

CRITICAL REVIEW

View Article Online  
View Journal | View Issue



Cite this: *Environ. Sci.: Processes Impacts*, 2026, 28, 1191

# A critical review of septic tanks as a pathway for active pharmaceutical ingredients to the aquatic environment – existing knowledge and future perspectives on their monitoring and management

Kai Wilschnack,<sup>a</sup> Elise Cartmell,<sup>b</sup> Kyari Yates<sup>a</sup> and Bruce Petrie<sup>\*a</sup>

Active pharmaceutical ingredients (APIs) are present in aquatic environments at concentrations that can impact ecosystems. Their major pathway to the environment is in the discharge of wastewater effluents from centralised wastewater treatment works (WWTWs). However, in most rural areas where houses are not connected to a public sewage network, single households or groups of houses rely on onsite wastewater treatment works (OWTWs), mainly septic tanks (STs). Therefore, STs are reviewed as a pathway for APIs to the aquatic environment. Despite STs being extensively used globally, there is a geographical bias in available data with most studies conducted in the USA. Furthermore, studies focus on a few APIs (e.g., carbamazepine, sulfamethoxazole and paracetamol) and the impact of STs to groundwater. Previous reliance on grab sampling and the heterogenous composition of influent wastewater characterised by the small contributing populations makes assessing ST removal efficiency challenging. Available data suggests little or no removal of APIs in the anaerobic environment of STs. Conducting an intensive monitoring approach (e.g., continuous 24 h composite sampling) for durations several times the ST hydraulic retention time will help benchmark their performance for API removal against other processes. Recent studies show surface waters receiving ST discharges have API concentrations exceeding their predicted no effect concentration (PNEC, the concentration below which no adverse effect is expected). Mean concentrations of 17 $\beta$ -estradiol, ampicillin, ibuprofen, memantine, palmitamid, paracetamol and trihexyphenidyl all exceeded their PNEC by up to 50 times. However, there is a lack of data for several APIs identified to be of possible environmental concern in prioritisation watch lists such as those outlined by the EU (e.g., amoxicillin, clarithromycin, desmethylenlafaxine and clindamycin). Receiving surface waters can be small ecologically important streams, demanding the need for further monitoring and intervention. Other than adopting secondary treatment (e.g., constructed wetlands where possible) or alternative OWTWs which achieve greater API removal, sustainable medicine use is proposed as a viable means of reducing the environmental impact of ST discharges where risks are identified. Utilising environmentally informed prescribing and other 'upstream' interventions such as return schemes for unused pharmaceuticals, have great potential for success where small populations of people can be specifically targeted.

Received 24th July 2025  
Accepted 29th April 2026

DOI: 10.1039/d5em00568j

rsc.li/espri

## Environmental significance

Septic tanks (STs) are an important, but often overlooked, pathway for active pharmaceutical ingredients (APIs) entering the environment. API concentrations in aquatic environments impacted by STs can exceed their predicted no-effect concentrations. This highlights the need to consider the influence and management of STs in the protection of aquatic ecosystems.

## 1 Introduction

Pharmaceuticals are critical for improving public health through the prevention, management, and treatment of various

diseases.<sup>1</sup> However, they are also widely recognised for their potential ecotoxicological risk to the environment,<sup>2–5</sup> and are present in water bodies worldwide at ng to  $\mu\text{g L}^{-1}$  concentrations.<sup>6–11</sup> Adverse effects have been observed at concentrations relevant to the aquatic environment. For example, long-term exposure to fluoxetine ( $3 \times 10^{-3} - 0.3 \mu\text{g L}^{-1}$ ) reduces growth and reproductive potential in *Mytilus californianus* mussels.<sup>12</sup> Active pharmaceutical ingredients (APIs)

<sup>a</sup>School of Pharmacy, Applied Sciences and Public Health, Robert Gordon University, Aberdeen, AB10 7GJ, UK. E-mail: b.r.petrie@rgu.ac.uk; Tel: +44 (0)1224 262824

<sup>b</sup>Scottish Water, 55 Buckstone Terrace, Edinburgh EH10 6XH, UK



can induce their designed effects on non-target organisms. For instance, the swimming activity of *Danio rerio* (zebrafish) embryos is reduced in the presence of  $\beta$ -blockers due to the decreasing heart rate, and thus decreasing swim bladder inflation.<sup>13</sup> They can also induce non-designed effects in the environment. Hormones cause endocrine disrupting effects, such as feminisation, e.g., as observed in *Rutilus rutilus* (roach) after early life exposure to  $3 \times 10^{-3} \mu\text{g L}^{-1}$  of the hormonal contraceptive agent 17 $\alpha$ -ethinylestradiol.<sup>14</sup> Furthermore, persistent exposure to antibiotics can promote antimicrobial resistance genes (ARGs).<sup>15</sup> The presence of APIs in complex mixtures in the environment can also result in synergistic or antagonistic effects.<sup>3,16,17</sup> The ecotoxicological risk to the environment of individual APIs can be described using the predicted no effect concentration (PNEC), the concentration below which no adverse effects are expected.<sup>18</sup>

Many countries and continental bodies started addressing the environmental risks of APIs by implementing different prioritisation and monitoring schemes in the last decade.<sup>2,19–24</sup> However, specific regulations, e.g., maximum discharge limits or minimum required removal efficiencies in wastewater treatment works (WWTWs) or maximum concentrations in the receiving environment are rare. Municipal WWTWs in Switzerland, for example, are required to include ozone based advanced treatment to remove 80% of selected organic micropollutants, including ten APIs.<sup>25,26</sup> The recent EU urban wastewater treatment directive also mandates tertiary and quaternary treatment in large WWTWs,<sup>27</sup> improving API removal, and a proposal for priority substances, including eleven APIs, is being revised.<sup>23</sup>

Pharmaceuticals are often not fully metabolised by humans and animals, and thus unchanged APIs are excreted alongside metabolites.<sup>28</sup> The main removal processes for APIs in secondary (aerobic) wastewater treatment are biodegradation and sorption onto sludge that are highly influenced by their individual physicochemical properties.<sup>29</sup> For example, 99% ibuprofen removal compared to 21% propranolol removal was achieved in activated sludge WWTWs.<sup>30</sup> Furthermore, around half of APIs are chiral, existing as mirror images of each other with identical chemical structures but different spatial arrangements (enantiomers).<sup>31</sup> The enantiomeric composition of chiral compounds is typically reported as the enantiomeric fraction (EF), calculated from the enantiomer concentrations.<sup>32</sup> Pairs of enantiomers can demonstrate enantioselectivity in their environmental occurrence, fate, and toxicity.<sup>32–35</sup>

Possible pathways of APIs, including unchanged pharmaceuticals, and wastewater and human metabolites, to the environment include treated effluents from municipal, hospital, and industrial WWTWs, untreated wastewater discharges, e.g., through combined sewage overflows (CSOs), surface water runoff from urban and agricultural areas, aquaculture and landfill leachate.<sup>28,36–40</sup> Due to the ubiquitous presence of APIs in municipal influent wastewater, their incomplete removal in conventional wastewater treatment, the continuous discharge of treated effluent, and their use by the majority of the population, they are considered pseudo-persistent in the environment with centralised WWTWs identified as the main pathway

of APIs to the environment.<sup>28,36,41,42</sup> Hence, research efforts have been directed toward these centralised WWTWs and their receiving surface waters.<sup>6,36,43–45</sup> One pathway that has received comparatively little attention are onsite WWTWs (OWTWs), e.g., septic tanks (STs), that treat wastewater of single households or small communities in mostly rural areas.<sup>46,47</sup>

## 2 Septic tanks for wastewater treatment

Wastewater can be treated in centralised WWTWs or close to the source in decentralised OWTWs. OWTWs are especially common in rural areas due to the high costs of building and operating centralised WWTWs and pipe networks in low-density population areas.<sup>46,47</sup> However, historically OWTWs were also used in more urban areas, some of which still remain, e.g., there are 603 STs in Edinburgh, the second largest city in Scotland, of which only some are located in the outskirts of the city.<sup>48</sup> Onsite treatment options include packaged treatment plants and settlement systems, such as STs, possibly followed by further treatment steps.<sup>49</sup> Alternatively, wastewater is stored in a watertight cesspit (cesspool) and regularly removed to be treated at a centralised facility.<sup>50</sup> The principle of STs for wastewater treatment was proposed in 1860, in France, by Mouras and Moigno, and is widely used since their introduction to England in 1895.<sup>51</sup> A ST is a watertight underground tank with an inlet and outlet pipe.<sup>52</sup> Wastewater is treated by the separation of the liquid phase from heavy solids that settle as sludge at the bottom of the tank, and oil, grease and low density solids that build a top layer called scum.<sup>52</sup> The organic matter is partially degraded by anaerobic microorganisms.<sup>49</sup> However, there is a build-up of sludge and scum within the ST which needs removed, typically every few months to years.<sup>51</sup> The removed material is then further treated at centralised WWTWs.<sup>53</sup> STs are designed as a rectangular chamber made of bricks, concrete, or as glass-reinforced plastic (GRP) with one or more compartments in series (Fig. 1a) or as GRP torpedo (onion-shaped) STs (Fig. 1b). Generally, the performance of rectangular STs increases with increasing number of compartments.<sup>51,54</sup> Rectangular STs with multiple compartments are also known as baffled reactors.<sup>55</sup>

The ST effluent may undergo further treatment before being discharged into the ground or a nearby water body, e.g., through infiltration fields or natural systems.<sup>52,55,56</sup> In an infiltration field (also referred to as soil infiltration system, drainfield, drainage field, leach field, soil absorption system or soil treatment unit), ST effluent is distributed into perforated pipes and spread into the soil, often after filtration through stone or gravel.<sup>49,57</sup> Infiltration fields, unlike soakaways where ST effluent is discharged to the ground *via* a single pipe, are considered additional secondary treatment *via* sorption and anaerobic biodegradation.<sup>56</sup> Deep, permeable soils and sufficient space, e.g., to allow sufficient distance from portable water sources, are required for their successful use.<sup>47,51,58</sup> Alternative further treatments are mound filters, constructed wetlands, packaged filters, reed beds and packaged treatment plants.<sup>49,55,56,59</sup> Packaged treatment



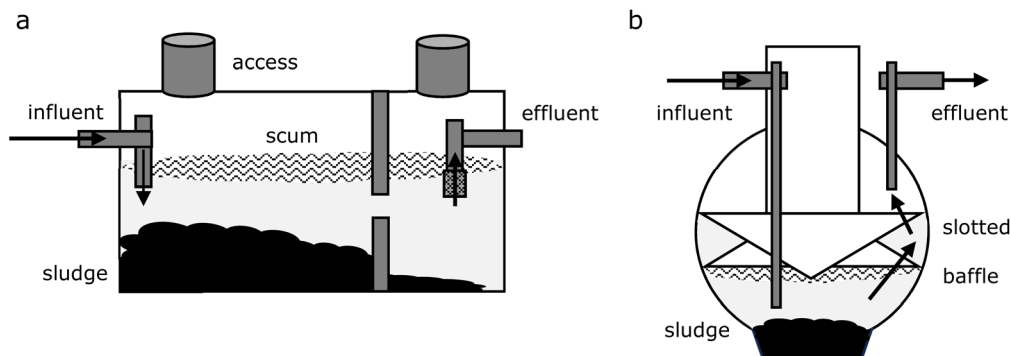


Fig. 1 Outline of different septic tank (ST) designs: rectangular ST with two compartments (a) and torpedo ST (b).

plants, such as activated sludge systems, submerged aerated filters, rotating biological contactors, sequencing batch reactors and biological filters, use aerobic processes and are used as secondary treatment units.<sup>55,56,60–62</sup>

Regulations on STs and how commonly STs are used vary widely between different countries. For instance, it is estimated that 3% of households in Germany, and 33% of households in Ireland use private OWTWs; traditionally a ST.<sup>52,63</sup> Regulatory differences exist even between geographically and politically similar countries, *e.g.*, different regulations on the registration process and discharges apply in the UK for England and Wales, Northern Ireland, and Scotland.<sup>64</sup> STs serve single houses or small communities (sometimes referred to as cluster STs) and can be publicly or privately owned.<sup>65–67</sup> While the majority of STs in the USA discharge to the ground, the direct discharge of ST effluent to rivers, lakes or coastal waters is also possible, and is commonplace in other countries.<sup>68,69</sup>

Regulations depend on the type of treatment, distance from a public sewer, the size of the contributing population and the nature of the receiving environment. Typically, existing STs and those receiving only domestic wastewater, are less strictly regulated than newly installed systems and those receiving other than just domestic inputs.<sup>68,70</sup> For example, trade effluent, such as water used in production, washing, or cooling facilities and businesses, including laundrettes and car washes, cannot be treated in STs in Scotland.<sup>68,71</sup> STs have received increasing attention by regulators in recent years, and stricter rules have been introduced. For instance, STs discharging to a watercourse were to be replaced or upgraded to a packaged treatment plant before January 2020 in England unless an exemption is given by the Environment Agency.<sup>64</sup>

Typical problems associated with STs are however often related to systems not working as intended or not being compliant with existing regulations. For example, Yates *et al.*<sup>72</sup> found that in one catchment in England only 15% of STs had the required permit. This could not only lead to significantly underestimating the number of ST discharges, but also increases the risk of performance related issues<sup>72,73</sup> including incorrect maintenance, defective design or malfunctioning, *e.g.*, caused by blockages.<sup>51,52,74</sup> For instance, 45% of participants reported a blockage or overflowing of their ST in a catchment survey in 2012.<sup>75</sup> When STs are not frequently emptied, sludge and scum accumulate in the tank,

which reduces the tank volume and thereby the hydraulic retention time (HRT). The HRT is an important factor in the tank performance,<sup>65</sup> as it controls the time for separation of sludge and scum from the wastewater and biodegradation, and thereby the extent and efficiency of the treatment process. STs that were never emptied or last emptied over 15 years ago are still in use.<sup>52,75–78</sup> Existing historic STs, built before current regulations, have increased risk of performance related issues as older STs are associated with out-dated design standards. Examples of out-dated designs include undersized tanks, misconnected pipes, STs made of brick, as they are more likely to leak into the ground, or unsuitable infiltration fields or discharge points.<sup>48,51</sup> When effluent pipes are too short or damaged, ST discharges do not reach the receiving watercourse, particularly during low flow conditions of the watercourse.<sup>48,52</sup> Even for registered STs, further information relevant to determine the possible impact to the environment, *e.g.*, the number of contributing population equivalents (PE), size and age of the ST, treatment type, desludging frequency and discharge point, are often missing.<sup>48,78</sup>

There are four existing literature reviews on organic contaminants in OWTWs.<sup>49,79–81</sup> A recent review on the impact of STs on groundwater contamination also mentions organic contaminants including APIs.<sup>82</sup> Sharma *et al.*<sup>80</sup> reviewed the treatment of hospital effluent for antimicrobial removal in advanced onsite wastewater treatment. However, STs treat wastewater to a lesser degree than secondary and tertiary (advanced) WWTWs as they only rely on the physical separation of sludge and scum from the liquid phase and anaerobic biodegradation.<sup>47</sup> Wardhani *et al.*<sup>81</sup> only included four peer-reviewed studies on seven APIs analysed in ST effluent, a small fraction of the conducted research, to discuss the impact to Indonesia specifically. Both Lusk *et al.*<sup>79</sup> and Schaidler *et al.*<sup>49</sup> included the potential impact of STs to groundwater quality but concentrations in receiving surface water were not included, potentially due to the lack of available data in 2017 (Fig. 2). Over the last ten years, OWTWs have received increasing attention as pathways for APIs into the environment, and ground- and surface water has been studied more frequently,<sup>46,83–89</sup> highlighting the need for an up to date review. The aim of this review was therefore to detail the progress made on understanding ST discharges as a pathway of APIs to the aquatic environment. The detection and removal of APIs in STs,



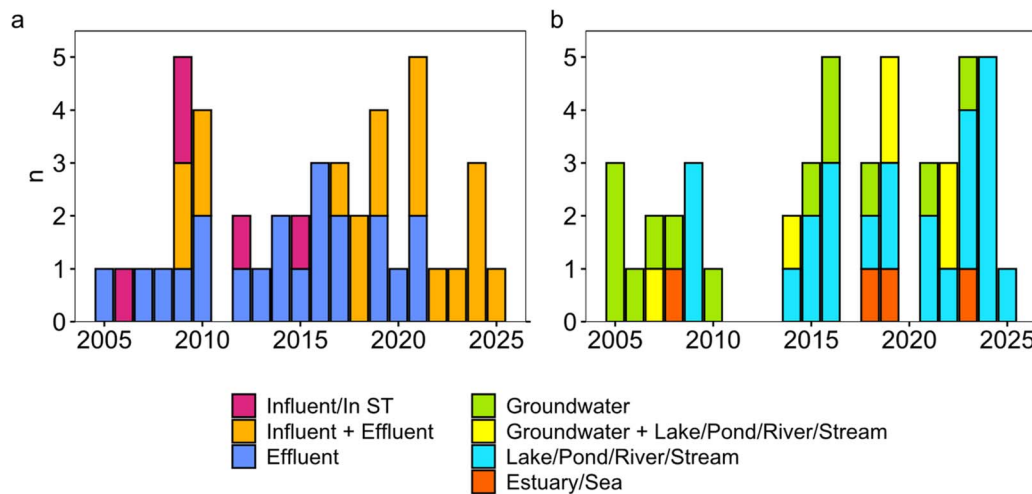


Fig. 2 Number of conducted studies per year ( $n$ ) on active pharmaceutical ingredients (APIs) in STs (a) and the receiving environment (b).

and the difference to other, alternative, OWTWs and secondary treatment steps, as well as their contribution to the receiving environment, and mitigation strategies are critically discussed.

