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## Hazard/Risk Assessment

## Pharmaceutical Pollution of the English National Parks

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**Abstract:** England's 10 national parks are renowned for their landscapes, wildlife, and recreational value. However, surface waters in the national parks may be vulnerable to pollution from human-use chemicals, such as active pharmaceutical ingredients (APIs), because of factors like ineffective wastewater treatment, seasonal tourism, a high proportion of elderly residents, and the presence of low-flow water bodies that limit dilution. The present study determined the extent of API contamination in the English national parks by monitoring 54 APIs in 37 rivers across all national parks over two seasons. Results were compared to existing data sets for UK cities and to concentration thresholds for ecological impacts and antimicrobial resistance selection. Results revealed widespread contamination of the national parks, with APIs detected at 52 out of 54 sites and in both seasons. Thirty-one APIs were detected, with metformin, caffeine, and paracetamol showing the highest mean concentrations and cetirizine, metformin, and fexofenadine being the most frequently detected. While total API concentrations were generally lower than seen previously in UK cities, locations in the Peak District and Exmoor had higher concentrations than most city rivers. Fourteen locations had concentrations of either amitriptyline, carbamazepine, clarithromycin, diltiazem, metformin, paracetamol, or propranolol above levels of concern for fish, invertebrates, and algae or for selection for antimicrobial resistance. Therefore, API pollution of the English national parks appears to pose risks to ecological health and potentially human health through recreational water use. Given that these parks are biodiversity hotspots with protected ecosystems, there is an urgent need for improved monitoring and management of pharmaceutical pollution and pollution more generally not only in national parks in England but also in similar environments across the world. *Environ Toxicol Chem* 2024;00:1–14. © 2024 The Author(s). *Environmental Toxicology and Chemistry* published by Wiley Periodicals LLC on behalf of SETAC.

**Keywords:** Active pharmaceutical ingredients; Antimicrobial resistance; Monitoring; Risk assessment

## INTRODUCTION

Ten national parks are designated in England for their landscape quality, wildlife, and value as a recreational resource. These special areas cover 9.3% of the land area in England and

provide an important wildlife habitat. Over 23% of land in national parks in England is designated as Sites of Special Scientific Interest (a formal conservation designation in England which describes an area that is of particular interest to science because of the presence of rare species of fauna or flora or geological or physiological features). Over 333,000 hectares of the national parks are recognized and protected as being of international conservation importance (National Parks UK, 2024). With a human population of approximately 320,000 permanent residents (Office for National Statistics, 2023), these areas provide a focus for recreation and tourism for 90 million visitors each year (Defra, 2016). The environmental quality of the English

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national parks could, however, be under threat from chemical pollution by substances like pharmaceuticals that arise from use in humans and other animals.

Approximately 2000 active pharmaceutical ingredients (APIs) are used to prevent and treat illness in humans (Burns, Carter, Snape, et al., 2018). These substances can be released to the natural environment during the manufacturing and formulation of APIs and products, following the use of a drug, or by improper disposal of unused medicines (Boxall, 2004). Some APIs may also be emitted to the environment from their use in veterinary medicine (Boxall et al., 2004). Consequently, a wide range of APIs, including substances used as antidepressants, anticonvulsants, antimicrobials, anti-inflammatory substances, lipid regulators, and diabetes treatments, has been detected in surface waters across the world, with concentrations typically in the nanogram per liter to microgram per liter concentration ranges (Aus der Beek et al., 2016; Wilkinson et al., 2022).

Because patient usage is the major source of human-use APIs in the environment, previous monitoring efforts for APIs have tended to focus on urban settings and river systems receiving wastewater inputs from populous areas (Hughes et al., 2013). Monitoring studies performed for APIs in Europe and North America have also typically been performed in areas with a high degree of connectivity of the human population to wastewater systems, with the monitoring performed around wastewater-discharge points. A range of exposure modeling exercises has characterized exposure more broadly across catchments, regions, and countries (see Johnson et al., 2013; Oldenkamp et al., 2018), but these exercises typically consider the influences of larger wastewater-treatment works, with population equivalents of 2000 or more, on surface water quality. Overall, with the exception of a handful of studies, for example, on veterinary inputs into surface waters and on select national parks, national protection areas, and national preserves in the United States (Battaglin, et al., 2018; Bradley et al., 2020, 2021), the occurrence and risks of human-use APIs in less populated settings, such as the English national parks, have received much less attention.

