentals to applications. Catalysts 15 (10), 946. https://doi.org/10.3390/catal15100946.

Gu, Y., Song, Z., Dong, Z., Sun, F., Jiang, C., Qi, J., 2022. Efficient degradation and deiodination of iopamidol by UV/sulfite process: assessment of typical process parameters and transformation paths. Environ. Int. 167, 107383. https://doi.org/10.1016/j.envint.2022.107383.

Gupta, A., Kumar, S., Bajpai, Y., Chaturvedi, K., Johri, P., Tiwari, R.K., Vivekanand, V., Trivedi, M., 2024. Pharmaceutically active micropollutants: origin, hazards and removal. Front. Microbiol. 15, 1339469. https://doi.org/10.3389/fmicb.2024.1339469.

He, K., Yuan, J., Lu, H., Asada, Y., Echigo, S., Wu, Q., Wang, H., 2024. Evaluating the behavior and environmental risks of carbamazepine and its metabolites in soil aquifer treatment: insights from deconjugation dynamics and toxicity assessment. J Hazard Mater 480, 135788. https://doi.org/10.1016/j.jhazmat.2024.135788.

Hollender, J., Zimmermann, S.G., Koepke, S., Krauss, M., McArdell, C.S., Ort, C., Singer, H., von Gunten, U., Siegrist, H., 2009. Elimination of organic micropollutants in a municipal wastewater treatment plant upgraded with a full-scale post-ozonation followed by sand filtration. Environ. Sci. Technol. 43 (20), 7862–7869. https://doi.org/10.1021/es9014629.

IFPMA, 2022. The Pharmaceutical Industry and Global Health. Facts and Figures 2022. International Federation of Pharmaceutical Manufacturers & Associations. https://www.ifpma.org/wp-content/uploads/2023/01/i2023_IFPMA-Facts-And-Figures-2022.pdf.

Inarmal, N., Moodley, B., 2024. Removal efficiencies and environmental risk assessment of selected pharmaceuticals and metabolites at a wastewater treatment plant in Pietermaritzburg, South Africa. Environ. Monit. Assess. 197 (1), 102. https://doi.org/10.1007/s10661-024-13515-z.

James, S.N., Sengar, A., Vijayanandan, A., 2023. Investigating the biodegradability of iodinated X-ray contrast media in simultaneous nitrification and denitrification system. J. Hazard Mater. 452, 131196. https://doi.org/10.1016/j.jhazmat.2023.131196.

Jani, M., Kumari, S., 2024. Pharmaceutical wastewater and environmental contamination: challenges, innovations, and future directions. PEXACY International Journal of Pharmaceutical Science. https://doi.org/10.5281/zenodo.14518026.

Jelic, A., Michael, I., Achilleos, A., Hapeshi, E., Lambropoulou, D., Perez, S., Petrovic, M., Fatta-Kassinos, D., Barceló, D., 2013. Transformation products and reaction pathways of carbamazepine during photocatalytic and sonophotocatalytic treatment. J. Hazard Mater. 263, 177–186. https://doi.org/10.1016/j.jhazmat.2013.07.068.

Johnson, A.C., Sumpter, J.P., 2014. Putting pharmaceuticals into the wider context of challenges to fish populations in rivers. Philos. Trans. R. Soc. Lond. B Biol. Sci. 369 (1656), 20130581. https://doi.org/10.1098/rstb.2013.0581.

Kabbani, H.M., Al-Hindi, M., Ayoub, G.M., Ahmad, M.N., 2021. The effects of salt concentration on the rejection of pharmaceutically active compounds by nanofiltration membranes. Journal of Sustainable Development of Energy, Water and Environment Systems 9 (3), 1–16. https://doi.org/10.13044/j.sdewes.d8.0356.

Kanakaraju, D., Glass, B., Oelgemöller, M., 2018. Advanced oxidation process-mediated removal of pharmaceuticals from water: a review. J. Environ. Manag. 219, 189–207. https://doi.org/10.1016/j.jenvman.2018.04.103.

Kanakaraju, D., Glass, B.D., Goh, P.S., 2025. Advanced oxidation process-mediated removal of pharmaceuticals from water: a review of recent advances. Environ. Sci. Pollut. Res. 32, 14316–14350. https://doi.org/10.1007/s11356-025-36547-5.