### 3 Search strategy and methods

A literature search was conducted on literature available in June 2025 on Scopus and Web of Science using relevant key words: (“pharmaceutical” OR “drug” OR “hormone”) AND (“septic tank” OR “septic system” OR “onsite wastewater treatment” OR “on-site wastewater treatment” OR “cluster” OR “decentralised wastewater treatment”) and (“emerging contaminant” OR “emerging concern” OR “emerging pollutant” OR “trace organic” OR “micropollutant” OR “organic contaminant”) AND (“septic tank” OR “septic system”). Results combining (“emerging contaminant” OR “emerging concern” OR “emerging pollutant” OR “trace organic” OR “micropollutant” OR “organic contaminant”) AND (“onsite wastewater treatment” OR “on-site wastewater treatment” OR “cluster” OR “decentralised wastewater treatment”) were filtered manually for relevant articles using the title and abstract if appropriate. Research that did not include APIs or hormones was excluded, and studies found through cross-references were added. Caffeine was not included, as its main source is not from pharmaceutical use. One scientific report was included in addition to peer-reviewed scientific articles.<sup>90</sup>

For the purpose of this review, ST refers to a conventional ST (Fig. 1) that can receive wastewater from one or multiple households, a community or from a specialised purpose, *e.g.*, a café, school or office building. When possible, a distinction between the effluent after conventional ST treatment (ST effluent) and after secondary treatment, *e.g.*, an infiltration field or constructed wetland, (final effluent) was made. Alternative treatment systems, such as small packaged treatment plants were also included. For the purpose of this review, an alternative OWTW is anything other than a ST.

To report the concentration of APIs, if it was not given, the arithmetic mean was calculated using only reported

concentrations (*i.e.*, not incorporating detection or quantification limits for samples below said limits) as this was the most common approach in studies that reported mean concentrations. When only influent concentrations ( $c_{\text{Inf}}$ ) and removal efficiencies (eqn (1)) were given, effluent concentrations ( $c_{\text{Eff}}$ ) were calculated using eqn (2). As a last option, concentrations were estimated from graphs.

$$\text{Removal (\%)} = \frac{c_{\text{Inf}} - c_{\text{Eff}}}{c_{\text{Inf}}} \times 100\% \quad (1)$$

$$c_{\text{Eff}} = c_{\text{Inf}} - \frac{\text{Removal(\%)} \times c_{\text{Inf}}}{100\%} \quad (2)$$

When only the median concentration was given, this was used instead.

To determine potential environmental implications, the hazard quotient (HQ) was calculated by dividing the measured environmental concentration of individual APIs by their lowest freshwater PNEC found in the NORMAN Ecotoxicology Database.<sup>69,91</sup>

Data was processed in Microsoft Excel (version 2505) and R92 (version 4.3.1) with RStudio<sup>93</sup> (2023.09.01) using the packages dplyr,<sup>94</sup> openxlsx,<sup>95</sup> readxl,<sup>96</sup> tidyverse<sup>97</sup> and rstatix<sup>98</sup> for data manipulation and statistical analysis. Significant differences ( $p < 0.05$ ) were determined using Wilcoxon tests, due to the nonparametric nature of the data. Graphs were made in R using ggplot2 (ref. 99) and patchwork.<sup>100</sup> The map was produced in QGIS<sup>101</sup> re (version 3.28.3) from open access data (<https://www.TechGEO.org> (ref. 102)).

## 4 Occurrence of active pharmaceutical ingredients in onsite wastewater treatment works

### 4.1 Wastewater concentrations

In total, 77 studies determining APIs in conventional STs, alternative OWTWs or in the receiving environment were





**Table 1** Conducted studies on active pharmaceutical ingredients (APIs) in STs and alternative OWTWs with study location, publishing year, the ST design, the wastewater (WW) source, type of receiving environment, types of samples taken, number of septic tanks sampled (STs), number of sampling events, and number of APIs analysed (*n*). Types of samples taken include influent (inf.) from STs, alternative OWTWs or centralised WWTWs, ST effluent (eff.) or effluent after secondary treatment (final eff.) or from alternative OWTWs

Study location	Year	Design	WW source	Receiving environment	Samples	STs	Sampling events	<i>n</i>	Study
Australia	2010	Alternative	Centralised WWTW (3800 PE) <sup>c</sup>	N/A	Inf. + final eff.	1	3	19	116
Belgium	2017	Alternative	Centralised WWTW (450 PE) and hospital	N/A	Inf. + final eff.	1	Lab study	6	114
Brazil <sup>c</sup>	2021	ST + secondary treatment	Residential (student housing, 10 PE)	N/A	Inf. + final eff.	1	16	10	112
Canada	2008	ST + secondary treatment	Households	Ground	ST eff.	2	2	11	104
China	2023	Alternative	N/A	N/A	Inf. + final eff.	3	1	Non-target	83
Denmark	2009	ST + secondary treatment	Households	Ponds, streams	ST eff. + final eff.	13	1	8	139
Germany	2018	Alternative	Households (2500 PE)	N/A	Inf. + final eff.	3	13	27	65
Iran	2018	ST	Hospital (85 beds)	N/A	Inf. + ST eff.	1	3	6	109
Japan	2009	Alternative	Households	N/A	In tank	3	1	5	125
Korea	2019	Alternative	N/A	Streams, creeks	Inf. + final eff.	24	1	8	115
Scotland	2019	ST + sometimes infiltration field	Households: 2–7 people	Streams	Final eff.	15	1	10	87
Scotland	2024	ST	Residential (292 PE)	River	Inf. + ST eff.	1	1	68	111
Scotland	2024	ST	Residential (217–475 PE)	Rivers and stream	Inf. + ST eff.	5	12	68	69
Scotland <sup>b</sup>	2025	ST	Residential (217–475 PE)	Rivers and stream	Inf. + ST eff.	5	12	25	120
South Africa	2021	ST + secondary treatment	Residential (84 households)	N/A	Inf. + ST eff.	1	6	21	110
South Africa <sup>a</sup>	2022	Alternative	Residential (410 PE)	N/A	Inf. + ST eff.	1	1	Non-target	108
Spain	2016	ST + secondary treatment	550–2000 PE	N/A	ST eff. + final eff.	1	2	6	66
Spain	2020	ST + secondary treatment	University campus	N/A	ST eff. + final eff.	1	12	15	138
Spain	2021	ST + secondary treatment	Office (50 people)	N/A	ST eff. + final eff.	1	8	13	103
Spain	2024	Alternative	Offices (3 buildings)	N/A	Inf. + final eff.	1	6	8	88
Sweden <sup>a</sup>	2017	ST + secondary treatment	Residential (1–40 PE)	N/A	ST eff. + final eff.	13	2	Non-target	61
Sweden <sup>a</sup>	2019	ST + secondary treatment	Residential (four households)	N/A	ST eff. + final eff.	1	1	Non-target	214
Sweden	2019	Outdoor pond + secondary treatment	Residential (500 and 3000 PE)	Ground	Inf. + final eff.	2	5	56	46
Switzerland <sup>c</sup>	2009	Alternative	Household (3 PE) spiked	Ground	Inf. + final eff.	1	11	23	60
USA	2006	ST + secondary treatment	Residential	Ground	In tank	1	1	2	148
USA	2007	ST + secondary treatment	High school (350 people)	Ground	ST eff.	1	2	18	149
USA <sup>d</sup>	2009	ST	N/A	N/A	Inf.	1	1	6	215
USA	2009	ST + secondary treatment	Residential	Ground	ST eff. + final eff.	15	1	10	140
USA	2009	ST + secondary treatment	Senior centre	Ground	ST eff.	1	1	15	90
USA	2010	ST + secondary treatment	Office + schools: high school (600 students), montessori school (51 students), girls boarding school (40 students)	Surface water and ground	ST eff. + final eff.	5	1–6	4	106
USA	2010	ST + secondary treatment	Households	Ground	Inf. + ST eff.	6	3	8	107
USA	2010	ST + secondary treatment	(4–5 PE < 65 years and 2 PE > 65)	Ground	ST eff.	3	3	13	151
USA	2012	ST/Cluster	Residential (student housing)	N/A	Inf.	2	26	17	119



Table 1 (Contd.)

Study location	Year	Design	WW source	Receiving environment	Samples	STs	Sampling events	n	Study
USA	2012	ST + secondary treatment or alternative	Households (2–6 PE)	N/A	ST eff.	8	1	3	67
USA	2013	Alternative	Centralised WWTWs	N/A	ST eff.	2	7	4	62
USA	2014	ST + secondary treatment	Households (2–4 PE)	Ground	ST eff. + final eff.	4	4	1	150
USA	2014	ST + secondary treatment	Centralised WWTW	N/A	ST eff.	2	2	16	74
USA	2015	ST + secondary treatment	Extended health care facility for the elderly (65 beds)	Ground	In tank	1	1	46	117
USA	2015	ST + secondary treatment	Household	Ground	Final eff.	4	7	8	158
USA	2016	ST + secondary treatment	Residential (graduate student housing, business units)	Ground	ST eff. + final eff.	1	34	7	153
USA	2017	ST + secondary treatment	Residential (graduate student housing, business units)	Ground	ST eff. + final eff.	1	1	8	124
USA	2021	ST + secondary treatment	Centralised WWTWs	Ground	Inf. + final eff.	3	Lab study	5	137
USA	2021	ST + secondary treatment	Centralised WWTW and single households	Ground	ST eff. + final eff.	13	42	21	105

<sup>a</sup> Concentrations could not be calculated from available data. <sup>b</sup> Enantioselective analysis of data available in ref. 69. <sup>c</sup> Wastewater was spiked, all are excluded from Fig. 3. <sup>d</sup> Sampling location not given, author affiliation used instead. <sup>e</sup> PE; population equivalents.

identified, of which 43 included wastewater analysis (Table 1). Most studies used grab sampling only ( $n = 40$ ), taking a specific volume from one location at one point in time. Furthermore, often only effluent samples were taken after ST treatment or/and at the final effluent point (Table 1).<sup>61,66,67,74,87,90,103–106</sup> This could be due to the difficulties associated with accessing the influent, but the expected high variability in household wastewater was also mentioned as a reason.<sup>61</sup> Despite a high number of studies reporting APIs in STs specifically ( $n = 32$ ), only eight studies analysed APIs in both ST influent and ST effluent ( $n = 6$ )<sup>69,107–111</sup> or ST influent and final effluent ( $n = 2$ ),<sup>66,112</sup> highlighting the challenge of fully assessing the behaviour of APIs in STs. Although additional treatment of ST effluent, *e.g.*, through an infiltration field is common, it is not always required.<sup>113</sup> In recent years, alternative OWTWs have gained increasing attention,<sup>60,62,65,88,108,114</sup> potentially due to the need to improve decentralised wastewater treatment. Influent samples are however usually taken in alternative OWTWs ( $n = 9$ ) or in pilot-scale STs receiving influent from centralised WWTWs (Table 1).<sup>60,65,83,88,114–116</sup>

Generally, API concentrations were higher in ST influent and effluent than in final effluent after secondary treatment and in effluent from alternative OWTWs (Fig. 3 using data from Table 1). However, a high variability of detected concentrations between different STs is observed.<sup>87,107</sup> For instance, Conn *et al.*<sup>107</sup> found naproxen at concentrations  $<0.1$ – $180 \mu\text{g L}^{-1}$  in influent and  $<0.1$ – $150 \mu\text{g L}^{-1}$  in effluent in composite samples from six different household STs. As STs are used by smaller groups than centralised WWTWs, individuals of the contributing population highly influence API concentrations. Mostly, OWTWs receiving wastewater from a specialised use, such as a school, hospital or café, can show a distinctive pattern in detected API concentrations.<sup>106,117</sup> For example, Stanford and Weinberg<sup>106</sup> reported  $17\alpha$ -ethinylestradiol, an active ingredient in hormonal contraceptives, at up to  $0.4 \mu\text{g L}^{-1}$  in a ST effluent serving a boarding school for girls, higher than typical for centralised WWTWs influents.<sup>118</sup> The temporal variability is also higher in OWTWs as they receive fewer discrete wastewater inputs than centralised WWTWs.<sup>119</sup> In community STs the differences between sampling events were smaller for commonly prescribed pharmaceuticals with chronic use, such as venlafaxine, metformin and propranolol, than for less common pharmaceuticals with chronic use, *e.g.*, metoprolol and sotalol, and for pharmaceuticals with acute use, *e.g.*, antibiotics and antifungals.<sup>69</sup> Differences between STs also demonstrate the impact of localised prescription behaviour. For example, high variability in the enantioselectivity of APIs prescribed in enantiopure and racemic forms, *e.g.*, citalopram and omeprazole, shows the greater use of enantiopure formulations at some locations.<sup>120</sup> While the EF in five centralised WWTWs was 0.29–0.39 for citalopram and 0.39–0.46 for desmethylcitalopram, respectively, EFs  $> 0.5$  were found in STs for both, indicating the prescription of enantiopure escitalopram over the racemate (Fig. 5).<sup>32,120,121</sup>

There are a few APIs that are often analysed using targeted analytical methods, *e.g.*, carbamazepine (56%), sulfamethoxazole (49%) and paracetamol (39%) were included in around half

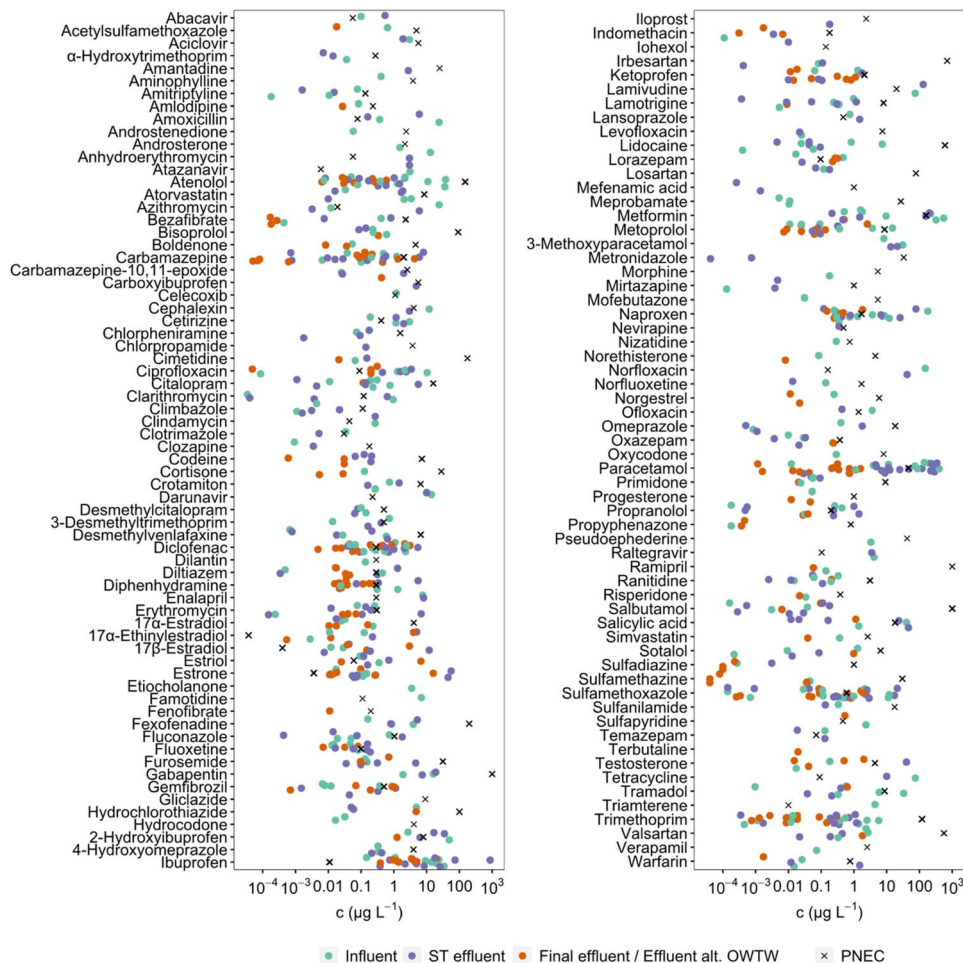


Fig. 3 Mean concentration (one data point for study and treatment type using studies in Table 1) and lowest freshwater PNEC<sup>122</sup> of detected active pharmaceutical ingredients (APIs) in influent, ST effluent, and final effluent (after infiltration field) or effluent from alternative OWTWs ( $c$  in  $\mu\text{g L}^{-1}$ ; logarithmic scale). For systems receiving influent from centralised WWTWs, only effluent values were included.

of the studies. This may be influenced by most studies being conducted in one country (the USA, Fig. 4), and their comparative ease of analysis. However, both carbamazepine and sulfamethoxazole are also recognised as priority substances impacting groundwater quality by the EU.<sup>23</sup> For a number of compounds that are included on EU watch lists as possible APIs of environmental concern,<sup>2,19,20,24</sup> e.g. desmethylvenlafaxine,<sup>69,111</sup> tetracycline,<sup>46,109</sup> ofloxacin,<sup>69,111</sup> clindamycin,<sup>110</sup> itraconazole, ketoconazole and oxytetracycline little or no data on their presence in STs is available. Since the performance of wastewater treatment for API removal highly depends on the properties of the individual compound,<sup>29</sup> a large variety of different APIs should be studied to fully assess STs for removal of APIs. Existing prioritisation schemes should be used as guidance to what APIs to include in future studies.<sup>4,19,21,23,25</sup>

Effluent concentrations exceeded the lowest reported PNEC found for freshwater<sup>122</sup> for a number of APIs (Fig. 3), highlighting the need for further treatment or dilution to mitigate environmental risk. The APIs most commonly detected at concentrations above the PNEC ( $\text{HQ} > 1$ ) in ST effluent and final effluent were ibuprofen ( $n = 19$ ), estrone ( $n = 15$ ), diclofenac

( $n = 12$ ) and sulfamethoxazole ( $n = 11$ ), all recognised for their ecotoxicological risk to the environment.<sup>20,123</sup> The highest HQs in effluent samples were found for  $17\alpha$ -ethinylestradiol (140 000),<sup>62</sup>  $17\beta$ -estradiol (30 000),<sup>62</sup> estrone (16 000)<sup>62</sup> and ibuprofen (79 000)<sup>124</sup> with at least one study determining a mean  $\text{HQ} > 10\,000$ ,<sup>62,124</sup> indicating the potential for STs to impact the receiving environment.