While the English national parks have lower population densities than urban environments, it is possible that levels of environmental exposure to APIs in these areas could still be significant. The English national parks are rural landscapes with lower connectivity to centralized wastewater-treatment systems than urban areas. The English national parks have a total of 835 water company outlets and 2517 non-water company outlets, while in England as a whole there are 27,115 water company outlets and 31,872 non-water company outlets (Rivers Trust, 2023). Hence, English national parks have a higher proportion of septic tanks, soakaway systems, and small-scale private treatment plants than more urbanized areas. Septic tanks have been shown to be an important contributor to environmental contamination by organic compounds such as APIs (see Phillips et al., 2015; Schaidler et al., 2016). Where wastewater-treatment systems do exist, these will often be small in size and employ a lower degree of treatment than larger urban systems, so the level of removal of some APIs may be lower than in larger systems. In the United Kingdom, unlike

their larger counterparts, treatment plants with a capacity of <2000 population equivalents are not legally required to employ secondary treatment technologies or advanced treatment methods, and there are no legal requirements for monitoring these systems (Environment Agency, 2019). Many of the surface waters in the national parks are located in the upper reaches of catchments, meaning that emissions from human populations are discharged into smaller and lower-flow river systems, so there is limited dilution. The influx of tourists to the English national parks in the summer months will increase the burden on typically small wastewater-treatment works, designed to treat a lower population equivalent. The English national parks are also characterized by an older population, with the median age in every national park (ranging from 49 years in the South Downs to 57 years in the Broads) being greater than in England as a whole (39 years; Office for National Statistics, 2023). Because the diversity and amounts of prescribed medicines used increase with age (National Health Service, 2017), it might therefore be expected that national parks will have higher emission rates of APIs, per capita of population, compared to other areas of England.

The presence of APIs in surface waters in the English national parks could pose a threat to the health of rivers and the human population. Active pharmaceuticals are designed to be biologically active and target biochemical pathways and receptors in humans (Gunnarsson et al., 2008). Because many of the same pathways and receptors are present in other groups of organisms, including fish, invertebrates, algae, and microbes, the occurrence of APIs in the environment can lead to unintended ecological consequences (Gunnarsson et al., 2019). A range of negative ecotoxicological effects of APIs has been reported on aquatic organisms including effects on reproduction and growth, organism behavior, histology, and biochemical endpoints (see Boxall, 2004). Comparison of measured concentrations in surface waters with ecotoxicity data for APIs suggests that the occurrence of these compounds at many of the more urban locations that have been monitored poses a threat to ecological health (Bouzas-Monroy et al., 2022). Due to a lack of occurrence data for APIs in the English national parks, we have no grasp of the level of ecological risk that these substances pose in these systems even though the English national parks are critically important for the conservation and enhancement of wildlife, and hence could be particularly vulnerable to any impacts of chemical pollution.

The presence of antimicrobial APIs in the freshwaters is also of concern because these substances may also negatively affect human health through the selection of antimicrobial resistance in microorganisms. In more populated areas, antibiotics are above levels thought to select for antimicrobial resistance in microbes in some locations (Boxall et al., 2022) and may be contributing to the global antimicrobial resistance crisis estimated to be killing more than one million people a year (Murray et al., 2022). The lack of monitoring data for antimicrobial antibiotics in the English national parks means that we do not know whether a selection pressure exists in these areas. If it does, the closer connectivity of humans to the environment through recreational activities, such as swimming,

could result in a greater human exposure than in more urban environments and therefore a greater threat to human health.

If we are to continue to gain the maximum ecological, social, mental, and physical health benefits from the English national parks and to preserve biodiversity, it is critical that we begin to understand the threats of pollution from APIs and other chemicals in these systems and, where appropriate, to manage these threats. We describe a study to characterize the levels of API pollution in 37 rivers across England's national parks. We use the results to answer the following questions: What are the scale and nature of pharmaceutical pollution in the English national parks? How do pollution levels compare to urban environments in the United Kingdom? And could these molecules be impacting ecological and human health in our national parks? We hope that the findings of the study will provide the foundations for further work to understand the broader occurrence and potential ecological and health risks of chemical pollutants in not only national parks in the United Kingdom but also similar environments around the world and, where needed, to help identify approaches to mitigate the impacts of chemical pollution on these special places.