Khan, H., Abdur Rehman, M., Malik, R., 2020. Fate and toxicity of pharmaceuticals in water environment: an insight on their occurrence in South Asia. J. Environ. Manag. 271, 111030. https://doi.org/10.1016/j.jenvman.2020.111030.

Kock, A., Glanville, H., Law, A., Stanton, T., Carter, L., Taylor, J., 2023. Emerging challenges of the impacts of pharmaceuticals on aquatic ecosystems: a diatom perspective. Sci. Total Environ. 878, 162939. https://doi.org/10.1016/j.scitotenv.2023.162939.

Kolpin, D., Furlong, E., Meyer, M., Thurman, E., Zaugg, S., Barber, L., Buxton, H., 2002. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: a national reconnaissance. Environ. Sci. Technol. 36 (6), 1202–1211. https://doi.org/10.1021/es011055j.

Kraemer, S.A., Ramachandran, A., Perron, G.G., 2019. Antibiotic pollution in the environment: from microbial ecology to public Policy. Microorganisms 7 (6), 180. https://doi.org/10.3390/microorganisms7060180.

Li, P., Wu, Y., He, Y., Zhang, B., Huang, Y., Yuan, Q., Chen, Y., 2020. Occurrence and fate of antibiotic residues and antibiotic resistance genes in a reservoir with ecological purification facilities for drinking water sources. Sci. Total Environ. 707, 135276. https://doi.org/10.1016/j.scitotenv.2019.135276.

Li, T., Xu, Z.-J., Zhou, N.-Y., 2023. Aerobic degradation of the antidiabetic drug metformin by Aminobacter sp. Strain NyZ550. Environ. Sci. Technol. 57 (3), 1510–1519. https://doi.org/10.1021/acs.est.2c07669.

Liu, T., Aniagor, C., Ejimofor, M., Menkiti, M., Tang, K., Chin, B., Chan, Y., Yiin, C., Cheah, K., Chai, Y., Lock, S., Yap, K., Wee, M., Yap, P.-S., 2023. Technologies for removing pharmaceuticals and personal care products (PPCPs) from aqueous solutions: recent advances, performances, challenges and recommendations for improvements. J. Mol. Liq. 374, 121144. https://doi.org/10.1016/j.molliq.2022.121144.

Liu, Y., Mancuso, G., Petrotto, L., Lavrnić, S., Dong, Z., Tian, Y., Zhang, J., Toscano, A., 2025. AI-driven solutions in wastewater treatment and agricultural reuse systems: a comprehensive review. J. Environ. Manag. 393, 127008. https://doi.org/10.1016/j.jenvman.2025.127008.

Malchi, T., Maor, Y., Tadmor, G., Shenker, M., Chefetz, B., 2014. Irrigation of root vegetables with treated wastewater: evaluating uptake of pharmaceuticals and the associated Human health risks. Environ. Sci. Technol. 48 (16), 9325–9333. https://doi.org/10.1021/es5017894.

Mansouri, F., Chouchene, K., Roche, N., Ksibi, M., 2021. Removal of pharmaceuticals from water by adsorption and advanced oxidation processes: state of the art and trends. Appl. Sci. 2021 11, 6659. https://doi.org/10.3390/app11146659.

Margot, J., Kienle, C., Magnet, A., Weil, M., Rossi, L., de Alencastro, L.F., Abegglen, C., Thonney, D., Chèvre, N., Schärer, M., Barry, D.A., 2013. Treatment of micropollutants in municipal wastewater: ozone or powdered activated carbon? Sci. Total Environ. 461–462, 480–498. https://doi.org/10.1016/j.scitotenv.2013.05.034.

Mateo-Sagasta, J., Al-Hamdi, M., AbuZeid, K. (Eds.), 2022. Water Reuse in the Middle East and North Africa: a Sourcebook, vol. 292. International Water Management Institute (IWMI), Colombo, Sri Lanka. https://doi.org/10.5337/2022.225.

Mathaba, M., Banza, J., 2023. A comprehensive review on artificial intelligence in water treatment for optimization. Clean water now and the future. J Environ Sci Health A Tox Hazard Subst Environ Eng 58 (14), 1047–1060. https://doi.org/10.1080/10934529.2024.2309102.