#### 4.2 Solid phase concentrations

Most studies solely focus on the liquid phase of wastewater when measuring APIs, potentially due to the additional cost and time associated with including analysis of the solids. So far, ST sludge has only been analysed in one preliminary study for APIs ( $n = 57$ ).<sup>111</sup> Furthermore, one other study analysed hormones in sludge from alternative OWTWs ( $n = 5$ ),<sup>125</sup> and one study investigated degradation and sorption of APIs ( $n = 23$ ) from spiked wastewater in an alternative OWTW.<sup>60</sup>

Sludge can contain a large variety of APIs at a wide concentration range from  $\text{ng kg}^{-1}$  to few  $\text{mg per kg}$  dry weight (dw).<sup>126–128</sup> For example, 53% of the analysed APIs ( $n = 30$ ) were found in a sludge sample from a community ST at



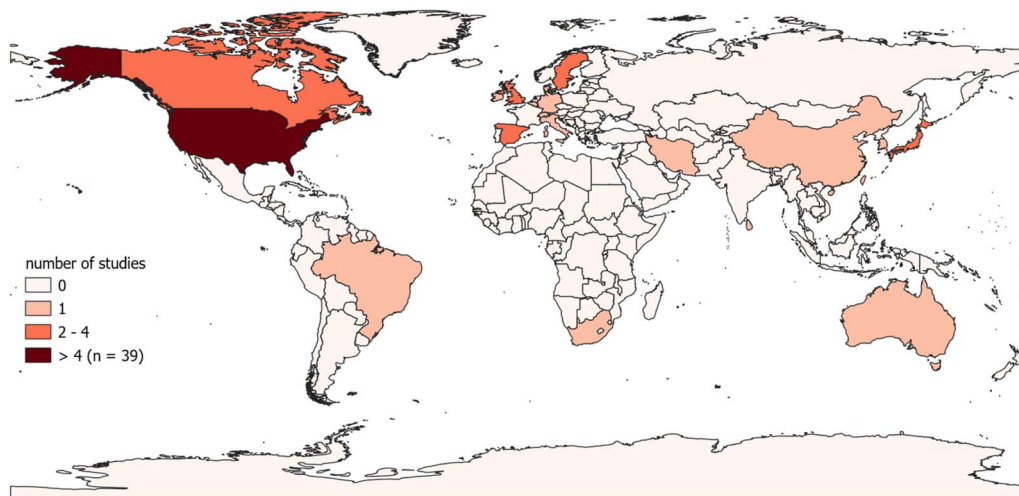


Fig. 4 Number of studies conducted in wastewater, groundwater and surface water (data in Tables 1 and 2).

concentrations from 4  $\mu\text{g}$  per kg dw (bisoprolol) to 3617  $\mu\text{g}$  per kg dw (paracetamol).<sup>111</sup> Similar concentrations are reported in sludge from centralised WWTWs, with concentrations  $>1$  mg per kg dw most frequently reported for antibiotics and anti-inflammatory drugs.<sup>129</sup> Estrone concentrations were similar in activated sludge from single household OWTWs ( $n = 3$ )<sup>125</sup> and community ST sludge ( $n = 1$ ),<sup>111</sup> but elevated for estriol in one of the single household OWTW, potentially due to pregnancy.<sup>125</sup> ST require regular emptying to remove sludge and scum that were separated from the liquid wastewater phase, and then treated in centralised WWTWs.<sup>51,53</sup> APIs can persist in conventional wastewater treatment and enter the environment when anaerobically digested (treated) sludge is applied in agriculture.<sup>128,130</sup> For example, eight pollutants (sertraline, venlafaxine, *N*-desethylamiodarone, amiodarone, nortriptyline, trazodone, amitriptyline and ketoconazole) were found to pose a risk to the environment in digested sludge-amended soils after sludge treatment from centralised wastewater treatment.<sup>126</sup> Although consideration of all possible pathways for APIs entering the environment from STs is required, ST sludge only makes up a small proportion of all sludge treated in a centralised WWTW.

APIs can be excreted in solid matter or sorb to particles present in wastewater influent and effluent. Hence, their total concentration can be underestimated by analysing the liquid phase only,<sup>6,45,111,131</sup> the most common analysis strategy used.<sup>66,88,105,114</sup> Sometimes, samples are not filtered and the total concentration (liquid and solid phase) is reported instead.<sup>119</sup> So far, only two studies analysed suspended solids and liquid phase separately in STs.<sup>69,111</sup> Although contributions of suspended solids to the total concentration of APIs in a sample are generally small, they can be significant for APIs with high sorption tendencies, such as antibiotics and antidepressants.<sup>127,132–134</sup> For instance, contributions of APIs in suspended solids to their total concentration in wastewater (liquid and solid) were found to be  $>99\%$  for oxytetracycline (1403  $\mu\text{g kg}^{-1}$ ), chlortetracycline (1623  $\mu\text{g kg}^{-1}$ ) and tetracycline (892  $\mu\text{g kg}^{-1}$ ) in final effluent of a centralised WWTW.<sup>134</sup>

A wider range of percentage contribution of APIs in suspended solids to the total concentration was found in STs than centralised WWTWs.<sup>69</sup> For example, the contribution of suspended solids to the total concentration of fluoxetine was 1.2–94% in effluents from five STs ( $n = 60$ )<sup>69</sup> but 39–74% in effluents from seven WWTWs ( $n = 84$ ),<sup>132</sup> both sampled monthly for one year. Wastewater properties including temperature, pH, ionic strength, organic matter and composition of suspended solids influence the sorption of APIs.<sup>127,135,136</sup> Hence, a range of percentage contribution is typically observed in wastewater, which is higher in STs due to the more variable wastewater composition.<sup>69,119</sup>

Suspended solids can act as a vector for API release into the environment, when particles are not completely removed in wastewater treatment.<sup>6,45</sup> Since, the removal of suspended solids is often lower in STs than centralised WWTWs,<sup>62,69,74</sup> APIs sorbed to particles can have a higher contribution to total concentrations.<sup>69</sup> Hence, the risk of underestimating the possible environmental impact of ST effluent discharges is higher, when the sorbed concentration is not accounted for. For instance, high HQs up to 39 for clotrimazole were found when the total concentration in ST effluent as opposed to the liquid phase only was used, where all HQs were  $<1$ .<sup>69</sup>

### 4.3 Removal

Removal efficiencies are typically calculated by dividing the difference in influent concentrations and effluent concentrations by influent concentrations (eqn (1)),<sup>74</sup> using either mean concentrations or individual detections. While, removal efficiencies were often calculated for advanced treatment ( $n = 11$ )<sup>65,74,88,103,110,114,115,137–140</sup> and in pilot scale studies or otherwise controlled environments ( $n = 8$ ),<sup>65,74,88,103,110,114,137,138</sup> only two studies report removal efficiencies in full-scale STs.<sup>74,110</sup> The high temporal variability in influent and effluent concentrations, differences between individual STs and often small sample sizes makes the determination of removal efficiencies difficult.<sup>69,107</sup> Alternatively, statistical analysis of influent and



effluent concentrations could be a useful tool to determine if there is removal in the STs. Significant differences between API concentrations in influent and effluent concentrations would indicate removal in STs.<sup>139</sup> Effluent concentrations that are significantly higher than in centralised WWTWs also indicate no removal, in particular if the API is easily degraded in secondary wastewater treatment such as metformin and ibuprofen.<sup>69</sup>

The two possible mechanisms discussed for API removal in STs are anaerobic biodegradation and the physical separation of solids from the wastewater when they are bound to sludge or scum particles.<sup>49</sup> Sorption processes have not been studied in STs. In single-house membrane bioreactors, sorption played a significant role in the removal of some APIs, *e.g.*, macrolide antibiotics (azithromycin, clarithromycin, roxithromycin) but was negligible for others, *e.g.*, ibuprofen and sulfonamide antibiotics (sulfamethoxazole, sulfadiazine, sulfamethazine, sulfadimethoxine, sulfapyridine).<sup>60</sup> For instance, due to little biodegradation and high sorption, 40% of clarithromycin remained sorbed to the sludge two weeks after spiking.<sup>60</sup> This is in line with research on sorption of APIs to the sludge in centralised WWTWs.<sup>126–128</sup>

Although, the degradation of APIs is greater under aerobic conditions, anaerobic biodegradation can still be a relevant removal mechanism.<sup>141–143</sup> For example, anaerobic transformation has been reported for sulfamethoxazole, trimethoprim, paracetamol, venlafaxine, atenolol and clarithromycin for iron and sulphate reducing conditions with removal >60% in an anaerobic reactor.<sup>143</sup> Anaerobic biodegradation has not been studied in STs. The comparatively longer solids retention times

and HRTs of STs could facilitate the development of different microbial populations that biodegrade APIs. Enantioselective analysis can also be useful to investigate removal processes in STs,<sup>120</sup> as enantiomers are considered to be affected equally by abiotic processes, such as sorption, but biological degradation processes and human metabolism can be stereoselective.<sup>144,145</sup> For instance, the preference of *S*(+)-citalopram over *R*(-)-citalopram in human metabolism and biological wastewater treatment, leads to enrichment of *R*(-)-citalopram in wastewater influent and effluent ( $EF < 0.5$ ).<sup>8,32</sup> In centralised WWTWs, the EF is reduced during aerobic biological wastewater treatment (Fig. 5,  $p = 7.37 \times 10^{-7}$ ). There are no significant differences between influent and effluent of STs ( $p = 0.1583$ ) and therefore no enantioselective degradation, adding further evidence to the lack of biological degradation processes for APIs in the anaerobic environments of STs. However, a high variability of EFs was found (Fig. 5), introducing uncertainty to identifying small differences in enantioselectivity.

Overall, API removal in STs is expected to be limited,<sup>110</sup> since sorption is generally small for the majority of APIs,<sup>29</sup> and biodegradation is greater under aerobic than anaerobic conditions.<sup>142</sup> Therefore, ST effluent is often further treated, *e.g.*, in infiltration fields, constructed wetlands (mainly anaerobic or aerated), bio- or sand filters or aerobic treatment units<sup>61,103,105,137,139</sup> to increase API removal.<sup>74,105,108</sup> For example, Du *et al.*<sup>74</sup> found 12% removal of atenolol in STs compared to 78% after secondary treatment in a wetland and 48% in a centralised activated sludge WWTW. The removal of APIs can be influenced by the season, *e.g.*, removal efficiencies of diclofenac during warm and cold seasons were 67% and 5% in

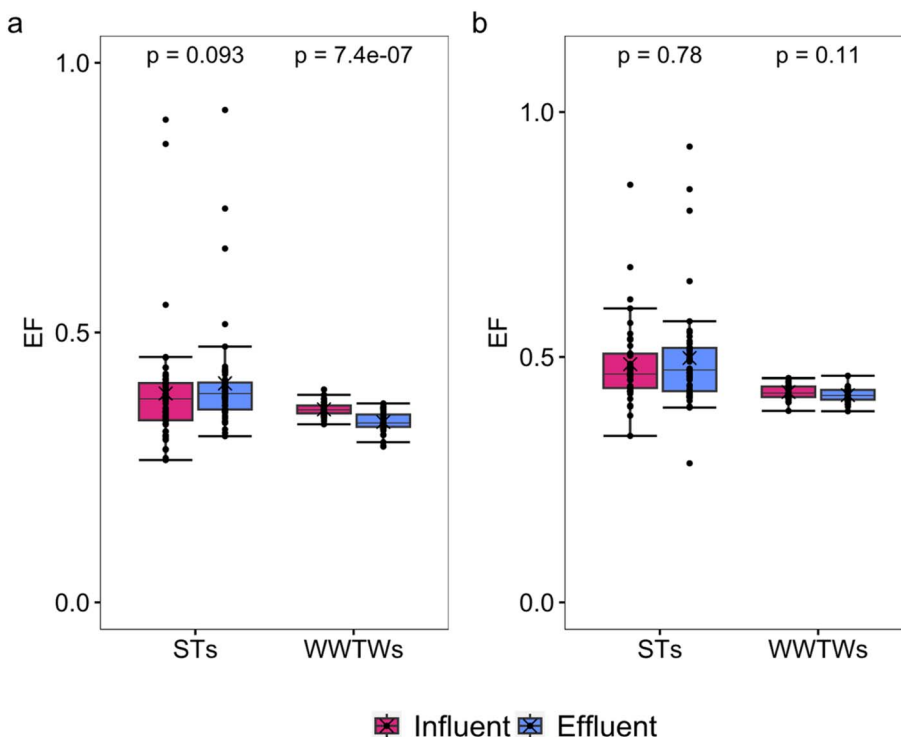


Fig. 5 Enantiomeric fraction (EF) of citalopram (a) and desmethylcitalopram (b) in influent and effluent of five community STs ( $n = 60$ )<sup>120</sup> and five centralised WWTWs ( $n = 35$ )<sup>216</sup> with Wilcoxon results (significant difference for  $p < 0.05$ ).



a constructed wetland, and 86% and 42% in an aerated treatment unit, respectively.<sup>66</sup> Removal is particularly high under aerated conditions, such as aerobic treatment systems and aerated wetlands.<sup>66,74,103</sup> For instance, removal of ketoprofen was –30–74% in anaerobic constructed wetlands, 64–100% in continuously aerated wetlands, and 60–97% under intermittent aeration.<sup>103</sup> Hence, the impact of OWTWs to the receiving environment varies depending on the location and treatment technology.

## 5 Impact of discharges from onsite wastewater treatment works to the aquatic environment

### 5.1 Groundwater

Discharges from STs and other OWTWs can contribute to API concentrations in ground- and surface water due to comparatively high effluent concentrations despite expected large

**Table 2** Conducted studies on active pharmaceutical ingredients (APIs) in the receiving environment impacted by OWTWs with study location, publishing year, environment sampled, number of sampling points, number of sampling events, number of APIs analysed and if any wastewater samples were also taken (WW)

Study location	Year	Environment	Sampling points	Sampling events	APIs	WW	Study
Brazil <sup>a</sup>	2021	River	4	2	10	Yes	112
Canada	2008	Groundwater	11	2	11	Yes	104
Canada	2008	Estuary	11	4–5	10	No	163
Canada <sup>a</sup>	2023	Stream	5	14–17	5	No	84
Canada	2024	River	6	3	5	No	147
China	2023	River	18	1	Non-target	No	83
Denmark	2009	Ponds and streams	13	1	8	Yes	139
Iran	2018	Sea	8	2	6	Yes	109
Ireland	2024	Rivers and streams	22	2	2	No	85
Italy	2021	Groundwater	53	1	1	No	217
Italy	2024	Drainage channels and canal	6	2	6	No	89
Japan	2016	River	30	1	1	No	170
Japan	2018	River	4	17	54	No	162
Korea	2019	Streams and creeks	48	1	8	Yes	115
Scotland	2019	River and streams	14	1	10	Yes	87
Scotland	2024	River	2	1	68	Yes	111
Scotland	2024	Rivers and stream	10	4	68	Yes	69
Scotland <sup>b</sup>	2025	Rivers and stream	10	4	25	Yes	120
Sri Lanka <sup>c</sup>	2022	Canals	11	3	5	No	218
Sweden	2019	Groundwater, lake and streams	9	5	56	Yes	46
USA <sup>c</sup>	1999	Groundwater	18	1	8	No	168
USA	2005	Groundwater	19–25	1	10	No	219
USA	2006	Groundwater	11	4	2	Yes	148
USA	2007	Groundwater	39	2	18	Yes	149
USA	2008	Groundwater and springs	5	2	12	No	156
USA	2008	Pond	6	2	24	No	154
USA	2009	Groundwater	11	1	15	Yes	90
USA	2009	Drainage systems and streams	27	17	15	No	161
USA	2010	Groundwater	3	3	13	Yes	151
USA	2014	Groundwater and streams	12	4	1	Yes	150
USA	2014	Streams	7	5	7	No	220
USA	2015	Groundwater	12	1	46	Yes	117
USA	2015	Lake	28	7	8	Yes	158
USA	2015	Stream	10	15–18	7	No	165
USA	2016	Groundwater	20	1	59	No	157
USA	2016	Groundwater	25	1	103	No	155
USA	2016	Streams and shoreline seeps	20	2	4	No	164
USA	2016	River	4	17	11	No	159
USA	2018	Groundwater	7	3	108	No	152
USA	2019	River, groundwater and springs	27	1	6	No	86
USA	2019	Estuary	12	2	4	No	160
USA	2022	Groundwater and stream	20	4–8	3–6	No	146
USA <sup>c</sup>	2022	Groundwater, canals and sea	18	3	Non-target	No	167
USA	2022	Lake and streams	30	1–4	15–20	No	166
USA	2023	Groundwater	450	1	2	No	169
USA	2023	Streams and springs	47	9	2	No	221
USA	2023	Sea	58	1	52	No	222

<sup>a</sup> Concentrations could not be calculated from available data. <sup>b</sup> Enantioselective analysis of data available in Wilschnack *et al.*<sup>69</sup> <sup>c</sup> APIs are identified but no concentration data is available, both are excluded from Fig. 6.



dilution factors in receiving waters.<sup>46,117,146</sup> Hence, STs and other OWTWs have received increasing attention as pathways for APIs into the environment in recent years (Table 2). Samples were usually taken as grab samples ( $n = 46$ ) but passive samplers were also used ( $n = 2$ ).<sup>112,147</sup> Again, the majority of research (57%) on APIs in ground- or surface water impacted by OWTWs was done in the USA (Fig. 4), mainly at the East coast, potentially driven by the high use of STs there. Approximately 25% of the total population in the USA use OWTWs, mostly being STs that discharge to the ground *via* an infiltration field. This is as high as 85% in some rural and forested areas in the Northeast.<sup>148</sup>

ST discharges have been identified as a pathway for APIs into underlying shallow groundwater and aquifers.<sup>149</sup> Prescription and over-the-counter drugs were detected in groundwater at concentrations from low  $\text{ng L}^{-1}$  to hundreds of  $\mu\text{g L}^{-1}$  (Fig. 6 using data from Table 2). The highest concentrations were found for commonly used nonsteroidal anti-inflammatory drugs (NSAIDs) ibuprofen ( $20 \mu\text{g L}^{-1}$ ) and the aspirin metabolite, salicylic acid ( $12 \mu\text{g L}^{-1}$ ).<sup>104</sup> Overall, a high variability in the detection and concentrations of APIs in groundwater is observed (Fig. 6). For example, the two most analysed APIs

sulfamethoxazole and carbamazepine were detected at mean concentrations of  $6.9 \times 10^{-5} - 0.19 \mu\text{g L}^{-1}$  and  $4.3 \times 10^{-5} - 0.29 \mu\text{g L}^{-1}$ , respectively (Fig. 6). Groundwater concentrations are impacted by varying household or site specific conditions.<sup>86</sup> Site specific conditions include for instance the type and design of OWTWs and its performance for API removal, the proximity to discharge points, and factors affecting sorption and degradation. Sorption and degradation are for example influenced by the soil type,<sup>150,151</sup> redox conditions,<sup>104,148</sup> pH,<sup>86</sup> organic carbon content,<sup>86,152</sup> water depth,<sup>104,146,152</sup> and travel time from release to sampling point.<sup>46,86,150</sup> Differences between individual APIs depend on their sorption potential, mobility and degradability in soil.<sup>46,104,117,153</sup> Similar to what has been discussed for APIs in ST effluents, groundwater concentrations are also impacted by the small contributing population leading to high temporal variability within OWTWs and spatial variability between different OWTWs.<sup>86</sup>