## METHODS

### *Study pharmaceuticals and other chemicals*

Our study explored the occurrence of 54 APIs drawn from the anesthetic (one API), analgesic (one API), antacid (one API), antibiotic (13 APIs), anticonvulsant (three APIs), antidepressant (seven APIs), antihyperglycemic (two APIs), antifungal (one API), antihistamine (four APIs), anti-inflammatory (two APIs), benzodiazepine (three APIs), bronchodilator (one API), Ca<sup>2+</sup> channel blocker (three APIs), estrogen (two APIs), H<sub>2</sub>-receptor agonist (one API), opioid (two APIs), progestin (one API), stimulant (two APIs), and  $\beta$ -blocker (three APIs) classes and one metabolite (see Supporting Information, S12 for a full list). These compounds were selected based on concerns around their potential environmental impacts and the results of our previous monitoring work (Wilkinson et al., 2022). All test chemical standards were purchased from Sigma-Aldrich and were of  $\geq 95\%$  purity. Deuterated internal standards were obtained from Sigma-Aldrich for 17 test APIs, and atrazine-D5 was used where a labeled standard was not available. Liquid chromatography–mass spectrometry (LC-MS)–grade water, acetonitrile and methanol were obtained from VWR.

### *Site selection*

The Rivers Trust Sewage Map (Rivers Trust, 2023) was used to characterize the number of sewage inputs from wastewater-treatment plants (WWTPs), storm overflows, and unconnected systems (i.e., inputs not connected to the sewer network such as septic tanks) across the English national parks. This included inputs outside the boundary of each park where sewage was discharged into a river that subsequently flowed into a park. The results were used to select monitoring sites that included sites upstream and downstream of wastewater inputs, locations

which were readily and safely accessible and which covered a range of water bodies within each park. Forty-nine locations were selected for sampling in winter 2022, with five additional locations added in summer 2022 (one on the Tavy on Dartmoor, two at Coniston in the Lake District, and two at Tideswell in the Peak District). The number of locations selected per park ranged from three (New Forest, Northumberland, and the Broads) to 11 (North York Moors; Table 1 and Figure 1). The sampling sites included rivers, streams, and becks. At one location in the North York Moors and one in Exmoor, there was evidence of wastewater being discharged through a pipe, so an additional sample was obtained from these sites at the point of discharge. Full details of the sampling locations are provided in Supporting Information, S11.

### *Sampling*

Samples were collected in duplicate from each sampling location in the winter and summer of 2022. Winter samples were taken between February 14 and March 1 and summer samples between August 1 and 18. Samples were typically taken from bridges from the center of the water body or in-stream (Supporting Information, S11). Where this was not possible, samples were taken from the riverbank. Water samples were taken using a metal bucket, and a 3-mL sample was then filtered into a glass vial using the rinsing and priming procedures described in Wilkinson et al. (2022). The collected samples were frozen before being transported on ice to the University of York (York, UK) for chemical analysis. Duplicate field blanks were also generated in the summer during the Peak District and Yorkshire Dales sampling campaigns by pouring high-performance liquid chromatography (HPLC)–grade water into the bucket and processing these in the same way as the river water samples. No APIs were detected in these field blanks. Where samplers had access to meters for measuring general water quality parameters (e.g., pH, water temperature, electrical conductivity, and total dissolved solids), these were also measured (Supporting Information, S18).

### *Chemical analysis*

The analytical method was adapted from a previously developed method for pharmaceutical compounds (Wilkinson et al., 2019). Analysis was by direct-injection (100- $\mu$ L injection volume) HPLC–MS/MS in multiple reaction monitoring mode with positive electrospray ionization using a Thermo Scientific Endura TSO triple quadrupole mass spectrometer coupled with a Thermo Scientific Dionex UltiMate 3000 HPLC. Two transition ions were optimized (for collision energy and retention time) in-house, one for quantitation (T1) and another for confirmation (T2) of precursor identity (Supporting Information, S13). The instrument-calibrated fragmentor voltage was used for all analyses. Mobile phase A was LC-MS-grade water with 0.01 M formic acid and 0.01 M ammonium formate, while mobile phase B was 90% methanol and 10% acetonitrile. The flow rate was 0.475 mL/min. Flow was diverted away from the spectrometer for the first

**TABLE 1:** Summary of the general characteristics of the 10 English national parks and information on number of sampling locations monitored in each park, the numbers of connected and unconnected treatment systems upstream of each sampling point, and flow data for the study rivers