Molnarova, L., Halesova, T., Vaclavikova, M., Bosakova, Z., 2023. Monitoring pharmaceuticals and personal care products in drinking water samples by the LC-MS/MS method to estimate their potential health risk. Molecules 28 (15), 5899. https://doi.org/10.3390/molecules28155899.

Morrison, C., Hogard, S., Pearce, R., Mohan, A., Pisarenko, A., Dickenson, E., von Gunten, U., Wert, E., 2023. Critical review on bromate Formation during ozonation and control options for its minimization. Environ. Sci. Technol. 57 (47), 18393–18409. https://doi.org/10.1021/acs.est.3c00538.

Mosharaf, M.K., Gomes, R., Cook, S., Alam, M., Rasmusssen, A., 2025. Wastewater reuse and pharmaceutical pollution in agriculture: uptake, transport, accumulation and metabolism of pharmaceutical pollutants within plants. Chemosphere 364, 143055. https://doi.org/10.1016/j.chemosphere.2024.143055.

Mousel, D., Palmowski, L., Pinnekamp, J., 2017. Energy demand for elimination of organic micropollutants in municipal wastewater treatment plants. Sci. Total Environ. 575, 1139–1149. https://doi.org/10.1016/j.scitotenv.2016.09.197.

Muambo, K., Kim, M.-G., Kim, D.-H., Park, S., Oh, J.-E., 2024. Pharmaceuticals in raw and treated water from drinking water treatment plants nationwide: insights into their sources and exposure risk assessment. Water Res. X 24, 100256. https://doi.org/10.1016/j.wroa.2024.100256.

Munuhe, L., Madivoli, E., Nzilu, D., Lemeitaron, P., Kinyanjui, P., 2025. Advances in adsorbent materials for pharmaceutical pollutant removal: a review of occurrence, fate, and state-of-the-art remediation. J. Chem. 17. https://doi.org/10.1155/joch/4477822, 4477822.

Nosek, K., Zhao, D., 2024. Transformation products of diclofenac: formation, occurrence, and toxicity implication in the aquatic environment. Water Res. 266, 122388. https://doi.org/10.1016/j.watres.2024.122388.

Oaks, J.L., Gilbert, M., Virani, M.Z., Watson, R.T., Meteyer, C.U., Rideout, B.A., Shivaprasad, H.L., Ahmed, S., Chaudhry, M.J.I., Arshad, M., Mahmood, S., Ali, A., Ahmed Khan, A., 2004. Diclofenac residues as the cause of vulture population decline in Pakistan. Nature 427 (6975), 630–633. https://doi.org/10.1038/nature02317.

OECD, 2019. Pharmaceutical Residues in Freshwater: Hazards and Policy Responses, OECD Studies on Water. OECD Publishing, Paris. https://doi.org/10.1787/c936f42d-en.

Omotola, E., Olatunji, O., 2020. Quantification of selected pharmaceutical compounds in water using liquid chromatography-electrospray ionisation mass spectrometry (LC-ESI-MS). Heliyon 6, e05787. https://doi.org/10.1016/j.heliyon.2020.e05787.

Parsoya, R., Bisht, B., Vlaskin, M.S., Jaiswal, K.K., Chauhan, P.K., Tripathi, M.K., Kurbatova, A., Rajput, V., Kumar, V., 2026. AI-based wastewater treatment for a circular economy and sustainable management of PFAS, heavy metals, microplastics, and antibiotics. Clean. Water(Washingt.) 5, 100189. https://doi.org/10.1016/j.clwat.2025.100189.

Patel, M., Kumar, R., Kishor, K., Mlsna, T., Pittman Jr, C.U., Mohan, D., 2019. Pharmaceuticals of emerging concern in aquatic systems: chemistry, occurrence, effects, and removal methods. Chemical reviews 119 (6), 3510–3673. https://doi.org/10.1021/acs.chemrev.8b00299.

Poursat, B., van Spanning, R., Braster, M., Helmus, R., de Voogt, P., Parsons, J., 2019. Biodegradation of metformin and its transformation product, guanylurea, by natural and exposed microbial communities. Ecotoxicol. Environ. Saf. 182, 109414. https://doi.org/10.1016/j.ecoenv.2019.109414.