Generally, concentrations and detection frequencies were lower in groundwater than in STs and infiltration fields<sup>150,151</sup> due to the reduction of many APIs *via* physical, chemical, and biological processes within the vadose “unsaturated” zone

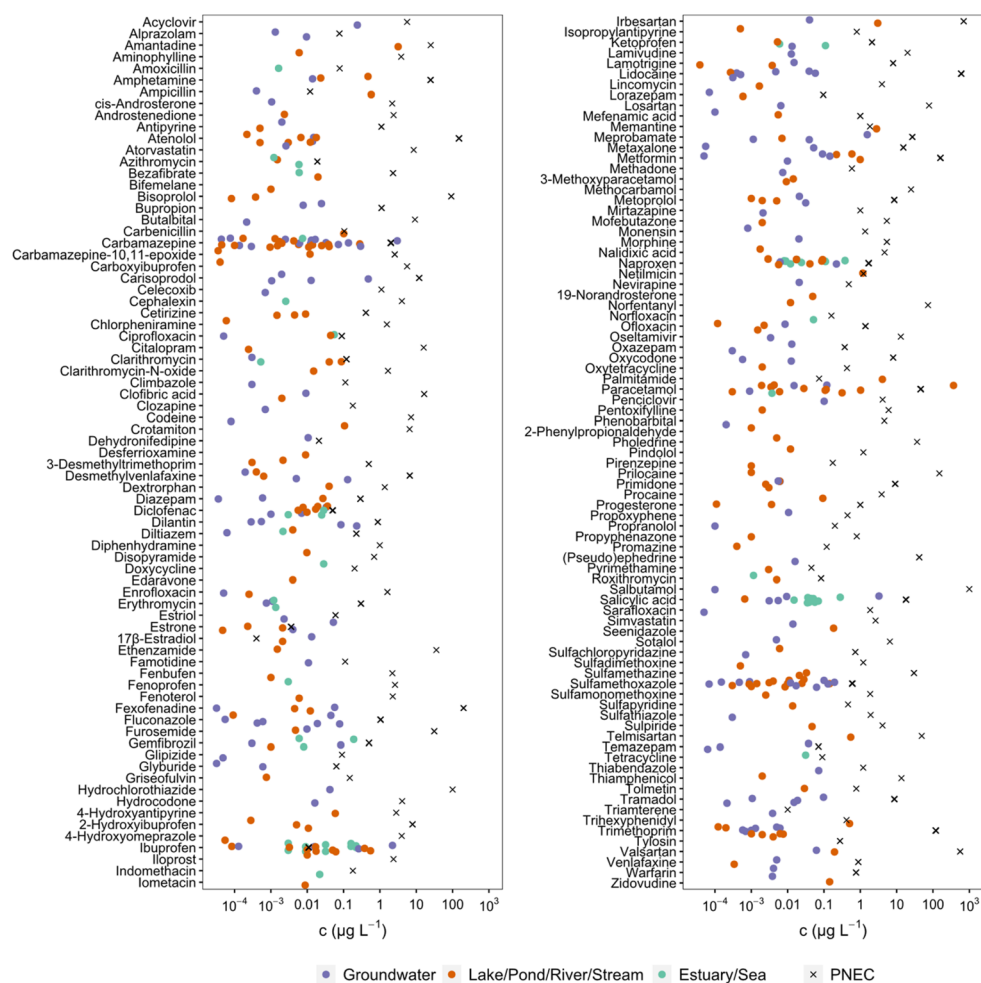


Fig. 6 Mean concentration (data from one study, studies in Table 2) and lowest freshwater PNEC<sup>122</sup> of active pharmaceutical ingredients (APIs) in ground- and surface water, including streams, lakes, ponds, canals and seawater, impacted by OWTWs ( $c$  in  $\mu\text{g L}^{-1}$ ; logarithmic scale). Some locations also receive discharges from centralised WWTWs, but known data points directly downstream of centralised WWTWs were excluded.



between the land surface and the groundwater table.<sup>46,104,117,149,153</sup> For instance, Godfrey *et al.*<sup>149</sup> found a reduction of carbamazepine and sulfamethoxazole concentrations by 1.2–5 times and 15–1200 times, but still detected both compounds in groundwater impacted by STs. However, higher groundwater concentrations similar to WWTW's influent also have been reported.<sup>104</sup> Groundwater concentrations can exceed concentrations found in the corresponding ST effluent.<sup>46,150</sup> This could be due to surface water run-off as a direct pathway for APIs to groundwater, deconjugation of metabolites back to the parent API, accumulation of persistent compounds due to continuous discharges, or desorption when APIs are released from suspended solids in wastewater into groundwater.<sup>29,46,131</sup> Furthermore, groundwater concentrations might appear higher due to the high variability in API concentrations in wastewater which cannot be accounted for by periodic grab sampling. Normally, groundwater concentrations are, as expected, higher at sampling points located on the down-rather than the up-gradient of the ST.<sup>46,149</sup> However, groundwater flow patterns can be difficult to predict<sup>154</sup> and lower or similar concentrations have also been reported down-gradient.<sup>46,150</sup> Del Rosario *et al.*<sup>150</sup> reported higher API concentrations up-gradient, and suggested other STs as the source.

For the majority of APIs and studies, concentrations were below the lowest PNEC found for freshwater,<sup>122</sup> suggesting that they pose a relatively low risk to the environment (Fig. 6). However, PNECs were exceeded for 17 $\beta$ -estradiol, estrone and ibuprofen (Fig. 6) using mean concentrations from individual studies,<sup>46,104,148,150,153</sup> and additionally for individual detections of diclofenac, naproxen and sulfamethoxazole in groundwater.<sup>46,104,152</sup> Since areas with OWTWs, also often rely on groundwater wells as a drinking water source, ST discharges can impact drinking water quality in rural areas.<sup>156–158</sup> Human consumption of the impacted drinking water is the major concern of the detected APIs in groundwater receiving discharges from OWTWs. API concentrations in tap water impacted by OWTWs may exceed those typically found in public drinking water supplies.<sup>157</sup>

## 5.2 Surface water

Nearby rivers, lakes, ponds or estuaries can be impacted through the transport of APIs from groundwater to surface water or *via* direct discharge of ST effluent or final effluent discharges.<sup>89</sup> Although many STs discharge to the ground through infiltration fields or secondary treatment systems (Table 1), direct effluent discharge to water bodies is possible.<sup>69</sup> For instance, in Scotland 21% of registered private STs discharge directly to an inland water body,<sup>59</sup> which was indicated by high paracetamol concentrations (1100  $\mu\text{g L}^{-1}$ ) in one sample by Ramage *et al.*<sup>87</sup> Furthermore, preferential flow paths *via* drainage networks such as storm drains can provide a direct entry pathway of APIs from ground discharge to surface water.<sup>84,89</sup>

In studies where both surface water and ground water were collected from the same geographical area, most API concentrations were lower in surface water than the corresponding

groundwater due to degradation and dilution effects.<sup>46,86,146,150</sup> However, similar concentrations for both matrices have also been found. For instance, Brewton *et al.*<sup>146</sup> reported primidone concentrations of  $1.1 \times 10^{-3}$ – $9.6 \times 10^{-3}$   $\mu\text{g L}^{-1}$  in groundwater and  $6.7 \times 10^{-3}$   $\mu\text{g L}^{-1}$  at the nearest surface water sampling point.

Surface water concentrations are often influenced by multiple sources, including point sources, *e.g.*, centralised WWTWs and direct discharge from OWTWs, and diffuse sources, *e.g.*, wastewater impacted groundwater and agricultural runoff.<sup>159–161</sup> Then, centralised WWTWs are generally the main entry source for APIs to the aquatic environment.<sup>89,159,162</sup> However, larger community STs can have significant contributions to river water concentrations for some APIs.<sup>111</sup> For example, concentrations of paracetamol and its metabolite 3-methoxyparacetamol increased by a factor of 14 and 10 in river water downstream of a community ST compared to upstream to 0.59 and 0.026  $\text{L}^{-1}$ , respectively.<sup>111</sup> Typically, API concentrations are lower in areas impacted by OWTWs only than in areas impacted by centralised WWTWs only, or centralised and decentralised systems.<sup>163</sup> For instance, carbamazepine and paracetamol concentrations were 0.026–0.21  $\mu\text{g L}^{-1}$  and  $2.0 \times 10^{-3}$ – $0.013$   $\mu\text{g L}^{-1}$  downstream of a centralised WWTWs, and  $<1.1 \times 10^{-4}$ – $2.2 \times 10^{-3}$   $\mu\text{g L}^{-1}$  and  $<5.6 \times 10^{-4}$ – $9.9 \times 10^{-3}$   $\mu\text{g L}^{-1}$  upstream of the WWTWs in a river receiving ST discharges only, respectively.<sup>159</sup> While centralised WWTWs have higher removal efficiencies, their greater impact to API concentrations in surface waters can be attributed to lower dilution factors.<sup>62,89,159,164</sup>

STs are still an important pathway for APIs demonstrated by their presence in the impacted environment at ecotoxicologically relevant concentrations.<sup>69,164</sup> For instance, mean concentrations of 17 $\beta$ -estradiol, ampicillin, ibuprofen, memantine, palmitamid, paracetamol and trihexyphenidyl exceeded the PNEC (HQ up to 50) in surface water at 18 detections from a total of nine studies (Fig. 6), representing a small proportion of the analysed samples ( $\leq 5\%$ ). In particular in surface waters with low effluent dilution factors, *e.g.*, small streams,<sup>69,85,87</sup> or in areas with a high density of OWTWs,<sup>84,154,165</sup> direct ST discharges<sup>87</sup> or malfunctioning STs,<sup>164</sup> concentrations can exceed those typically reported for catchments impacted by centralised WWTWs.<sup>85</sup> Repairing or replacing failing STs can reduce API concentrations in nearby surface waters substantially.<sup>164</sup>

In rural areas with low population densities, other sources than human wastewater such as agriculture, *e.g.* large animal husbandry operations, recreational activities and improper waste disposal, can contribute to API concentrations in surface water.<sup>115,159,161,166</sup> Therefore, effort was made to distinguish between different pathways (STs *vs.* centralised WWTWs and STs *vs.* agriculture) into the environment. Proposed tracers include human consumption products, *e.g.*, sucralose<sup>46,146,167</sup> and caffeine,<sup>85,149,168</sup> human APIs, *e.g.*, paracetamol, carbamazepine<sup>146,149,156</sup> or sulfamethoxazole,<sup>169</sup> traditional water quality parameters, *e.g.*, chloride,<sup>46</sup> or ratios of different compounds or parameters.<sup>85,170</sup> Differences in the enantioselective composition of effluent from centralised WWTWs and STs, *e.g.*, using



the EF of naproxen, were also proposed as ST tracers.<sup>120</sup> The simultaneous presence of infrequently used pharmaceuticals, *e.g.*, carbamazepine and sulfamethoxazole, indicates influence of multiple waste streams found in centralised WWTWs or effluent from multiple households over single house STs.<sup>164</sup>

## 6 Future perspectives

### 6.1 Monitoring strategy

Previous research, has often focused on the liquid phase of the ST effluent only.<sup>46,61,87,103–105</sup> One challenge of sampling ST influent, particularly for smaller systems, is the accessibility to a suitable sampling point. The majority of STs are used by one or few households over whole communities, where normally the influent pipe directly connects the house to the ST underground. Community STs or STs specifically designed for research purposes are often equipped with suitable sampling points, allowing the collection of influent and effluent samples.<sup>69,109–111,137</sup> However, they are maintained better than smaller systems and their performance therefore may not be representative of such typical ST systems. Furthermore, API concentrations might not be representative of typical single-household STs, as they are used by larger groups of people or people with specific demographics, *e.g.*, university students (Table 1). For full-scale STs, information on maintenance, *e.g.*, the emptying frequency, and design, *e.g.*, torpedo *vs.* rectangular, number of compartments in baffled reactors and tank size are often not discussed, potentially due to limited data availability. However, obtaining this information in future studies is important as it can impact the ST performance for API removal. Future studies should include both private STs (the most commonly used OWTW) and community STs that have highest likely risk due to their smallest dilution factor of discharges in the environment.

Most studies are not extensive in nature, *e.g.*, around half of the studies ( $n = 20$ ; 47%) only sampled once or twice (Table 1) and all except three studies<sup>107,108,112</sup> used grab sampling only ( $n = 40$ ), not allowing to address maintenance related changes in the STs' performance. Owing to the small contributing populations to STs, the temporal variability in influent and effluent concentrations of APIs and the differences between different STs are high,<sup>69,106,119</sup> demanding a composite sampling approach. For instance, Ort *et al.*<sup>171</sup> recommended a flow-weighted sampling process with a sub-sampling frequency of 5 minutes, as time- or flow-weighted samples taken at larger intervals might not be representative of highly dynamic wastewater. This is especially important for STs with highly variable flow conditions and API concentrations. Conn *et al.*<sup>107</sup> took flow-weighted samples from ST influents but time-weighted samples from ST effluent, potentially due to access difficulties at ST effluent points. Mladenov *et al.*<sup>108</sup> collected 24 h time-weighted composite samples from ST influent and effluent points 24 h apart to account for the HRT of 1.4 days. Flow-weighted composite sampling with a high sample number and low sub-sampling frequencies is recommended for future work when investigating API removal in small WWTWs such as STs. Even though this is more expensive and logistically challenging due

to the rural location of many STs, benchmarking the removal efficiency of STs accurately for comparison to other WWTWs is essential. This would also allow determining ST performance for API removal at different temperatures and before or after sludge removal. In general, microbial activity and therefore biodegradation increases at higher temperatures, which can impact the efficiency of wastewater treatment.<sup>172–174</sup> Emptying the STs can impact their performance due to an increase in volume and thereby HRT and removal of beneficial microorganisms. Sampling should be conducted over consecutive days equivalent to several times the estimated HRT to account for the temporal variability in wastewater concentrations. Alternatively, passive sampling also allows the determination of time weighted average concentrations over week-long deployment periods,<sup>175,176</sup> and hence the removal efficiencies in STs.<sup>112</sup> Due to changes in ST performance, multiple deployments throughout the year are necessary. Information on short-term variability, only assessable by grab sampling, provide useful information on individual's practices,<sup>120</sup> and it might be beneficial to combine multiple sampling approaches after carefully evaluating the objectives of each study.

Further research on a broad range of APIs in ground- and surface water is needed as their occurrence depends on the physicochemical characteristics of individual APIs that impact their sorption potential, mobility and degradability in soil.<sup>104,117,153</sup> However, 75% of studies ( $n = 34$ ) using targeted methods included 20 or less APIs (Table 2) and often the same APIs, such as carbamazepine ( $n = 32$ ), sulfamethoxazole ( $n = 28$ ), paracetamol ( $n = 18$ ) and ibuprofen ( $n = 17$ ), are analysed (Fig. 6). Alongside ibuprofen (HQ up to 200),<sup>104</sup> high HQ  $\geq 10$  were also found for less frequently analysed APIs palmitamide,<sup>83</sup> ampicillin,<sup>83</sup> 17 $\beta$ -estradiol,<sup>148</sup> and estrone,<sup>148</sup> that are not all recognised as priority substances,<sup>23</sup> highlighting the need for intensive monitoring to further our understanding. There is limited information available on some APIs included on the last EU watch list,<sup>24</sup> *e.g.*, clindamycin ( $n = 1$ ),<sup>161</sup> itraconazole ( $n = 0$ ), ketoconazole ( $n = 1$ ),<sup>155</sup> oxytetracycline ( $n = 1$ ),<sup>162</sup> and guany- lura ( $n = 2$ ). As discussed for ST effluent, the high temporal and spatial variability need to be considered. Both long-term, due to the seasonality of pharmaceutical use and river flow, and short-term variability should be taken into account.<sup>85,159,164</sup> Again, composite or passive samplers would allow to determine average contribution of ST discharges to the receiving environment.<sup>147</sup>

Antimicrobial resistance (AMR) is a significant concern to global human health.<sup>177–179</sup> So far, few studies have been conducted in areas impacted by STs, potentially because discharges from centralised WWTWs and agricultural inputs are usually highlighted as the most important pathways for ARGs into the environment.<sup>177,180–184</sup> Few studies have reported ARGs in effluents from STs, alternative OWTWs and the receiving ground- and surface water.<sup>178,179,185–191</sup> However, all reported a strong abundance of ARGs, *e.g.*, Tan *et al.*<sup>190</sup> found 441 ARGs relating to 26 antibiotic classes in STs, and the contribution to AMR abundance in the environment is highlighted.<sup>185,190,191</sup> For instance, Damashek *et al.*<sup>185</sup> reported samples with the highest abundance of ARGs in a watershed were associated with STs



over discharges from centralised WWTWs or agricultural industry, highlighting the need for further research on the contribution of STs to AMR and associated antibiotics.

## 6.2 Approaches to reduce the impact of septic tank discharges to pharmaceutical concentrations in the environment

The numbers of APIs detected above the PNEC in ST effluent and the receiving environment, highlighted the need for alternative approaches at some locations. Locations with low dilutions, a high density of STs, proximity to bathing waters or environmental protection zones, and where private drinking wells are being used need priority.