Park	Area (km <sup>2</sup> ) <sup>a</sup>	Residential population <sup>b</sup>	Visitors per year (million) <sup>a</sup>	Visitor days per year (million) <sup>a</sup>	No. of sampling sites	No. of WWTPs upstream of sites <sup>c</sup>	No. of storm overflows upstream of sites <sup>c</sup>	No. of nonconnected systems upstream of sites <sup>c</sup>	Long-term mean daily flow (m <sup>3</sup> s <sup>-1</sup> ) <sup>d</sup>	Mean daily flow winter (m <sup>3</sup> s <sup>-1</sup> ) <sup>d</sup>	Mean daily flow summer (m <sup>3</sup> s <sup>-1</sup> ) <sup>d</sup>
Dartmoor	953	34,124	2.4	3.1	4	2–11	1–13	0–8	1.91–11.402	1.899–31.12	0.274–1.047
Exmoor	694	10,192	1.4	2	3	1–3	1–3	1–8	4.486–5.23	7.012–11.2	0.255–0.795
Lake District	2362	38,993	16.4	24	6/8	1–6	0–11	0–15	3.93	7.00	1.092
New Forest	570	34,166	–	13.5	3	2–3	1–3	6–8	1.131–19.923	0.896–18.8	4.219
North York Moors	1434	22,935	7	10.8	10/11	0–10	0–17	0–36	0.206–4.804	0.695–16.1	0.043–0.773
Northumberland	1048	1848	1.5	1.7	3	1–2	0–2	0–5	2.08–5.07	0.428–0.696	3.938–5.86
Peak District	1437	35,901	8.75	11.75	6	1–9	1–15	0–8	3.357–6.451	12.36–22.70	1.123–1.738
South Downs	1624	113,339	–	39	4	4–33	6–39	5–173	1.312–4.745	0.135–0.864	1.398–5.576
The Broads	303	6275	8	15.5	3	7–44	4–23	13–114	0.413–3.67	0.12–0.962	0.32–2.465
Yorkshire Dales	2179	22,798	9.5	12.6	6	2–12	0–11	1–14	15.4–28	1.54–31.51	6.653–16.499

<sup>a</sup>National Parks UK (2024).

<sup>b</sup>Office for National Statistics (2023).

<sup>c</sup>The inputs for each of the three types of sewage discharges were derived by combining all upstream inputs across all sampling locations for each park (Rivers Trust, 2023).

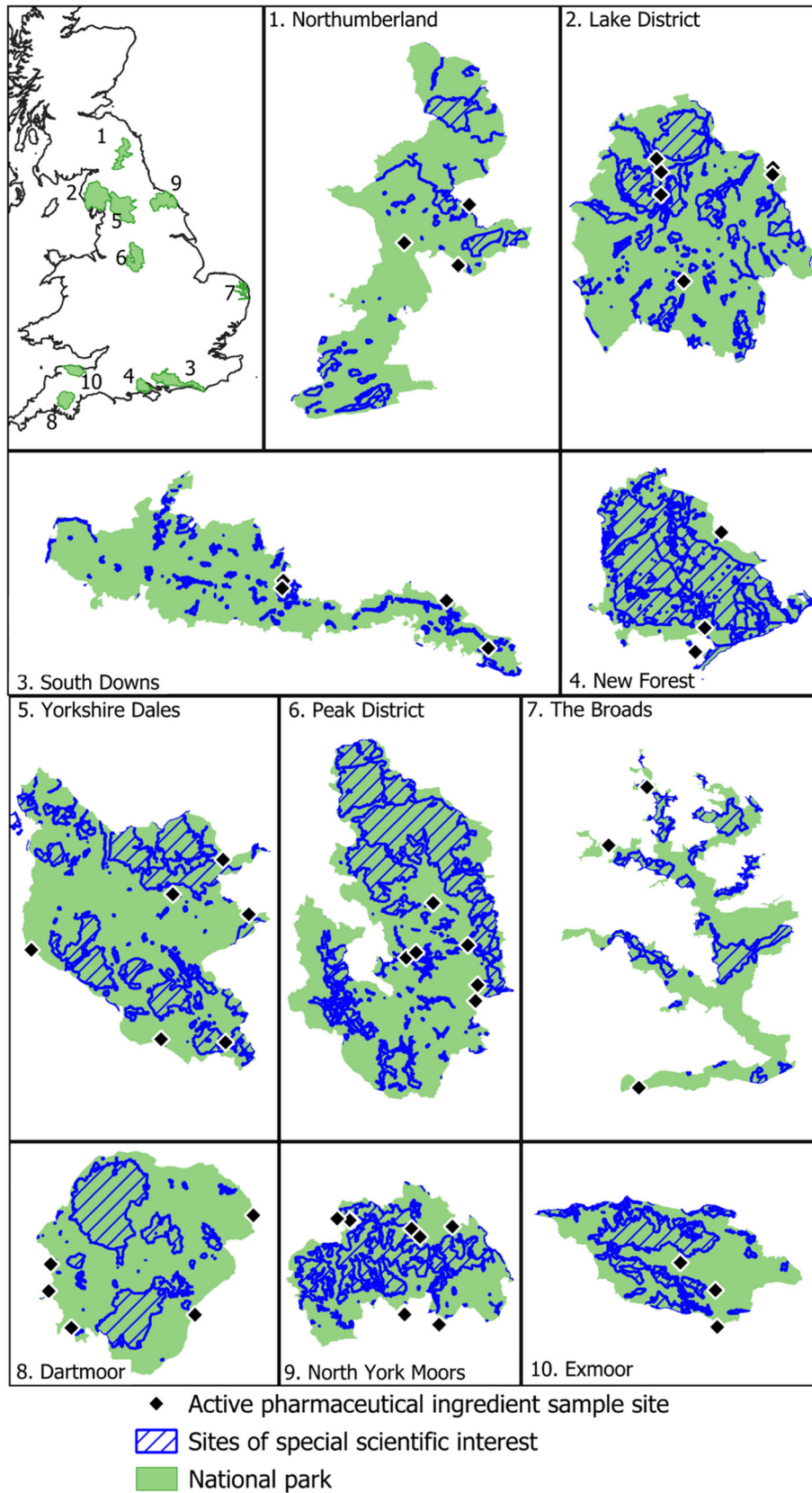
<sup>d</sup>Long-term mean daily flows and mean daily flows for the sampling periods were obtained from the closest gauging stations located on the same river as the sampling point (UK Centre for Ecology & Hydrology, 2024). Detailed data are provided in the Supporting Information.