Radjenović, J., Petrović, M., Ventura, F., Barceló, D., 2008. Rejection of pharmaceuticals in nanofiltration and reverse osmosis membrane drinking water treatment. Water Res. 42 (14), 3601–3610. https://doi.org/10.1016/j.watres.2008.05.020.

Rilstone, V., Filion, Y., Champagne, P., 2025. Study on the persistence of ciprofloxacin and sulfamethoxazole in simulated drinking water systems. Environ. Syst. Res. 14, 7. https://doi.org/10.1186/s40068-025-00396-5.

Sambaza, S., Naicker, N., 2023. Contribution of wastewater to antimicrobial resistance: a review article. J. Glob. Antimicrob. Resist. 34, 23–29. https://doi.org/10.1016/j.jgar.2023.05.010.

Satyam, S., Patra, S., 2025. The evolving landscape of advanced oxidation processes in wastewater treatment: challenges and recent innovations. Processes 13 (4), 987. https://doi.org/10.3390/pr13040987.

Sgariboldi, A., Posté, E., Chirico, N., Sangion, A., Evangelista, M., Morosini, C., Re, A., Torretta, V., Papa, E., 2025. Global assessment of emerging contaminant removal in wastewater treatment plants: in Silico hazard screening and risk evaluation. Toxics 13 (1), 6. https://doi.org/10.3390/toxics13010006.

Shearer, L., Pap, S., Gibb, S., 2022. Removal of pharmaceuticals from wastewater: a review of adsorptive approaches, modelling and mechanisms for metformin and macrolides. J. Environ. Chem. Eng. 10, 108106. https://doi.org/10.1016/j.jece.2022.108106.

Simon, E., Duffek, A., Stahl, C., Frey, M., Scheurer, M., Tuerk, J., Gehrmann, L., Könemann, S., Swart, K., Behnisch, P., Olbrich, D., Brion, F., Aït-Aïssa, S., Pasanen-Kase, R., Werner, I., Vermeirssen, E.L.M., 2022. Biological effect and chemical monitoring of Watch List substances in European surface waters: steroidal estrogens and diclofenac - effect-based methods for monitoring frameworks. Environ. Int. 159, 107033. https://doi.org/10.1016/j.envint.2021.107033.

Soriano, Y., Carmona, E., Renovell, J., Picó, Y., Brack, W., Krauss, M., Backhaus, T., Inostroza, P.A., 2024. Co-occurrence and spatial distribution of organic micropollutants in surface waters of the River Aconcagua and Maipo basins in Central Chile. Sci. Total Environ. 954, 176314. https://doi.org/10.1016/j.scitotenv.2024.176314.

Trognon, J., Albasi, C., Choubert, J.-M., 2024. A critical review on the pathways of carbamazepine transformation products in oxidative wastewater treatment processes. Sci. Total Environ. 912, 169040. https://doi.org/10.1016/j.scitotenv.2023.169040.

Uluseker, C., Kaster, K.M., Thorsen, K., Basiry, D., Shobana, S., Jain, M., Kumar, G., Kommedal, R., Pala-Ozkok, I., 2021. A review on occurrence and spread of antibiotic resistance in wastewaters and in wastewater treatment plants: mechanisms and perspectives. Front. Microbiol. 12, 717809. https://doi.org/10.3389/fmicb.2021.717809.

UNDP, 2024. Fact Sheet: Persistent Organic Pollutants and the Stockholm Convention. United Nations Development Programme. Available at: https://www.undp.org/sites/g/files/zskgke326/files/2024-06/factsheet.pdf.

UNEP, 2001. United Nations Environment programme. https://chm.pops.int/TheConvention/Overview.

UNEP, 2025. Persistent organic pollutants (POPs) and pesticides. United Nations Environment Programme. Available at: https://www.unep.org/cep/persistent-organic-pollutants-pops-and-pesticides. (Accessed 10 November 2025).

Völker, J., Stapf, M., Miehe, U., Wagner, M., 2019. Systematic review of toxicity removal by advanced wastewater treatment technologies via ozonation and activated carbon. Environ. Sci. Technol. 53 (13), 7215–7233. https://doi.org/10.1021/acs.est.9b00570.