A large variety of secondary treatments and alternatives to STs exist that are known to increase API removal and are already in use at full-scale. Existing treatment options include infiltration fields, anaerobic or aerated constructed wetlands or packaged treatment plants.<sup>61,103,105,137,139</sup> Traditionally, ST discharges are treated by infiltration fields, which are easy to construct and can be added to existing STs, but require sufficient space and deep, permeable soils.<sup>47,51,58</sup> Although API concentrations are reduced through sorption and biodegradation in infiltration fields and underlying soil, discharges are still known to contribute to APIs in ground- and surface water.<sup>124,150,151</sup> Furthermore, they are not effective at locations with a high water table or low soil permeability. Here, mound systems, sand filters or constructed wetlands can be used.<sup>49,59</sup> Constructed wetlands combine natural processes such as biodegradation, sorption and plant uptake,<sup>28,138,192</sup> are low in cost and require little maintenance,<sup>138</sup> whilst reducing API concentrations.<sup>103</sup> API removal can be further increased using aeration,<sup>103</sup> *e.g.*, in aerated wetlands or packaged treatment plants. Packaged treatment plants are normally relatively small, but require electricity to operate, can be expensive and challenging to install or/and maintain, have higher operating costs than constructed wetlands, and can produce odour due to ventilation openings.<sup>55,193</sup> The operation costs, maintenance requirements and therefore increased responsibilities for individuals who manage them, increase the risk of these plants not working properly. For example, it was found during inspections that they were not switched on and therefore not operating as intended.<sup>48</sup> Overall, different decentralised wastewater treatment options exist that reduce API concentrations to various degrees and at varying costs.<sup>193</sup> There is no one size fits all approach, but rather the type of wastewater treatment should be decided for each individual site.

Alternatively, the impact of STs to API concentrations in the receiving environment might be reduced by targeting a reduction in their concentrations in influent wastewater, *e.g.*, by improving pharmaceutical design towards more environmentally friendly compounds and optimising their delivery, changing prescribing practices and reducing pharmaceutical waste.<sup>194–198</sup> Environmentally informed “green” prescribing includes changes in medicine selection, use, and dosages.<sup>195,196,199</sup> For instance, diclofenac purchases were reduced in Swedish pharmacies when it was placed behind the

counter due to its harmful effects on the environment.<sup>200</sup> For chiral APIs with racemic prescription, switching to enantiopure formulations with the less environmentally toxic enantiomer, when both enantiomers have equal effects on the human body, or by using the enantiomer that has more activity towards the desired therapeutic effect in humans over the racemate can also reduce environmental impact.<sup>120</sup> Furthermore, non-pharmacological interventions, *e.g.*, psychotherapy, exercises or physical therapy, could effectively reduce pharmaceutical use by simultaneously benefitting the patient.<sup>195,199</sup> One of the APIs frequently found above the PNEC was ibuprofen (Fig. 6), hence over-the-counter purchases also need to be considered. Leftover or unwanted pharmaceuticals can enter the environment through landfill leachate<sup>40</sup> and direct down-the-drain disposal.<sup>120,201</sup> Potential direct disposal of antidepressants was previously observed in ST influent.<sup>120</sup> Hence, reducing the need for disposal by decreasing the number of unused pharmaceuticals, preventing waste by controlled reuse or redistribution programs, and encouraging safe disposal, can have a beneficial effect on environmental concentrations.<sup>197</sup> Since those efforts would be targeted towards a small population when considering OWTWs, they are expected to have a greater effect than in more densely populated areas. Deprescribing interventions successfully reduced the numbers of used pharmaceuticals, but are labour intensive,<sup>202,203</sup> and can therefore currently only be directed at small groups. The impact of localised prescription and population behaviour on API concentrations in STs used by smaller populations has previously been shown,<sup>69,88,106</sup> and rural communities have already been targeted in programmes to reduce APIs in the environment *via* upstream solutions.<sup>204</sup> Furthermore, barriers to environmentally informed prescribing, such as lack of knowledge, confidence, time and resources<sup>205</sup> could be more easily addressed at a local level when targeting fewer prescribers. Overall, upstream solutions, such as sustainable medicine use, have great potential of being successful for small populations that can be specifically targeted by interventions. Keeping ethical considerations and the protection of individuals in mind is essential when these interventions are established in small communities.

## 6.3 Ethical considerations

Considering the ethical implications of any work is important, but essential when working with small groups, or vulnerable individuals or groups. Wastewater data is usually collected without obtaining informed consent from the contributing population as wastewater is considered an environmental matrix and no information on individuals are acquired.<sup>206–210</sup> However, with the COVID-19 pandemic and the increasing use of wastewater based epidemiology for monitoring illicit drug use and pathogens, ethical concerns of wastewater surveillance have received increasing considerations.<sup>207,208,210,211</sup> Wastewater surveillance can generally be justified due its benefits to public health or the environment,<sup>209</sup> and analysing APIs in wastewater or the receiving aquatic environment does not usually raise privacy concerns as individuals cannot be identified when large populations are monitored.<sup>206,208</sup> However, special



considerations need to be made when obtaining data related to small groups, *e.g.*, from ST wastewater, or marginalised communities, as results could potentially have negative effects on individuals, *e.g.*, through increased stigmatisation or the creation of adverse policies.<sup>206,208</sup>

Anonymising locations is an essential measure to protect individuals' privacy but might not be sufficient when small populations are monitored. The fewer people that use the ST, the more carefully ethical implications need to be considered. For instance, while anonymising locations for a community ST might be sufficient, informed consent should always be obtained before analysing APIs in household wastewater. The type of APIs selected for a study should also be carefully considered. Even the use of commonly prescribed pharmaceuticals, such as anti-depressants, is still stigmatised.<sup>212,213</sup> Analysing APIs that are taken without the knowledge of other household members or that are illegal in the area, *e.g.*, the abortion medication mifepristone, might put individuals at risk when the use is revealed. Furthermore, study locations should be carefully selected, and implications for marginalised communities considered. For instance, the presence or absence of HIV medications could further increase assumptions around the virus. It is always essential to evaluate the benefits of the study to public health or the environment, against the potential harm to individuals or small groups.

## 7 Conclusion

This review demonstrates the progress that has been made in understanding OWTWs as a pathway for APIs to the aquatic environment. Investigating APIs in OWTWs and their contribution to the aquatic environment poses several challenges, such as the high variability in API concentrations in wastewater from small communities and the difficulties associated with sampling influent, effluent and groundwater in rural locations. Further research on the detection and removal of a variety of APIs in OWTWs and their impact to ground- and surface water is needed. One priority in future should be to determine removal efficiencies in STs and alternative OWTWs by carefully selecting study design and sampling strategy. The high temporal and spatial variability need to be considered by sampling multiple OWTWs throughout the year. Available data suggests limited removal of APIs in STs, and a potential impact to surface and groundwater, indicated by concentrations exceeding the PNEC. Efforts towards sustainable medicine use and achieving greater API removal in OWTWs should be made.

## Author contributions

Kai Wilschnack: writing – original draft, visualization, investigation, formal analysis, data curation, conceptualization. Elise Cartmell: writing – review & editing. Kyari Yates: writing – review & editing, supervision. Bruce Petrie: writing – review & editing, supervision, project administration, funding acquisition, conceptualization.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

No primary research results have been included, and no new data was generated as part of this review.

## Acknowledgements

This work was funded by a joined studentship from Scottish Water and the Robert Gordon University. The authors wish to acknowledge Anna Baran, Sarah Gillman and Bess Homer for their contributions.

## References

- 1 Y. Li, M. A. Taggart, C. McKenzie, Z. Zhang, Y. Lu, S. Pap and S. W. Gibb, A SPE-HPLC-MS/MS method for the simultaneous determination of prioritised pharmaceuticals and EDCs with high environmental risk potential in freshwater, *J. Environ. Sci.*, 2021, **100**, 18–27.
- 2 European Commission, *Commission Implementing Decision (EU) 2018/840 of 5 June 2018 Establishing a Watch List of Substances for Union-wide Monitoring in the Field of Water Policy Pursuant to Directive 2008/105/EC of the European Parliament and of the Council and Repealing Commission Implementing Decision (EU) 2015/495*, 2018, vol. 141.
- 3 M. Cleuvers, Aquatic ecotoxicity of pharmaceuticals including the assessment of combination effects, *Toxicol. Lett.*, 2003, **142**, 185–194.
- 4 European Commission, *Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000, Establishing a Framework for Community Action in the Field of Water Policy*, 2000.
- 5 L. H. M. L. M. Santos, A. N. Araújo, A. Fachini, A. Pena, C. Delerue-Matos and M. C. B. S. M. Montenegro, Ecotoxicological aspects related to the presence of pharmaceuticals in the aquatic environment, *J. Hazard. Mater.*, 2010, **175**, 45–95.
- 6 H. Darwano, S. V. Duy and S. Sauvé, A New Protocol for the Analysis of Pharmaceuticals, Pesticides, and Hormones in Sediments and Suspended Particulate Matter From Rivers and Municipal Wastewaters, *Arch. Environ. Contam. Toxicol.*, 2014, **66**, 582–593.
- 7 M. Scheurer, A. Michel, H.-J. Brauch, W. Ruck and F. Sacher, Occurrence and fate of the antidiabetic drug metformin and its metabolite guanylurea in the environment and during drinking water treatment, *Water Res.*, 2012, **46**, 4790–4802.
- 8 B. Petrie and C. F. Moffat, Occurrence and fate of chiral and achiral drugs in estuarine water – a case study of the Clyde Estuary, Scotland, *Environ. Sci.: Processes Impacts*, 2022, **24**, 547–556.
- 9 Z. Zhang, M. Lebleu, M. Osprey, C. Kerr and E. Courtot, Risk estimation and annual fluxes of emerging contaminants



- from a Scottish priority catchment to the estuary and North Sea, *Environ. Geochem. Health*, 2018, **40**, 1987–2005.
- 10 J. L. Wilkinson, A. B. A. Boxall, D. W. Kolpin, K. M. Y. Leung, R. W. S. Lai, C. Galbán-Malagón, A. D. Adell, J. Mondon, M. Metian, R. A. Marchant, A. Bouzas-Monroy, A. Cuni-Sanchez, A. Coors, P. Carriquiriborde, M. Rojo, C. Gordon, M. Cara, M. Moermond, T. Luarte, V. Petrosyan, Y. Perikhanyan, C. S. Mahon, C. J. McGurk, T. Hofmann, T. Kormoker, V. Iniguez, J. Guzman-Otazo, J. L. Tavares, F. G. D. Figueiredo, M. T. P. Razzolini, V. Dougnon, G. Gbaguidi, O. Traoré, J. M. Blais, L. E. Kimpe, M. Wong, D. Wong, R. Ntchantcho, J. Pizarro, G.-G. Ying, C.-E. Chen, M. Páez, J. Martínez-Lara, J.-P. Otamonga, J. Poté, S. A. Ifo, P. Wilson, S. Echeverría-Sáenz, N. Udikovic-Kolic, M. Milakovic, D. Fatta-Kassinou, L. Ioannou-Ttofa, V. Belušová, J. Vymazal, M. Cárdenas-Bustamante, B. A. Kassa, J. Garric, A. Chaumot, P. Gibba, I. Kunchulia, S. Seidensticker, G. Lyberatos, H. P. Halldórsson, M. Melling, T. Shashidhar, M. Lamba, A. Nastiti, A. Supriatin, N. Pourang, A. Abedini, O. Abdullah, S. S. Gharbia, F. Pilla, B. Chefetz, T. Topaz, K. M. Yao, B. Aubakirova, R. Beisenova, L. Olaka, J. K. Mulu, P. Chatanga, V. Ntuli, N. T. Blama, S. Sherif, A. Z. Aris, L. J. Looi, M. Niang, S. T. Traore, R. Oldenkamp, O. Ogunbanwo, M. Ashfaq, M. Iqbal, Z. Abdeen, A. O'Dea, J. M. Morales-Saldaña, M. Custodio, H. de la Cruz, I. Navarrete, F. Carvalho, A. B. Gogra, B. M. Koroma, V. Cerkenik-Flajs, M. Gombač, M. Thwala, K. Choi, H. Kang, J. L. C. Ladu, A. Rico, P. Amerasinghe, A. Sobek, G. Horlitz, A. K. Zenker, A. C. King, J.-J. Jiang, R. Kariuki, M. Tumbo, U. Tezel, T. T. Onay, J. B. Lejju, Y. Vystavna, Y. Vergeles, H. Heinzen, A. Pérez-Parada, D. B. Sims, M. Figy, D. Good and C. Teta, Pharmaceutical pollution of the world's rivers, *Proc. Natl. Acad. Sci. U. S. A.*, 2022, **119**, e2113947119.
  - 11 E. E. Burns, L. J. Carter, D. W. Kolpin, J. Thomas-Oates and A. B. A. Boxall, Temporal and spatial variation in pharmaceutical concentrations in an urban river system, *Water Res.*, 2018, **137**, 72–85.
  - 12 J. R. Peters and E. F. Granek, Long-term exposure to fluoxetine reduces growth and reproductive potential in the dominant rocky intertidal mussel, *Mytilus californianus*, *Sci. Total Environ.*, 2016, **545–546**, 621–628.
  - 13 L. Bittner, E. Teixido, B. Seiwert, B. I. Escher and N. Klüver, Influence of pH on the uptake and toxicity of  $\beta$ -blockers in embryos of zebrafish, *Danio rerio*, *Aquat. Toxicol.*, 2018, **201**, 129–137.
  - 14 A. Lange, Y. Katsu, R. Ichikawa, G. C. Paull, L. L. Chidgey, T. S. Coe, T. Iguchi and C. R. Tyler, Altered Sexual Development in Roach (*Rutilus rutilus*) Exposed to Environmental Concentrations of the Pharmaceutical 17 $\alpha$ -Ethinylestradiol and Associated Expression Dynamics of Aromatases and Estrogen Receptors, *Toxicol. Sci.*, 2008, **106**, 113–123.
  - 15 J. Bengtsson-Palme and D. G. J. Larsson, Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation, *Environ. Int.*, 2016, **86**, 140–149.
  - 16 T. Backhaus, T. Porsbring, Å. Arrhenius, S. Brosche, P. Johansson and H. Blanck, Single-substance and mixture toxicity of five pharmaceuticals and personal care products to marine periphyton communities, *Environ. Toxicol. Chem.*, 2011, **30**, 2030–2040.
  - 17 C. Di Poi, K. Costil, V. Bouchart and M.-P. Halm-Lemeille, Toxicity assessment of five emerging pollutants, alone and in binary or ternary mixtures, towards three aquatic organisms, *Environ. Sci. Pollut. Res.*, 2018, **25**, 6122–6134.
  - 18 A. Bouzas-Monroy, J. L. Wilkinson, M. Melling and A. B. A. Boxall, Assessment of the Potential Ecotoxicological Effects of Pharmaceuticals in the World's Rivers, *Environ. Toxicol. Chem.*, 2022, **41**, 2008–2020.
  - 19 European Commission, *Common Implementation Strategy for the Water Framework Directive and the Floods Directive: Voluntary Groundwater Watch List*, 2019.
  - 20 European Commission, *Commission Implementing Decision (EU) 2022/1307 of 22 July 2022 Establishing a Watch List of Substances for Union-wide Monitoring in the Field of Water Policy Pursuant to Directive 2008/105/EC of the European Parliament and of the Council (Notified under Document C, 2022, 5098, 2022.*
  - 21 UKWIR, *Ellor (Project Management, on Behalf of UKWIR), B., Castle (Atkins, Author), G, Yates (Atkins, Author), C., the National Chemical Investigations Programme 2020-2022, Volume 5, Monitoring Substances of Emerging Concern*, UKWIR, 2023.
  - 22 UKWIR, *Ellor (Project Management, on Behalf of UKWIR), B., Gardner (Author), M. J, The National Chemical Investigations Programme 2015-2020, Volume 2, Monitoring Substances of Emerging Concern*, UKWIR, 2018.
  - 23 European Commission, *Proposal for a DIRECTIVE of the EUROPEAN PARLIAMENT and of the COUNCIL Amending Directive 2000/60/EC Establishing a Framework for Community Action in the Field of Water Policy, Directive 2006/118/EC on the Protection of Groundwater against Pollution and Deterioration and Directive 2008/105/EC on Environmental Quality Standards in the Field of Water Policy (COM/2022/540 Final)*, 2022.
  - 24 European Commission, *Commission Implementing Decision (EU) 2025/439 of 28 February 2025 Establishing a Watch List of Substances for Union-wide Monitoring in the Field of Water Policy Pursuant to Directive 2008/105/EC of the European Parliament and of the Council (Notified under Document C, 2025, 1244, 2025.*
  - 25 The Swiss Federal Council, Waters Protection Ordinance 814.201, In *German: Der Schweizerische Bundesrat. Gewässerschutzverordnung (GSchV)*, 2016.
  - 26 O. Miarov, A. Tal and D. Avisar, A critical evaluation of comparative regulatory strategies for monitoring pharmaceuticals in recycled wastewater, *J. Environ. Manage.*, 2020, **254**, 109794.
  - 27 European Commission, *Directive (EU) 2024/3019 of the European Parliament and of the Council of 27 November 2024 Concerning Urban Wastewater Treatment (Recast)*, 2024.