WWTPs = wastewater-treatment plants.

## Data and statistical analyses

Cumulative API concentrations and number of detections were calculated for each sample and sampling time point. For the cumulative concentration, it was assumed that the concentration of a nondetected compound was zero. Statistical analysis was performed in RStudio (Ver. 2024.04.1) (RStudio, 2024). Prior to statistical analysis, all data were tested for normality using a Shapiro-Wilk test. A Kruskal-Wallis test was performed to explore differences in cumulative concentrations of APIs across the parks in the summer and the winter. This was followed by a Dunn's test to see which parks were significantly different from one another. Where data were normally distributed, *t* tests were used to determine differences between summer and winter concentrations for individual APIs; a Wilcoxon test was used where data was not normally distributed. For the statistical analyses for individual APIs, where a substance was not detected, a concentration of zero was assumed. The significance level in all statistical analyses was  $p < 0.05$ .





**FIGURE 1:** Locations of the different national parks in England and of the sites of special scientific interest and the locations for sampling of water for the present study. Detailed information on the sampling locations is provided in Supporting Information, Table S11.

## Comparison of English national park data with data for UK urban environments

To explore how pharmaceutical concentrations and patterns of exposure in the national parks compared to urban environments, we compared our findings with those obtained from previous monitoring of urban locations in five cities in the United Kingdom (Belfast, Glasgow, London, Leeds, and York) reported in a recent global monitoring study (Wilkinson et al., 2022). While the analytical methods used in the two studies had differing numbers of determinands (61 in the Wilkinson study and 54 in the present study), the compounds detected in the UK city rivers were included in our analytical method and, with the exception of amitriptyline, cetirizine, and cotinine, where the LOQs were subtly different, the LOQs were the same. To perform the urban versus national parks comparison, the data were initially tested for normality using a Shapiro-Wilk test. A Dunn's test was then performed to see if there were any differences between cumulative concentrations between the urban settings and the national park settings in the winter and summer.

## Impacts on ecological and human health

The implications of the detected concentrations for ecological and human health were assessed by comparing concentrations of APIs for each location with the predicted-no-effect concentration ( $PNEC_{apical}$ ) obtained from apical aquatic ecotoxicity tests with fish, daphnids, and algae; the lowest-observed effect concentration ( $LOEC_{nonapical}$ ) where nonapical effects, such as cytotoxicity and effects on organism behavior, have been reported; and target concentrations to protect against selection for antimicrobial resistance. If the ratio of the measured concentration to the effect concentration for an API exceeded 1, then it was assumed that the API could cause an adverse effect at the location. The apical PNEC and nonapical LOEC data were obtained from Bouzas-Monroy et al. (2022), and the targets for antimicrobial resistance were obtained from Tell et al. (2019).