VSA Platform Process Engineering Micropollutants (2025). Evaluation of the energy and cost key figures of processes for the elimination of micropollutants in wastewater treatment plants. Eawag, Dübendorf, Switzerland. Available at: https://micropoll.ch/en/mediathek/evaluation-of-the-energy-and-cost-figures-of-processes-for-the-elimination-of-micropollutants-in-wastewater-treatment-plants.

Wada, O., Olawade, D., 2025. Recent occurrence of pharmaceuticals in freshwater, emerging treatment technologies, and future considerations: a review. Chemosphere 374, 144153. https://doi.org/10.1016/j.chemosphere.2025.144153.

Wang, G., Wang, X., Luo, F., Man, Y., He, Z., Liang, S., Yang, Z., 2026. Wastewater treatment process optimization in stochastic game based on multiagent deep reinforcement learning. Water Res. 303, 126252. https://doi.org/10.1016/j.watres.2026.126252.

Wang, A.-G., Zhang, J.-N., Hu, L.-X., Liu, Y.-S., Ying, G.-G., Liang, Y.-X., Xu, M.-Y., Yu, Z.-Q., 2025. Fate and transformation of psychotropic drugs in urban wastewater systems and receiving rivers via the integration of targeted and suspect screening analysis. Water Res. 276, 123292. https://doi.org/10.1016/j.watres.2025.123292.

Weber, F.-A., aus der Beek, T., Bergmann, A., Carius, A., Grüttner, G., Hickmann, S., Ebert, I., Hein, A., Küster, A., Rose, J., Koch-Jugl, J., Stolzenberg, H.-C., 2016. Pharmaceuticals in the Environment – the Global Perspective: Occurrence, Effects, and Potential Cooperative Action Under SAICM. German Environment Agency (UBA), Dessau-Roßlau. Available at: https://www.umweltbundesamt.de/en/publikationen/pharmaceuticals-in-the-environment-the-global.

WHO, 2012. Pharmaceuticals in drinking-water. World Health Organization, Geneva. https://www.who.int/publications/i/item/9789241502085.

Wilkinson, j., Boxall, a., Kolpin, D., Leung, K., Lai, R., Galbán-Malagón, C., Adell, A., Mondon, J., Metian, M., Marchant, R., Bouzas-Monroy, A., Cuni-Sanchez, A., Coors, A., Carriquiriborde, P., Rojo, M., Gordon, C., Cara, M., Moermond, M., Luarte, T., Teta, C., 2022. Pharmaceutical pollution of the world's rivers. Proc. Natl. Acad. Sci. USA. 119 (8), e2113947119. https://doi.org/10.1073/pnas.2113947119.

Wu, Y., Shi, Y., Gu, T., Du, X., Du, Z., Zhang, C., Sun, K., Zhang, Y., Guo, X., Wang, S., Zheng, W., He, Y., Liu, W., 2024. Global trends and hotspots in non-targeted screening of water pollution research: bibliometric and visual analysis. Toxics 12 (12), 844. https://doi.org/10.3390/toxics12120844.

Yan, H., Zhang, T., Yang, Y., Li, J., Liu, Y., Qu, D., Feng, L., Zhang, L., 2024. Occurrence of iodinated contrast media (ICM) in water environments and their control strategies with a particular focus on iodinated by-products formation: a comprehensive review. J. Environ. Manag. 351, 119931. https://doi.org/10.1016/j.jenvman.2023.119931.

Yu, Y., Wang, Z., Yao, B., Zhou, Y., 2024. Occurrence, bioaccumulation, fate, and risk assessment of emerging pollutants in aquatic environments: a review. Sci. Total Environ. 923, 171388. https://doi.org/10.1016/j.scitotenv.2024.171388.

Zhang, P., Liu, C., Lao, D., Nguyen, X.C., Paramasivan, B., Qian, X., Inyinbor, A.A., Hu, X., Yu, Y., Li, F., 2023a. Unveiling the drives behind tetracycline adsorption capacity with biochar through machine learning. Sci. Rep. 13 (1), 11512. https://doi.org/10.1038/s41598-023-38579-8.

Zhang, W., Fourcade, F., Amrane, A., Geneste, F., 2023b. Removal of iodine-containing X-ray contrast media from environment: the challenge of a total mineralization. Molecules 28 (1), 341. https://doi.org/10.3390/molecules28010341.