- 28 Y. Li, G. Zhu, W. J. Ng and S. K. Tan, A review on removing pharmaceutical contaminants from wastewater by constructed wetlands: Design, performance and mechanism, *Sci. Total Environ.*, 2014, **468–469**, 908–932.
- 29 P. Verlicchi, M. Al Aukidy and E. Zambello, Occurrence of pharmaceutical compounds in urban wastewater: Removal, mass load and environmental risk after a secondary treatment—A review, *Sci. Total Environ.*, 2012, **429**, 123–155.
- 30 S. Comber, M. Gardner, P. Sörme and B. Ellor, The removal of pharmaceuticals during wastewater treatment: Can it be predicted accurately?, *Sci. Total Environ.*, 2019, **676**, 222–230.
- 31 E. Sanganyado, Z. Lu, Q. Fu, D. Schlenk and J. Gan, Chiral pharmaceuticals: A review on their environmental occurrence and fate processes, *Water Res.*, 2017, **124**, 527–542.
- 32 S. Evans, J. Bagnall and B. Kasprzyk-Hordern, Enantiomeric profiling of a chemically diverse mixture of chiral pharmaceuticals in urban water, *Environ. Pollut.*, 2017, **230**, 368–377.
- 33 S. J. Khan, L. Wang, N. H. Hashim and J. A. McDonald, Distinct Enantiomeric Signals of Ibuprofen and Naproxen in Treated Wastewater and Sewer Overflow, *Chirality*, 2014, **26**, 739–746.
- 34 A. Pérez-Pereira, J. S. Carrola, M. E. Tiritan and C. Ribeiro, Enantioselectivity in ecotoxicity of pharmaceuticals, illicit drugs, and industrial persistent pollutants in aquatic and terrestrial environments: A review, *Sci. Total Environ.*, 2024, **912**, 169573.
- 35 F. Cui, Y. Zhu, S. Di, X. Wang, Y. Zhang and T. Chai, Toxicological Study on Chiral Fluoxetine Exposure to Adult Zebrafish (*Danio rerio*): Enantioselective and Sexual Mechanism on Disruption of the Brain Serotonergic System, *Environ. Sci. Technol.*, 2021, **55**, 7479–7490.
- 36 S. Comber, M. Gardner, P. Sörme, D. Leverett and B. Ellor, Active pharmaceutical ingredients entering the aquatic environment from wastewater treatment works: A cause for concern?, *Sci. Total Environ.*, 2018, **613–614**, 538–547.
- 37 K. Munro, C. P. B. Martins, M. Loewenthal, S. Comber, D. A. Cowan, L. Pereira and L. P. Barron, Evaluation of combined sewer overflow impacts on short-term pharmaceutical and illicit drug occurrence in a heavily urbanised tidal river catchment (London, UK), *Sci. Total Environ.*, 2019, **657**, 1099–1111.
- 38 L. Niemi, M. Taggart, K. Boyd, Z. Zhang, P. P. J. Gaffney, S. Pflieger and S. Gibb, Assessing hospital impact on pharmaceutical levels in a rural 'source-to-sink' water system, *Sci. Total Environ.*, 2020, **737**, 139618.
- 39 H. Xie, H. Hao, N. Xu, X. Liang, D. Gao, Y. Xu, Y. Gao, H. Tao and M. Wong, Pharmaceuticals and personal care products in water, sediments, aquatic organisms, and fish feeds in the Pearl River Delta: Occurrence, distribution, potential sources, and health risk assessment, *Sci. Total Environ.*, 2019, **659**, 230–239.
- 40 X. Yu, Q. Sui, S. Lyu, W. Zhao, J. Liu, Z. Cai, G. Yu and D. Barcelo, Municipal Solid Waste Landfills: An Underestimated Source of Pharmaceutical and Personal Care Products in the Water Environment, *Environ. Sci. Technol.*, 2020, **54**, 9757–9768.
- 41 B. Petrie, R. Barden and B. Kasprzyk-Hordern, A review on emerging contaminants in wastewaters and the environment: Current knowledge, understudied areas and recommendations for future monitoring, *Water Res.*, 2015, **72**, 3–27.
- 42 D. White, D. J. Lapworth, W. Civil and P. Williams, Tracking changes in the occurrence and source of pharmaceuticals within the River Thames, UK; from source to sea, *Environ. Pollut.*, 2019, **249**, 257–266.
- 43 M. Gros, M. Petrović and D. Barceló, Development of a multi-residue analytical methodology based on liquid chromatography–tandem mass spectrometry (LC–MS/MS) for screening and trace level determination of pharmaceuticals in surface and wastewaters, *Talanta*, 2006, **70**, 678–690.
- 44 K. Proctor, B. Petrie, R. Barden, T. Arnot and B. Kasprzyk-Hordern, Multi-residue ultra-performance liquid chromatography coupled with tandem mass spectrometry method for comprehensive multi-class anthropogenic compounds of emerging concern analysis in a catchment-based exposure-driven study, *Anal. Bioanal. Chem.*, 2019, **411**, 7061–7086.
- 45 D. R. Baker and B. Kasprzyk-Hordern, Multi-residue determination of the sorption of illicit drugs and pharmaceuticals to wastewater suspended particulate matter using pressurised liquid extraction, solid phase extraction and liquid chromatography coupled with tandem mass spectrometry, *J. Chromatogr. A*, 2011, **1218**, 7901–7913.
- 46 Q. Gao, K. M. Blum, P. Gago-Ferrero, K. Wiberg, L. Ahrens and P. L. Andersson, Impact of on-site wastewater infiltration systems on organic contaminants in groundwater and recipient waters, *Sci. Total Environ.*, 2019, **651**, 1670–1679.
- 47 M. A. Massoud, A. Tarhini and J. A. Nasr, Decentralized approaches to wastewater treatment and management: Applicability in developing countries, *J. Environ. Manage.*, 2009, **90**, 652–659.
- 48 I. Akoumianaki and A. Ibiyemi, *Understanding Problems Associated with Small-Scale Private Sewage Systems (PSS) from Regulators' Perspectives. Scotland's Centre of Expertise for Waters (CREW) Project 2020/07*, [https://www.crew.ac.uk/publication/private\\_sewage\\_systems](https://www.crew.ac.uk/publication/private_sewage_systems), 2022.
- 49 L. A. Schaidler, K. M. Rodgers and R. A. Rudel, Review of Organic Wastewater Compound Concentrations and Removal in Onsite Wastewater Treatment Systems, *Environ. Sci. Technol.*, 2017, **51**, 7304–7317.
- 50 P. Bugajski, A. Operacz, D. Młyński, A. Wałęga and K. Kurek, Optimizing Treatment of Cesspool Wastewater at an Activated Sludge Plant, *Sustainability*, 2020, **12**, 10196.
- 51 D. Butler and J. Payne, Septic tanks: Problems and practice, *Build. Environ.*, 1995, **30**, 419–425.



- 52 S. Richards, E. Paterson, P. J. A. Withers and M. Stutter, Septic tank discharges as multi-pollutant hotspots in catchments, *Sci. Total Environ.*, 2016, **542**, 854–863.
- 53 L. Gill, J. Mac Mahon, J. Knappe, S. Gharbia and F. Pilla, *Desludging Rates and Mechanisms for Domestic Wastewater Treatment System Sludges in Ireland (2016-W-DS-26)*, Environmental Protection Agency, Dublin, 2018.
- 54 L. Keshtgar, A. Rostami, A. A. Azimi, M. Dehghani and S. Ataollahi, The impact of barrier walls (baffle) on performance of septic tanks in domestic wastewater treatment, *Desalination Water Treat.*, 2019, **161**, 254–259.
- 55 K. Ramsay, A. Escudero, G. Frascaroli, F. Henderson and K. Helwig, Guidance on Small Sewage Systems in Scotland, *Scotland's Centre of Expertise for Waters (CREW) Project 2019/08*, <https://www.crew.ac.uk/publication/international-policy-review-small-sewage-systems>, 2022.
- 56 D. Dubber and L. Gill, Application of On-Site Wastewater Treatment in Ireland and Perspectives on Its Sustainability, *Sustainability*, 2014, **6**, 1623–1642.
- 57 D. Li, X. Wang, L. Chi and J. Wang, The design and operation of subsurface wastewater infiltration systems for domestic wastewater, *Water Environ. Res.*, 2019, **91**, 843–854.
- 58 L. Dawes and A. Goonetilleke, An Investigation into the role of site and soil characteristics in onsite sewage treatment, *Eng. Geol.*, 2003, **44**, 467–477.
- 59 J. O'Keeffe, J. Akunna, J. Olszewska, A. Bruce, L. May and R. Allan, *Practical Measures for Reducing Phosphorus and Faecal Microbial Loads from Onsite Wastewater Treatment System Discharges to the Environment: A Review*. Centre of Expertise for Waters (CREW), <https://www.crew.ac.uk/publication/reducing-phosphorus-faecal-loads-owts>, 2015.
- 60 C. Abegglen, A. Joss, C. S. Mc Ardell, G. Fink, M. P. Schlüsener, T. A. Ternes and H. Siegrist, The fate of selected micropollutants in a single-house MBR, *Water Res.*, 2009, **43**, 2036–2046.
- 61 K. M. Blum, P. L. Andersson, G. Renman, L. Ahrens, M. Gros, K. Wiberg and P. Haglund, Non-target screening and prioritization of potentially persistent, bioaccumulating and toxic domestic wastewater contaminants and their removal in on-site and large-scale sewage treatment plants, *Sci. Total Environ.*, 2017, **575**, 265–275.
- 62 S. N. Garcia, R. L. Clubbs, J. K. Stanley, B. Scheffe, J. C. Yelderman and B. W. Brooks, Comparative analysis of effluent water quality from a municipal treatment plant and two on-site wastewater treatment systems, *Chemosphere*, 2013, **92**, 38–44.
- 63 Statistisches Bundesamt, Water management: Public sewage systems, In *German: Wasserwirtschaft: Gemeinden mit öffentlicher und privater Abwasserentsorgung - Öffentliche Abwasserentsorgung nach Ländern*, 2019, last accessed 24/01/2025, <https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Umwelt/Wasserwirtschaft/Tabellen/ww-02-abwasserentsorgung-2019.html>.
- 64 UK Government, Septic tanks and sewage treatment plants: permits and general binding rules. <https://www.gov.uk>, last accessed 15/10/2024, <https://www.gov.uk/permits-you-need-for-septic-tanks>, accessed 7 January 2021.
- 65 H. Ejhed, J. Fång, K. Hansen, L. Graae, M. Rahmberg, J. Magnér, E. Dorgeloh and G. Plaza, The effect of hydraulic retention time in onsite wastewater treatment and removal of pharmaceuticals, hormones and phenolic utility substances, *Sci. Total Environ.*, 2018, **618**, 250–261.
- 66 V. Matamoros, Y. Rodríguez and J. Albaigés, A comparative assessment of intensive and extensive wastewater treatment technologies for removing emerging contaminants in small communities, *Water Res.*, 2016, **88**, 777–785.
- 67 J. A. Oppenheimer, M. Badruzzaman and J. G. Jacangelo, Differentiating sources of anthropogenic loading to impaired water bodies utilizing ratios of sucralose and other microconstituents, *Water Res.*, 2012, **46**, 5904–5916.
- 68 Scottish Government, in *Technical Handbook – Domestic 2020*, 2020, pp. 164–174.
- 69 K. Wilschnack, E. Cartmell, K. Yates and B. Petrie, Septic tanks as a pathway for emerging contaminants to the aquatic environment—Need for alternative rural wastewater treatment?, *Environ. Pollut.*, 2024, **362**, 124988.
- 70 Department for Environment, Food & Rural Affairs, Policy paper: General binding rules for small sewage discharges (SSDs) with effect from January 2015, <https://www.gov.uk/government/publications/small-sewage-discharges-in-england-the-general-binding-rules>, Guidance for the registration of small sewage effluent discharges Accessed Feb 2023, 2015.
- 71 Scottish Water, Byelaws & Trade Effluent - Trade Effluent - What is Trade Effluent?, last accessed 21/11/2024., <https://www.scottishwater.co.uk/Business-and-Developers/Byelaws-and-Trade-Effluent/Trade-Effluent>, accessed 21 November 2024.
- 72 C. A. Yates, P. J. Johnes and R. G. M. Spencer, Characterisation of treated effluent from four commonly employed wastewater treatment facilities: A UK case study, *J. Environ. Manage.*, 2019, **232**, 919–927.
- 73 D. McKibbin, *The Use of Onsite Wastewater Treatment Systems in Northern Ireland in Providing Research and Information Services to the Northern Ireland Assembly*, 2015, NIAR 585-15, Paper 110/15.
- 74 B. Du, A. E. Price, W. C. Scott, L. A. Kristofco, A. J. Ramirez, C. K. Chambliss, J. C. Yelderman and B. W. Brooks, Comparison of contaminants of emerging concern removal, discharge, and water quality hazards among centralized and on-site wastewater treatment system effluents receiving common wastewater influent, *Sci. Total Environ.*, 2014, **466–467**, 976–984.
- 75 W. J. Brownlie, B. Spears, S. Patidar, M. Linda and S. Roaf, Assessing Pro-environmental Behaviour in Relation to the Management of Pollution from Private Sewage Systems, *Hum. Ecol.*, 2015, **43**, 131–140.
- 76 K. Conaway, S. Lebu, K. Heilferty, A. Salzberg and M. Manga, On-site sanitation system emptying practices and influential factors in Asian low- and middle-income



- countries: A systematic review, *Hyg. Environ. Health Adv.*, 2023, **6**, 100050.
- 77 J. Moonkawin, L. T. Huynh, M. Y. Schneider, S. Fujii, S. Echigo, L. P. H. Nguyen, T.-H. T. Hoang, H. T. Huynh and H. Harada, Challenges to Accurate Estimation of Methane Emission from Septic Tanks with Long Emptying Intervals, *Environ. Sci. Technol.*, 2023, **57**, 16575–16584.
- 78 P. J. A. Withers, L. May, H. P. Jarvie, P. Jordan, D. Doody, R. H. Foy, M. Bechmann, S. Cooksley, R. Dils and N. Deal, Nutrient emissions to water from septic tank systems in rural catchments: Uncertainties and implications for policy, *Environ. Sci. Policy*, 2012, **24**, 71–82.
- 79 M. G. Lusk, G. S. Toor, Y.-Y. Yang, S. Mechtensimer, M. De and T. A. Obreza, A review of the fate and transport of nitrogen, phosphorus, pathogens, and trace organic chemicals in septic systems, *Crit. Rev. Environ. Sci. Technol.*, 2017, **47**, 455–541.
- 80 M. Sharma, A. Yadav, K. K. Dubey, J. Tipple and D. B. Das, Decentralized systems for the treatment of antimicrobial compounds released from hospital aquatic wastes, *Sci. Total Environ.*, 2022, **840**, 156569.
- 81 W. K. Wardhani, E. S. Soedjono, H. S. Titah and M. A. Mardiyanto, Pharmaceutical emerging micropollutants potential in septic tanks: Its fate and transport study in Indonesia – A literature review, *Environ. Qual. Manag.*, 2024, **34**, e22176.
- 82 R. Gyimah, S. Lebu, I. Owusu-Frimpong, S. Semiyaga, A. Salzberg and M. Manga, Effluents from septic systems and impact on groundwater contamination: a systematic review, *Environ. Sci. Pollut. Res.*, 2024, **31**, 62655–62675.
- 83 X. Cheng, X. Jiang, L. Liu and J. Huang, Analysis of Emerging Contaminants in Surface Water, Aquaculture Ponds and Wastewater Treatment Facilities in the Taige Canal Basin, *Chem. Res. Chin. Univ.*, 2023, **39**, 516–524.
- 84 M. Digaletos, C. J. Ptacek, J. Thomas and Y. Liu, Chemical and biological tracers to identify source and transport pathways of septic system contamination to streams in areas with low permeability soils, *Sci. Total Environ.*, 2023, **870**, 161866.
- 85 D. Dubber, L. Brophy, D. O'Connell, P. Behan, M. Danaher, C. Evans, P. Geary, B. Misstear and L. Gill, The use of sterol profiles, supported with other faecal source tracking methods, to apportion septic tanks contamination in rural catchments, *Environ. Pollut.*, 2024, **341**, 122884.
- 86 F. A. Kibuye, H. E. Gall, K. R. Elkin, B. Swistock, T. L. Veith, J. E. Watson and H. A. Elliott, Occurrence, Concentrations, and Risks of Pharmaceutical Compounds in Private Wells in Central Pennsylvania, *J. Environ. Qual.*, 2019, **48**, 1057–1066.
- 87 S. Ramage, D. Camacho-Muñoz and B. Petrie, Enantioselective LC-MS/MS for anthropogenic markers of septic tank discharge, *Chemosphere*, 2019, **219**, 191–201.
- 88 M. Rivadulla, M. Lois, A. X. Elena, S. Balboa, S. Suarez, T. U. Berendonk, J. L. Romalde, J. M. Garrido and F. Omil, Occurrence and fate of CECS (OMPs, ARGs and pathogens) during decentralised treatment of black water and grey water, *Sci. Total Environ.*, 2024, **915**, 169863.
- 89 R. Rossetto, C. Marchina and L. Ercoli, Onsite wastewater treatment systems are a major source of pharmaceutical products in surface water of peri-urban/rural areas, *City Environ. Interac.*, 2024, **21**, 100140.
- 90 S. R. Hinkle, R. J. Weick, J. M. Johnson, J. D. Cahill, S. G. Smith and B. J. Rich, Scientific Investigations Report 2005–5055: Organic Wastewater Compounds, Pharmaceuticals, and Coliphage in Ground Water Receiving Discharge from Onsite Wastewater Treatment Systems near La Pine, Oregon: Occurrence and Implications for Transport, <https://pubs.usgs.gov/sir/2005/5055/>, accessed 22 October 2024.
- 91 H. Rapp-Wright, F. Regan, B. White and L. P. Barron, A year-long study of the occurrence and risk of over 140 contaminants of emerging concern in wastewater influent, effluent and receiving waters in the Republic of Ireland, *Sci. Total Environ.*, 2023, **860**, 160379.
- 92 R Core Team, *R, A Language and Environment for Statistical Computing*, R Foundation for Statistical Computing, 2025.
- 93 Posit team, *RStudio: Integrated Development Environment for R*, Posit Software, PBC, 2025.
- 94 H. Wickham, F. Romain, L. Henry, K. Müller and D. Vaughan, *dplyr: A Grammar of Data Manipulation*, *R Package Version 1.1.3*, 2023.
- 95 P. Schaubberger and A. Walker, *Openxlsx: Read, Write and Edit Xlsx Files*, *R Package, Version 4.2.5.2*, 2023.
- 96 H. Wickham and J. Bryan, *Readxl: Read Excel Files*, *R Package Version 1.4.3*, 2023.
- 97 H. Wickham, M. Averick, J. Bryan, W. Chang, L. D'Agostino McGowan, R. François, G. Grolemond, A. Hayes, L. Henry, J. Hester, M. Kuhn, T. L. Pedersen, E. Miller, S. Milton Bache, K. Müller, J. Ooms, D. Robinson, D. P. Seidel, V. Spinu, K. Takahashi, D. Vaughan, C. Wilke, K. M. Joseph and H. Yutan, Welcome to the tidyverse, *J. Open Source Softw.*, 2019, **4**, 1686.
- 98 A. Kassambara, *Rstatix: Pipe-Friendly Framework for Basic Statistical Tests*, *R Package Version 0.7.2*, 2023.
- 99 H. Wickham, *ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag, New York, 2016.
- 100 T. L. Pedersen, *Patchwork: the Composer of Plots*, *R Package Version 1.1.3*, 2023.
- 101 QGIS Development Team and QGIS\_software, *QGIS Geographic Information System*, Open Source Geospatial Foundation, 2025.
- 102 TechGEO.org, Download World Map Shapefile, GeoJSON and KML Format free - TechGEO Mapping, last accessed 12/05/2025, <https://techgeo.org/download-world-map-shapefile-kml/>, accessed 16 May 2025.
- 103 C. Ávila, M. J. García-Galán, E. Uggetti, N. Montemurro, M. García-Vara, S. Pérez, J. García and C. Postigo, Boosting pharmaceutical removal through aeration in constructed wetlands, *J. Hazard. Mater.*, 2021, **412**, 125231.
- 104 C. Carrara, C. J. Ptacek, W. D. Robertson, D. W. Blowes, M. C. Moncur, E. Sverko and S. Backus, Fate of Pharmaceutical and Trace Organic Compounds in Three