## RESULTS

Pharmaceutical contamination was found to be widespread across the 10 English national parks (full analytical data sets are provided in Supporting Information, S14 and S15). With the exception of the Lake District and the Yorkshire Dales, APIs were detected in at least one of the two sampling seasons at all of the sites monitored in each national park (Figure 2A). For the North York Moors and Exmoor, while all sampling locations were found to be contaminated with APIs in August, in the winter, APIs were not detected at six locations in the North York Moors and at two locations on Exmoor (Figure 2A). At two sites, Bampton in the Lake District and Barden Bridge in the Yorkshire Dales, no APIs were detected in either the winter or the summer.

Thirty one of the 54 APIs were detected, with 17 $\alpha$ -ethinylestradiol, azlocillin, cefazolin, diclofenac, enrofloxacin,

fluoxetine, ketoconazole, ketotifen, lincomycin, loratadine, mefenamic acid, metoprolol, norethisterone, norfluoxetine, norverapamil, oxazepam, raloxifene, ranitidine, salbutamol, temazepam, tilmicosin, tylosin, and verapamil being below the LOD. Twenty-three APIs were detected across the samples collected in the winter, while 29 APIs were detected in samples obtained in the summer. Sulfadiazine and nicotine were only detected in samples collected in the winter, while amitriptyline, clarithromycin, ciprofloxacin, diltiazem, hydrocodone, lidocaine, metronidazole, and pregabalin were only detected in samples collected in the summer.

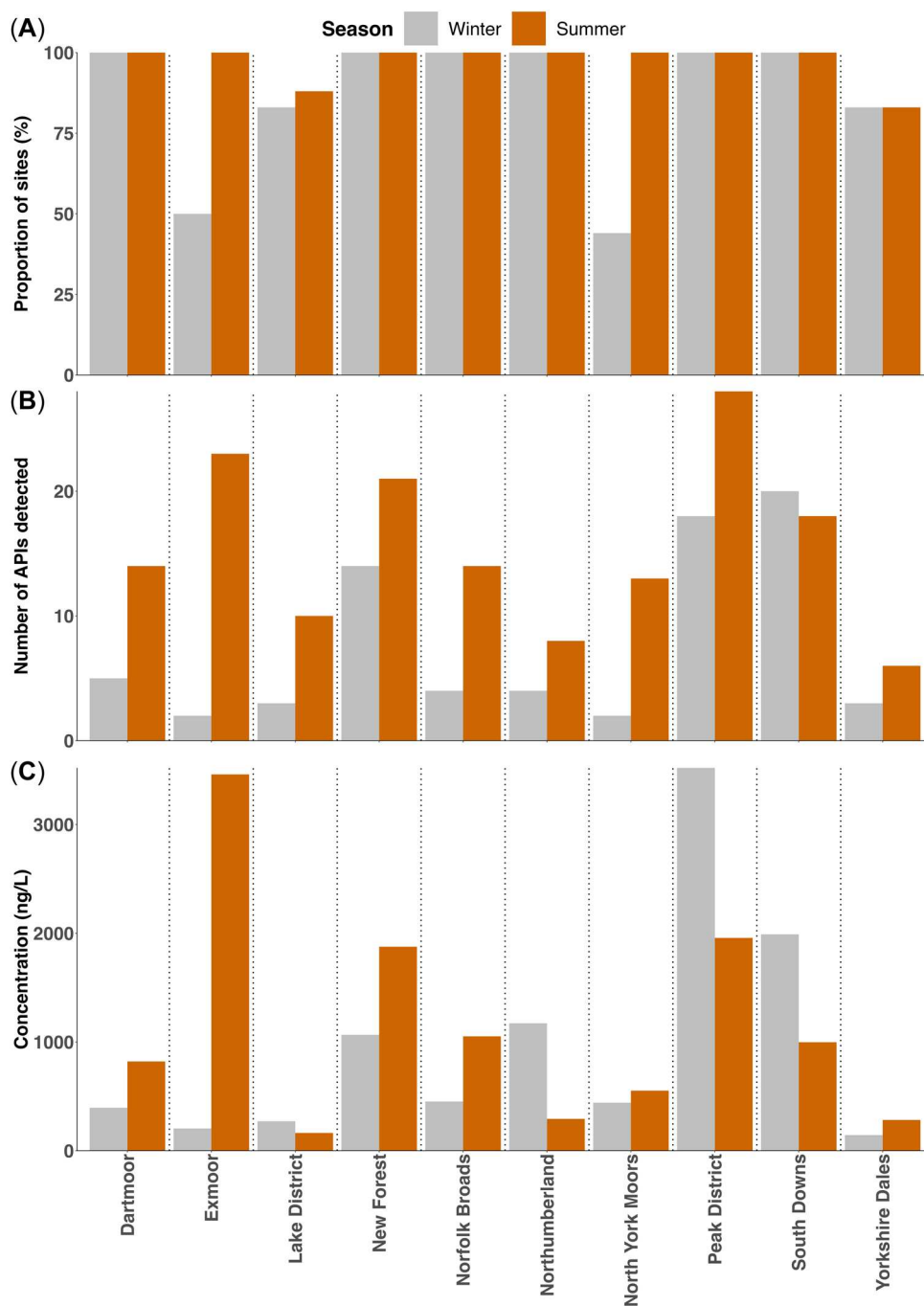
The greatest number of APIs (29) was detected in the Peak District in central England, with the fewest APIs (seven) being detected in the Yorkshire Dales in northern England. With the exception of the South Downs in the south of England, higher numbers of APIs were detected in all national parks in the summer than in the winter (Figure 2B). The antihistamines cetirizine and fexofenadine and the Type 2 diabetes treatment metformin were detected in all national parks.