- Septic System Plumes, Ontario, Canada, *Environ. Sci. Technol.*, 2008, **42**, 2805–2811.
- 105 P. M. Clyde, C.-S. Lee, R. E. Price, A. K. Venkatesan and B. J. Brownawell, Occurrence and removal of PPCPs from on-site wastewater using nitrogen removing biofilters, *Water Res.*, 2021, **206**, 117743.
- 106 B. D. Stanford and H. S. Weinberg, Evaluation of On-Site Wastewater Treatment Technology to Remove Estrogens, Nonylphenols, and Estrogenic Activity from Wastewater, *Environ. Sci. Technol.*, 2010, **44**, 2994–3001.
- 107 K. E. Conn, K. S. Lowe, J. E. Drewes, C. Hoppe-Jones and M. B. Tucholke, Occurrence of Pharmaceuticals and Consumer Product Chemicals in Raw Wastewater and Septic Tank Effluent from Single-Family Homes, *Environ. Eng. Sci.*, 2010, **27**, 347–356.
- 108 N. Mladenov, N. G. Dodder, L. Steinberg, W. Richardot, J. Johnson, B. S. Martincigh, C. Buckley, T. Lawrence and E. Hoh, Persistence and removal of trace organic compounds in centralized and decentralized wastewater treatment systems, *Chemosphere*, 2022, **286**, 131621.
- 109 R. Kafaei, F. Papari, M. Seyedabadi, S. Sahebi, R. Tahmasebi, M. Ahmadi, G. A. Sorial, G. Asgari and B. Ramavandi, Occurrence, distribution, and potential sources of antibiotics pollution in the water-sediment of the northern coastline of the Persian Gulf, Iran, *Sci. Total Environ.*, 2018, **627**, 703–712.
- 110 J. Späth, P. Arumugam, R. H. Lindberg, O. A. Abafe, S. Jansson, J. Fick and C. A. Buckley, Biochar for the removal of detected micropollutants in South African domestic wastewater: a case study from a demonstration-scale decentralised wastewater treatment system in eThekweni, *Water SA*, 2021, **47**(4), 396–416.
- 111 K. Wilschnack, B. Homer, E. Cartmell, K. Yates and B. Petrie, Targeted multi-analyte UHPLC-MS/MS methodology for emerging contaminants in septic tank wastewater, sludge and receiving surface water, *Anal. Methods*, 2024, **16**, 709–720.
- 112 J. P. R. De Vargas, M. C. Bastos, M. Al Badany, R. Gonzalez, D. Wolff, D. R. D. Santos and J. Labanowski, Pharmaceutical compound removal efficiency by a small constructed wetland located in south Brazil, *Environ. Sci. Pollut. Res.*, 2021, **28**, 30955–30974.
- 113 Scottish Government, *Directorate: Local Government and Housing Directorate*, 2020.
- 114 H. Auvinen, I. Havran, L. Hubau, L. Vanseveren, W. Gebhardt, V. Linnemann, D. Van Oirschot, G. Du Laing and D. P. L. Rousseau, Removal of pharmaceuticals by a pilot aerated sub-surface flow constructed wetland treating municipal and hospital wastewater, *Ecol. Eng.*, 2017, **100**, 157–164.
- 115 Y.-M. Kang, M.-K. Kim, T. Kim, T.-K. Kim and K.-D. Zoh, Occurrence and Fate of Micropollutants in Private Wastewater Treatment Facility (WTF) and Their Impact on Receiving Water, *Environ. Manage.*, 2019, **64**, 650–660.
- 116 N. Le-Minh, H. M. Coleman, S. J. Khan, Y. van Luer, T. T. T. Trang, G. Watkins and R. M. Stuetz, The application of membrane bioreactors as decentralised systems for removal of endocrine disrupting chemicals and pharmaceuticals, *Water Sci. Technol.*, 2010, **61**, 1081–1088.
- 117 P. J. Phillips, C. Schubert, D. Argue, I. Fisher, E. T. Furlong, W. Foreman, J. Gray and A. Chalmers, Concentrations of hormones, pharmaceuticals and other micropollutants in groundwater affected by septic systems in New England and New York, *Sci. Total Environ.*, 2015, **512–513**, 43–54.
- 118 Z. Tang, Z. Liu, H. Wang, Z. Dang and Y. Liu, Occurrence and removal of 17 $\alpha$ -ethynylestradiol (EE2) in municipal wastewater treatment plants: Current status and challenges, *Chemosphere*, 2021, **271**, 129551.
- 119 J. Teerlink, A. S. Hering, C. P. Higgins and J. E. Drewes, Variability of trace organic chemical concentrations in raw wastewater at three distinct sewershed scales, *Water Res.*, 2012, **46**, 3261–3271.
- 120 K. Wilschnack, E. Cartmell, V. J. Sundström, K. Yates and B. Petrie, Enantiomeric fraction evaluation for assessing septic tanks as a pathway for chiral pharmaceuticals entering rivers, *Environ. Sci.: Processes Impacts*, 2025, **27**, 779–793.
- 121 R. Wu, E. Y. Sin, K. Zhang, S. Xu, Y. Ruan, Y. L. Mak, Y. Yung, S. W. Sun, R. Yang and P. K. S. Lam, Medicating the coast in a metropolitan city: Enantiomeric profiles and joint probabilistic risk assessment of antidepressants and antihistamines, *Environ. Int.*, 2024, **184**, 108434.
- 122 NORMAN Ecotoxicology Database, NORMAN Ecotoxicology Database - Lowest PNECs, last accessed 13/12/2023, <https://www.norman-network.com/nds/ecotox/lowestPnecsIndex.php>.
- 123 Y. Yang, X. Zhang, J. Jiang, J. Han, W. Li, X. Li, K. M. Yee Leung, S. A. Snyder and P. J. J. Alvarez, Which Micropollutants in Water Environments Deserve More Attention Globally?, *Environ. Sci. Technol.*, 2022, **56**, 13–29.
- 124 Y.-Y. Yang, G. S. Toor, P. C. Wilson and C. F. Williams, Micropollutants in groundwater from septic systems: Transformations, transport mechanisms, and human health risk assessment, *Water Res.*, 2017, **123**, 258–267.
- 125 S. Nakagawa, H. Matsuo, M. Motoyama, K. Nomiya and R. Shinohara, Behavior of Endocrine Disrupting Chemicals in Johkasou Improved Septic Tank in Japan, *Bull. Environ. Contam. Toxicol.*, 2009, **83**, 328–333.
- 126 S. Aydın, A. Ulvi, F. Bedük and M. E. Aydın, Pharmaceutical residues in digested sewage sludge: Occurrence, seasonal variation and risk assessment for soil, *Sci. Total Environ.*, 2022, **817**, 152864.
- 127 H. Lin, H. Li, L. Chen, L. Li, L. Yin, H. Lee and Z. Yang, Mass loading and emission of thirty-seven pharmaceuticals in a typical municipal wastewater treatment plant in Hunan Province, Southern China, *Ecotoxicol. Environ. Saf.*, 2018, **147**, 530–536.
- 128 V. Fernández-Fernández, M. Ramil and I. Rodríguez, Basic micro-pollutants in sludge from municipal wastewater treatment plants in the Northwest Spain: Occurrence and risk assessment of sludge disposal, *Chemosphere*, 2023, **335**, 139094.



- 129 C. Mejías, J. Martín, J. L. Santos, I. Aparicio and E. Alonso, Occurrence of pharmaceuticals and their metabolites in sewage sludge and soil: A review on their distribution and environmental risk assessment, *Trends Environ. Anal. Chem.*, 2021, **30**, e00125.
- 130 J. L. Malvar, J. L. Santos, J. Martín, I. Aparicio and E. Alonso, Comparison of ultrasound-assisted extraction, QuEChERS and selective pressurized liquid extraction for the determination of metabolites of parabens and pharmaceuticals in sludge, *Microchem. J.*, 2020, **157**, 104987.
- 131 I. L. Costa Junior, C. S. Machado, A. L. Pletsch and Y. R. Torres, Sorption and desorption behavior of residual antidepressants and caffeine in freshwater sediment and sewage sludge, *Int. J. Sediment Res.*, 2022, **37**, 346–354.
- 132 D. R. Baker and B. Kasprzyk-Hordern, Spatial and temporal occurrence of pharmaceuticals and illicit drugs in the aqueous environment and during wastewater treatment: New developments, *Sci. Total Environ.*, 2013, **454–455**, 442–456.
- 133 B. Subedi and K. Kannan, Occurrence and fate of select psychoactive pharmaceuticals and antihypertensives in two wastewater treatment plants in New York State, USA, *Sci. Total Environ.*, 2015, **514**, 273–280.
- 134 M. Ashfaq, Y. Li, Y. Wang, W. Chen, H. Wang, X. Chen, W. Wu, Z. Huang, C.-P. Yu and Q. Sun, Occurrence, fate, and mass balance of different classes of pharmaceuticals and personal care products in an anaerobic-anoxic-oxic wastewater treatment plant in Xiamen, China, *Water Res.*, 2017, **123**, 655–667.
- 135 F. Polesel, K. Lehnberg, W. Dott, S. Trapp, K. V. Thomas and B. Gy. Plósz, Factors influencing sorption of ciprofloxacin onto activated sludge: Experimental assessment and modelling implications, *Chemosphere*, 2015, **119**, 105–111.
- 136 Y. Xu, X. Yu, B. Xu, D. Peng and X. Guo, Sorption of pharmaceuticals and personal care products on soil and soil components: Influencing factors and mechanisms, *Sci. Total Environ.*, 2021, **753**, 141891.
- 137 C. J. Gobler, S. Waugh, C. Asato, P. M. Clyde, S. C. Nyer, M. Graffam, B. Brownawell, A. K. Venkatesan, J. A. Goleski, R. E. Price, X. Mao, F. M. Russo, G. Heufelder and H. W. Walker, Removing 80%–90% of nitrogen and organic contaminants with three distinct passive, lignocellulose-based on-site septic systems receiving municipal and residential wastewater, *Ecol. Eng.*, 2021, **161**, 106157.
- 138 R. Guedes-Alonso, S. Montesdeoca-Esponda, J. A. Herrera-Melián, R. Rodríguez-Rodríguez, Z. Ojeda-González, V. Landívar-Andrade, Z. Sosa-Ferrera and J. J. Santana-Rodríguez, Pharmaceutical and personal care product residues in a macrophyte pond-constructed wetland treating wastewater from a university campus: Presence, removal and ecological risk assessment, *Sci. Total Environ.*, 2020, **703**, 135596.
- 139 V. Matamoros, C. Arias, H. Brix and J. M. Bayona, Preliminary screening of small-scale domestic wastewater treatment systems for removal of pharmaceutical and personal care products, *Water Res.*, 2009, **43**, 55–62.
- 140 J. D. Wilcox, J. M. Bahr, C. J. Hedman, J. D. C. Hemming, M. A. E. Barman and K. R. Bradbury, Removal of Organic Wastewater Contaminants in Septic Systems Using Advanced Treatment Technologies, *J. Environ. Qual.*, 2009, **38**, 149–156.
- 141 W. Lin, Z. Huang, S. Gao, Z. Luo, W. An, P. Li, S. Ping and Y. Ren, Evaluating the stability of prescription drugs in municipal wastewater and sewers based on wastewater-based epidemiology, *Sci. Total Environ.*, 2021, **754**, 142414.
- 142 M. B. Ahmed, J. L. Zhou, H. H. Ngo, W. Guo, N. S. Thomaidis and J. Xu, Progress in the biological and chemical treatment technologies for emerging contaminant removal from wastewater: A critical review, *J. Hazard. Mater.*, 2017, **323**, 274–298.
- 143 P. Falås, A. Wick, S. Castronovo, J. Habermacher, T. A. Ternes and A. Joss, Tracing the limits of organic micropollutant removal in biological wastewater treatment, *Water Res.*, 2016, **95**, 240–249.
- 144 M. Arenas, J. Martín, J. L. Santos, I. Aparicio and E. Alonso, Enantioselective behavior of environmental chiral pollutants: A comprehensive review, *Crit. Rev. Environ. Sci. Technol.*, 2022, **52**, 2995–3034.
- 145 S. L. MacLeod, P. Sudhir and C. S. Wong, Stereoisomer analysis of wastewater-derived  $\beta$ -blockers, selective serotonin re-uptake inhibitors, and salbutamol by high-performance liquid chromatography–tandem mass spectrometry, *J. Chromatogr. A*, 2007, **1170**, 23–33.
- 146 R. A. Brewton, L. B. Kreiger, K. N. Tyre, D. Baladi, L. E. Wilking, L. W. Herren and B. E. Lapointe, Septic system–groundwater–surface water couplings in waterfront communities contribute to harmful algal blooms in Southwest Florida, *Sci. Total Environ.*, 2022, **837**, 155319.
- 147 Y. Liu, M. Digaletos, C. J. Ptacek and J. L. Thomas, Active and passive sampling techniques in headwater streams to characterize acesulfame-K, pharmaceutical and phosphorus contamination from on-site wastewater disposal systems in Canadian rural hamlets, *Sci. Total Environ.*, 2024, **956**, 177194.
- 148 C. H. Swartz, S. Reddy, M. J. Benotti, H. Yin, L. B. Barber, B. J. Brownawell and R. A. Rudel, Steroid Estrogens, Nonylphenol Ethoxylate Metabolites, and Other Wastewater Contaminants in Groundwater Affected by a Residential Septic System on Cape Cod, MA, *Environ. Sci. Technol.*, 2006, **40**, 4894–4902.
- 149 E. Godfrey, W. W. Woessner and M. J. Benotti, Pharmaceuticals in On-Site Sewage Effluent and Ground Water, Western Montana, *Groundwater*, 2007, **45**, 263–271.
- 150 K. L. Del Rosario, S. Mitra, C. P. Humphrey and M. A. O'Driscoll, Detection of pharmaceuticals and other personal care products in groundwater beneath and adjacent to onsite wastewater treatment systems in a coastal plain shallow aquifer, *Sci. Total Environ.*, 2014, **487**, 216–223.



- 151 B. G. Katz, D. W. Griffin, P. B. McMahon, H. S. Harden, E. Wade, R. W. Hicks and J. P. Chanton, Fate of Effluent-Borne Contaminants beneath Septic Tank Drainfields Overlying a Karst Aquifer, *J. Environ. Qual.*, 2010, **39**, 1181–1195.
- 152 S. M. Elliott, M. L. Erickson, A. L. Krall and B. A. Adams, Concentrations of pharmaceuticals and other micropollutants in groundwater downgradient from large on-site wastewater discharges, *PLoS One*, 2018, **13**, e0206004.
- 153 Y.-Y. Yang, G. S. Toor, P. C. Wilson and C. F. Williams, Septic systems as hot-spots of pollutants in the environment: Fate and mass balance of micropollutants in septic drainfields, *Sci. Total Environ.*, 2016, **566–567**, 1535–1544.
- 154 L. J. Standley, R. A. Rudel, C. H. Swartz, K. R. Atfield, J. Christian, M. Erickson and J. G. Brody, Wastewater-contaminated groundwater as a source of endogenous hormones and pharmaceuticals to surface water ecosystems, *Environ. Toxicol. Chem.*, 2008, **27**, 2457–2468.
- 155 I. J. Fisher, P. J. Phillips, K. M. Colella, S. C. Fisher, T. Tagliaferri, W. T. Foreman and E. T. Furlong, The impact of onsite wastewater disposal systems on groundwater in areas inundated by Hurricane Sandy in New York and New Jersey, *Mar. Pollut. Bull.*, 2016, **107**, 509–517.
- 156 B. G. Katz and D. W. Griffin, Using chemical and microbiological indicators to track the impacts from the land application of treated municipal wastewater and other sources on groundwater quality in a karstic springs basin, *Environ. Geol.*, 2008, **55**, 801–821.
- 157 L. A. Schaidler, J. M. Ackerman and R. A. Rudel, Septic systems as sources of organic wastewater compounds in domestic drinking water wells in a shallow sand and gravel aquifer, *Sci. Total Environ.*, 2016, **547**, 470–481.
- 158 B. Subedi, N. Codru, D. M. Dziewulski, L. R. Wilson, J. Xue, S. Yun, E. Braun-Howland, C. Minihane and K. Kannan, A pilot study on the assessment of trace organic contaminants including pharmaceuticals and personal care products from on-site wastewater treatment systems along Skaneateles Lake in New York State, USA, *Water Res.*, 2015, **72**, 28–39.
- 159 D. J. Fairbairn, M. E. Karpuzcu, W. A. Arnold, B. L. Barber, E. F. Kaufenberg, W. C. Koskinen, P. J. Novak, P. J. Rice and D. L. Swackhamer, Sources and transport of contaminants of emerging concern: A two-year study of occurrence and spatiotemporal variation in a mixed land use watershed, *Sci. Total Environ.*, 2016, **551–552**, 605–613.
- 160 W. C. Scott, C. S. Breed, S. P. Haddad, S. R. Burket, G. N. Saari, P. J. Pearce, C. K. Chambliss and B. W. Brooks, Spatial and temporal influence of onsite wastewater treatment systems, centralized effluent discharge, and tides on aquatic hazards of nutrients, indicator bacteria, and pharmaceuticals in a coastal bayou, *Sci. Total Environ.*, 2019, **650**, 354–364.
- 161 C. Wu, J. D. Witter, A. L. Sponberg and K. P. Czajkowski, Occurrence of selected pharmaceuticals in an agricultural landscape, western Lake Erie basin, *Water Res.*, 2009, **43**, 3407–3416.
- 162 S. Hanamoto, N. Nakada, N. Yamashita and H. Tanaka, Source estimation of pharmaceuticals based on catchment population and in-stream attenuation in Yodo River watershed, Japan, *Sci. Total Environ.*, 2018, **615**, 964–971.
- 163 F. Comeau, C. Surette, G. L. Brun and R. Losier, The occurrence of acidic drugs and caffeine in sewage effluents and receiving waters from three coastal watersheds in Atlantic Canada, *Sci. Total Environ.*, 2008, **396**, 132–146.
- 164 C. A. James, J. P. Miller-Schulze, S. Ultican, A. D. Gipe and J. E. Baker, Evaluating Contaminants of Emerging Concern as tracers of wastewater from septic systems, *Water Res.*, 2016, **101**, 241–251.
- 165 K. Schenck, L. Rosenblum, B. Ramakrishnan, J. Carson, D. Macke and C. Nietch, Correlation of trace contaminants to wastewater management practices in small watersheds, *Environ. Sci.: Processes Impacts*, 2015, **17**, 956–964.
- 166 A. T. Kullberg, G. L. Carlson, S. M. Haver and W. G. McDowell, Contamination of Maine lakes by pharmaceuticals and personal care products, *J. Environ. Stud. Sci.*, 2022, **12**, 248–259.
- 167 K. Troxell, B. Ng, I. Zamora-Ley and P. Gardinali, Detecting Water Constituents Unique to Septic Tanks as a Wastewater Source in the Environment by Nontarget Analysis: South Florida's Deering Estate Rehydration Project Case Study, *Environ. Toxicol. Chem.*, 2022, **41**, 1165–1178.
- 168 R. L. Seiler, S. D. Zaugg, J. M. Thomas and D. L. Howcroft, Caffeine and Pharmaceuticals as Indicators of Waste Water Contamination in Wells, *Groundwater*, 1999, **37**, 405–410.
- 169 M. Silver, W. Phelps, K. Masarik, K. Burke, C. Zhang, A. Schwartz, M. Wang, A. L. Nitka, J. Schutz, T. Trainor, J. W. Washington and B. D. Rheineck, Prevalence and Source Tracing of PFAS in Shallow Groundwater Used for Drinking Water in Wisconsin, USA, *Environ. Sci. Technol.*, 2023, **57**, 17415–17426.
- 170 O. Kiguchi, G. Sato and T. Kobayashi, Source-specific sewage pollution detection in urban river waters using pharmaceuticals and personal care products as molecular indicators, *Environ. Sci. Pollut. Res.*, 2016, **23**, 22513–22529.
- 171 C. Ort, M. G. Lawrence, J. Reungoat and J. F. Mueller, Sampling for PPCPs in Wastewater Systems: Comparison of Different Sampling Modes and Optimization Strategies, *Environ. Sci. Technol.*, 2010, **44**, 6289–6296.
- 172 S. Luostarinen, W. Sanders, K. Kujawa-Roeleveld and G. Zeeman, Effect of temperature on anaerobic treatment of black water in UASB-septic tank systems, *Bioresour. Technol.*, 2007, **98**, 980–986.
- 173 S. Suárez, R. Reif, J. M. Lema and F. Omil, Mass balance of pharmaceutical and personal care products in a pilot-scale single-sludge system: Influence of *T*, SRT and recirculation ratio, *Chemosphere*, 2012, **89**, 164–171.
- 174 J. Li, J. Gao, Q. Zheng, P. K. Thai, H. Duan, J. F. Mueller, Z. Yuan and G. Jiang, Effects of pH, Temperature,