Mean cumulative concentrations of APIs for each national park ranged from 144 ng/L in the Yorkshire Dales in the winter to 3521 ng/L in the Peak District in the winter (Figure 2C). Generally, there was no significant difference in the cumulative concentrations observed across the national parks, the exceptions being the South Downs and Yorkshire Dales, which were significantly different in the winter ( $p = 0.0298$ ), and the Peak District and the Lake District ( $p = 0.0386$ ) and the Lake District and the New Forest ( $p = 0.038$ ), which were significantly different in the summer.

For the Peak District, South Downs, Northumberland and Lake District, highest mean cumulative API concentrations were observed in the winter, while for the other national parks, highest cumulative concentrations were found in the summer (Figure 2C), although, with the exception of the South Downs ( $p = 0.0013$ ), the summer/winter differences were not significant. The highest cumulative API concentration (16,600 ng/L) was found at Brook Head, a small stream running through Tideswell Dale in the Peak District.

The most frequently detected APIs were caffeine, carbamazepine, metformin, fexofenadine, and cetirizine, which were detected at >60% of the sampling locations in either the summer (carbamazepine, metformin, fexofenadine, cetirizine) or winter (caffeine; Figure 3A). With the exception of caffeine, paracetamol, nicotine, and sulfadiazine, the detection frequency of individual APIs across the monitoring locations was greater in the summer than in the winter (Figure 3A).

Caffeine, metformin, and paracetamol also had the highest mean concentrations (Figure 3B). For those APIs detected in both seasons, statistically significant differences in mean concentrations between the winter and summer were seen for paracetamol, where highest concentrations were seen in the winter ( $p < 0.0001$ ), and carbamazepine, cetirizine, citalopram, codeine, cotinine, desvenlafaxine, fexofenadine, tramadol, and desvenlafaxine, where greatest concentrations were seen in the summer ( $p < 0.0469$ ; Figure 3B). Across the whole study, the API found at the highest concentration was paracetamol,



**FIGURE 2:** Summary of the results of monitoring of active pharmaceutical ingredients (APIs) in river water across the 10 English national parks in February/March (winter) and August (summer) 2022. **(A)** Proportion of sites monitored by national park where at least one API was detected. **(B)** Number of APIs detected in each national park. **(C)** Mean cumulative concentration of APIs for each national park.