- Suspended Solids, and Biological Activity on Transformation of Illicit Drug and Pharmaceutical Biomarkers in Sewers, *Environ. Sci. Technol.*, 2021, **55**, 8771–8782.
- 175 L. Mutzner, E. L. M. Vermeirssen and C. Ort, Passive samplers in sewers and rivers with highly fluctuating micropollutant concentrations – Better than we thought, *J. Hazard. Mater.*, 2019, **361**, 312–320.
- 176 Y. Meng, W. Liu, X. Liu, J. Zhang, M. Peng and T. Zhang, A review on analytical methods for pharmaceutical and personal care products and their transformation products, *J. Environ. Sci.*, 2021, **101**, 260–281.
- 177 D. Cacace, D. Fatta-Kassinos, C. M. Manaia, E. Cytryn, N. Kreuzinger, L. Rizzo, P. Karaolia, T. Schwartz, J. Alexander, C. Merlin, H. Garelick, H. Schmitt, D. de Vries, C. U. Schwermer, S. Meric, C. B. Ozkal, M.-N. Pons, D. Kneis and T. U. Berendonk, Antibiotic resistance genes in treated wastewater and in the receiving water bodies: A pan-European survey of urban settings, *Water Res.*, 2019, **162**, 320–330.
- 178 J. L. Hayward, Y. Huang, L. T. Hansen, C. K. Yost, C. Lake and R. C. Jamieson, Fate and distribution of determinants of antimicrobial resistance in lateral flow sand filters used for treatment of domestic wastewater, *Sci. Total Environ.*, 2021, **767**, 145481.
- 179 A. M. S. Mortensen, S. J. Poulsen, M. á F. Berbisá and A. Djurhuus, Distribution of antibiotic resistant bacteria and genes in sewage and surrounding environment of Tórshavn, Faroe Islands, *Front. Env. Sci.*, 2024, **12**, 1–13.
- 180 J. S. Cedeño-Muñoz, S. A. Aransiola, K. V. Reddy, P. Ranjit, M. O. Victor-Ekwebelem, O. J. Oyedele, I. B. Pérez-Almeida, N. R. Maddela and J. M. Rodríguez-Díaz, Antibiotic resistant bacteria and antibiotic resistance genes as contaminants of emerging concern: Occurrences, impacts, mitigations and future guidelines, *Sci. Total Environ.*, 2024, **952**, 175906.
- 181 J. C. Chee-Sanford, R. I. Mackie, S. Koike, I. G. Krapac, Y.-F. Lin, A. C. Yannarell, S. Maxwell and R. I. Aminov, Fate and Transport of Antibiotic Residues and Antibiotic Resistance Genes following Land Application of Manure Waste, *J. Environ. Qual.*, 2009, **38**, 1086–1108.
- 182 Y. He, Q. Yuan, J. Mathieu, L. Stadler, N. Senéhi, R. Sun and P. J. J. Alvarez, Antibiotic resistance genes from livestock waste: occurrence, dissemination, and treatment, *npj Clean Water*, 2020, **3**, 1–11.
- 183 X.-X. Zhang, T. Zhang and H. H. P. Fang, Antibiotic resistance genes in water environment, *Appl. Microbiol. Biotechnol.*, 2009, **82**, 397–414.
- 184 D. G. J. Larsson and C.-F. Flach, Antibiotic resistance in the environment, *Nat. Rev. Microbiol.*, 2022, **20**, 257–269.
- 185 J. Damashek, J. R. Westrich, J. M. B. McDonald, M. E. Teachey, C. R. Jackson, J. G. Frye, E. K. Lipp, K. A. Capps and E. A. Ottesen, Non-point source fecal contamination from aging wastewater infrastructure is a primary driver of antibiotic resistance in surface waters, *Water Res.*, 2022, **222**, 118853.
- 186 H. Su, W. Li, S. Okumura, Y. Wei, Z. Deng and F. Li, Transfer, elimination and accumulation of antibiotic resistance genes in decentralized household wastewater treatment facility treating total wastewater from residential complex, *Sci. Total Environ.*, 2024, **912**, 169144.
- 187 G. E. Ramos, H. Pak, R. Gerlich, A. Jantrania, B. L. Smith and M. D. King, Aerosol partitioning potential of bacteria presenting antimicrobial resistance from different stages of a small decentralized septic treatment system, *Aerosol Sci. Tech.*, 2023, **57**, 517–531.
- 188 T. R. Burch, J. P. Stokdyk, A. D. Firnstahl, B. A. Kieke Jr., R. M. Cook, S. A. Opelt, S. K. Spencer, L. M. Durso and M. A. Borchardt, Microbial source tracking and land use associations for antibiotic resistance genes in private wells influenced by human and livestock fecal sources, *J. Environ. Qual.*, 2023, **52**, 270–286.
- 189 J. L. Hayward, Y. Huang, C. K. Yost, L. T. Hansen, C. Lake, A. Tong and R. C. Jamieson, Lateral flow sand filters are effective for removal of antibiotic resistance genes from domestic wastewater, *Water Res.*, 2019, **162**, 482–491.
- 190 L. Tan, C. Zhang, F. Liu, P. Chen, X. Wei, H. Li, G. Yi, Y. Xu and X. Zheng, Three-compartment septic tanks as sustainable on-site treatment facilities? Watch out for the potential dissemination of human-associated pathogens and antibiotic resistance, *J. Environ. Manage.*, 2021, **300**, 113709.
- 191 A. S. Sidhu, F. N. Mikolajczyk and J. C. Fisher, Antimicrobial Resistance Linked to Septic System Contamination in the Indiana Lake Michigan Watershed, *Antibiotics*, 2023, **12**, 569.
- 192 D. Parde, A. Patwa, A. Shukla, R. Vijay, D. J. Killedar and R. Kumar, A review of constructed wetland on type, treatment and technology of wastewater, *Environ. Technol. Innov.*, 2021, **21**, 101261.
- 193 A. Akyürek and O. N. Ağdağ, Comparison of constructed wetlands and package type sequencing batch biological treatment plants in rural areas in terms of efficiency and cost in a full-scale example, *Ecol. Eng.*, 2024, **201**, 107190.
- 194 A. B. A. Boxall, M. A. Rudd, B. W. Brooks, D. J. Caldwell, K. Choi, S. Hickmann, E. Innes, K. Ostapyyk, J. P. Staveley, T. Verslycke, G. T. Ankley, K. F. Beazley, S. E. Belanger, J. P. Berninger, P. Carriquiriborde, A. Coors, P. C. DeLeo, S. D. Dyer, J. F. Ericson, F. Gagné, J. P. Giesy, T. Guoin, L. Hallstrom, M. V. Karlsson, D. G. J. Larsson, J. M. Lazorchak, F. Mastrocco, A. McLaughlin, M. E. McMaster, R. D. Meyerhoff, R. Moore, J. L. Parrott, J. R. Snape, R. Murray-Smith, M. R. Servos, P. K. Sibley, J. O. Straub, N. D. Szabo, E. Topp, G. R. Tetreault, V. L. Trudeau and G. Van Der Kraak, Pharmaceuticals and Personal Care Products in the Environment: What Are the Big Questions?, *Environ. Health Perspect.*, 2012, **120**, 1221–1229.
- 195 C. G. Daughton, Eco-directed sustainable prescribing: feasibility for reducing water contamination by drugs, *Sci. Total Environ.*, 2014, **493**, 392–404.
- 196 C. G. Daughton and I. S. Ruhoy, Lower-dose prescribing: Minimizing “side effects” of pharmaceuticals on society



- and the environment, *Sci. Total Environ.*, 2013, **443**, 324–337.
- 197 K. Helwig, L. Niemi, J.-Y. Stenuick, J. C. Alexandre, S. Pflieger, J. Roberts, J. Harrower, I. Nafu and O. Pahl, Broadening the Perspective on Reducing Pharmaceutical Residues in the Environment, *Environ. Toxicol. Chem.*, 2024, **43**, 653–663.
- 198 K. Thornber, M. Bentham, S. Pflieger, C. Kirchhelle, F. Adshead, S. Owen, H. Holmes, R. Brown, C. Farmer, M. Eii, L. Niemi, L. Wohler, E. Wilson, M. Wade, W. Tyler-Batt, M. Taylor, G. Sowman, P. Southall, R. Smith and C. Tyler, Pharmaceutical pollution from health care: a systems-based strategy for mitigating risks to public and environmental health, *Lancet Planet. Health*, 2026, **10**(1), 101404.
- 199 A. Cussans, G. Harvey, T. Kemple and M. Tomson, Interventions to reduce the environmental impact of medicines: A UK perspective, *J. Climate Change Health*, 2021, **4**, 100079.
- 200 E. Salehi, C. Ljungberg Persson and H. Håkonsen, Green pharmacy practice – a multi method study of environmental sustainability measures implemented in Swedish pharmacies, *J. Pharm. Policy Pract.*, 2025, **18**, 2512983.
- 201 B. Petrie, J. Youdan, R. Barden and B. Kasprzyk-Hordern, New Framework To Diagnose the Direct Disposal of Prescribed Drugs in Wastewater – A Case Study of the Antidepressant Fluoxetine, *Environ. Sci. Technol.*, 2016, **50**, 3781–3789.
- 202 A. Aharaz, J. H. Rasmussen, H. B. Ø. McNulty, A. Cyron, P. K. Fabricius, A. K. Bengaard, H. R. C. Sejberg, R. R. L. Simonsen, C. Trelldal and M. B. Houllind, A Collaborative Deprescribing Intervention in a Subacute Medical Outpatient Clinic: A Pilot Randomized Controlled Trial, *Metabolites*, 2021, **11**, 204.
- 203 C. Weeks and T. Thomas, Sustainable Prescribing in Secure Services – a Quality Improvement Initiative, *BJPsych Open*, 2022, **8**, S116.
- 204 J. Wang, M. Zhang, J. Liu, X. Hu and B. He, Using a targeted ecopharmacovigilance intervention to control antibiotic pollution in a rural aquatic environment, *Sci. Total Environ.*, 2019, **696**, 134007.
- 205 L. Niemi, C. Anderson, N. Arakawa, M. Taggart, S. Gibb and S. Pflieger, Do you think medicines can be prescribed in a more eco-directed, greener way? A qualitative study based on public and prescriber focus groups on the impact of pharmaceuticals in Scotland's water environment, *BMJ Open*, 2025, **15**, e088066.
- 206 W. Hall, J. Prichard, P. Kirkbride, R. Bruno, P. K. Thai, C. Gartner, F. Y. Lai, C. Ort and J. F. Mueller, An analysis of ethical issues in using wastewater analysis to monitor illicit drug use, *Addiction*, 2012, **107**, 1767–1773.
- 207 S. E. Hrudehy, D. S. Silva, J. Shelley, W. Pons, J. Isaac-Renton, A. H.-S. Chik and B. Conant, Ethics Guidance for Environmental Scientists Engaged in Surveillance of Wastewater for SARS-CoV-2, *Environ. Sci. Technol.*, 2021, **55**, 8484–8491.
- 208 D. Jacobs, T. McDaniel, A. Varsani, R. U. Halden, S. Forrest and H. Lee, Wastewater Monitoring Raises Privacy and Ethical Considerations, *IEEE-TTS*, 2021, **2**, 116–121.
- 209 C. Klingler, D. S. Silva, C. Schuermann, A. A. Reis, A. Saxena and D. Strech, Ethical issues in public health surveillance: a systematic qualitative review, *BMC Public Health*, 2017, **17**, 295.
- 210 R. Kwiatkowska, A. Ruhaak, B. Kasprzyk-Hordern, F. Hassard, L. Lundy, M. D. Cesare, M. Hickman and A. Singer, Wastewater-based epidemiology and group privacy: the elephant in the sewer?, Pre-print of a viewpoint submitted to, *Environ. Sci. Technol.*, 2021.
- 211 M. M. Coffman, J. S. Guest, M. K. Wolfe, C. C. Naughton, A. B. Boehm, J. D. Vela and J. S. Carrera, Preventing Scientific and Ethical Misuse of Wastewater Surveillance Data, *Environ. Sci. Technol.*, 2021, **55**, 11473–11475.
- 212 J. R. Kelly, M. Cosgrove, C. Judd, K. Scott, A. M. Loughlin and V. O'Keane, Mood matters: a national survey on attitudes to depression, *Ir. J. Med. Sci.*, 2019, **188**, 1317–1327.
- 213 L. R. Martinez, S. Xu and M. Hebl, Utilizing Education and Perspective Taking to Remediate the Stigma of Taking Antidepressants, *Community Ment. Health. J.*, 2018, **54**, 450–459.
- 214 K. M. Blum, C. Gallampos, P. L. Andersson, G. Renman, A. Renman and P. Haglund, Comprehensive assessment of organic contaminant removal from on-site sewage treatment facility effluent by char-fortified filter beds, *J. Hazard. Mater.*, 2019, **361**, 111–122.
- 215 R. A. Trenholm, B. J. Vanderford and S. A. Snyder, On-line solid phase extraction LC-MS/MS analysis of pharmaceutical indicators in water: A green alternative to conventional methods, *Talanta*, 2009, **79**, 1425–1432.
- 216 B. Petrie and B. Kasprzyk-Hordern, Monitoring emerging contaminants in wastewaters and the environment: The catchment approach, *15th EuCheMS International Conference on Chemistry and the Environment*, 2015.
- 217 S. Ebrahimzadeh, S. Castiglioni, F. Riva, E. Zuccato and A. Azzellino, Carbamazepine Levels Related to the Demographic Indicators in Groundwater of Densely Populated Area, *Water*, 2021, **13**, 2539.
- 218 Q. T. T. Do, M. Otaki, Y. Otaki, C. Tushara and I. W. Sanjeewa, Pharmaceutical Contaminants in Shallow Groundwater and Their Implication for Poor Sanitation Facilities in Low-Income Countries, *Environ. Toxicol. Chem.*, 2022, **41**, 266–274.
- 219 I. m. Verstraeten, G. s. Fetterman, M. t. Meyer, T. Bullen and S. k. Sebree, Use of tracers and isotopes to evaluate vulnerability of water in domestic wells to septic waste, *Groundwater Monit. Rem.*, 2005, **25**, 107–117.
- 220 G. M. Ferrell and B. H. Grimes, Effects of Centralized and Onsite Wastewater Treatment on the Occurrence of Traditional and Emerging Contaminants in Streams, *J. Environ. Health*, 2014, **76**, 18–27.
- 221 S. Spengler and M. Heskett, Impact to Stream Water Quality from Sewage Exfiltration and Legacy On-Site Disposal



Systems on the Island of O'ahu, Hawaii | IIETA, *Int. J. Environ. Impact*, 2023, **6**, 13–23.

222 E. Hain, K. He, J. A. Batista-Andrade, A. Feerick, M. Tarnowski, A. Timm and L. Blaney, Geospatial and co-occurrence analysis of antibiotics, hormones, and UV

filters in the Chesapeake Bay (USA) to confirm inputs from wastewater treatment plants, septic systems, and animal feeding operations, *J. Hazard. Mater.*, 2023, **460**, 132405.