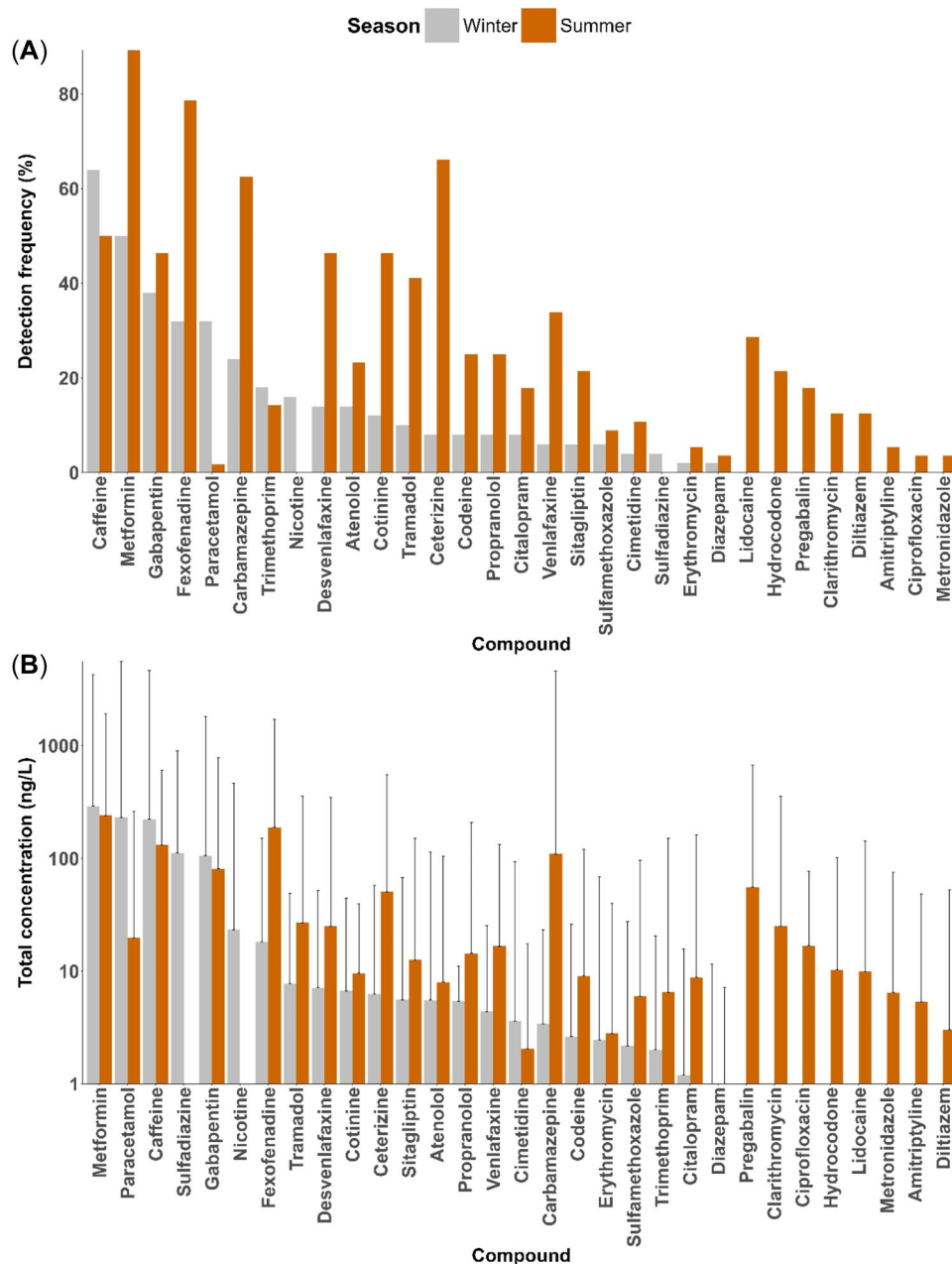
where a concentration of 5597 ng/L was measured in a sample taken from Brook Head stream in the Peak District in February.

### Comparison of data for the English national parks with UK urban environments

The overall number of APIs detected in the national parks was slightly lower than the number detected in UK urban systems (31 vs. 34), with norethisterone, salbutamol, and ranitidine

being detected in the urban settings but not the national parks (Figure 4). The mean of the cumulative concentrations for locations monitored in the urban systems was significantly greater than the mean of the cumulative concentrations in the national parks for the summer and winter sampling periods ( $p < 0.0001$ ; Figure 4). However, when individual sites were considered, locations in the Peak District and on Exmoor had cumulative concentrations in a similar range as seen in some of the most contaminated urban systems (Figure 4).





**FIGURE 3:** (A) Frequency of detection of individual active pharmaceuticals in the samples taken from locations across England's 10 national parks in February/March (winter) and August 2022 (summer). (B) Mean (+maximum) concentrations of individual active ingredients detected in samples obtained from England's 10 national parks in February/March (winter) and August 2022 (summer).

### Risks of active pharmaceuticals to aquatic organisms and human health

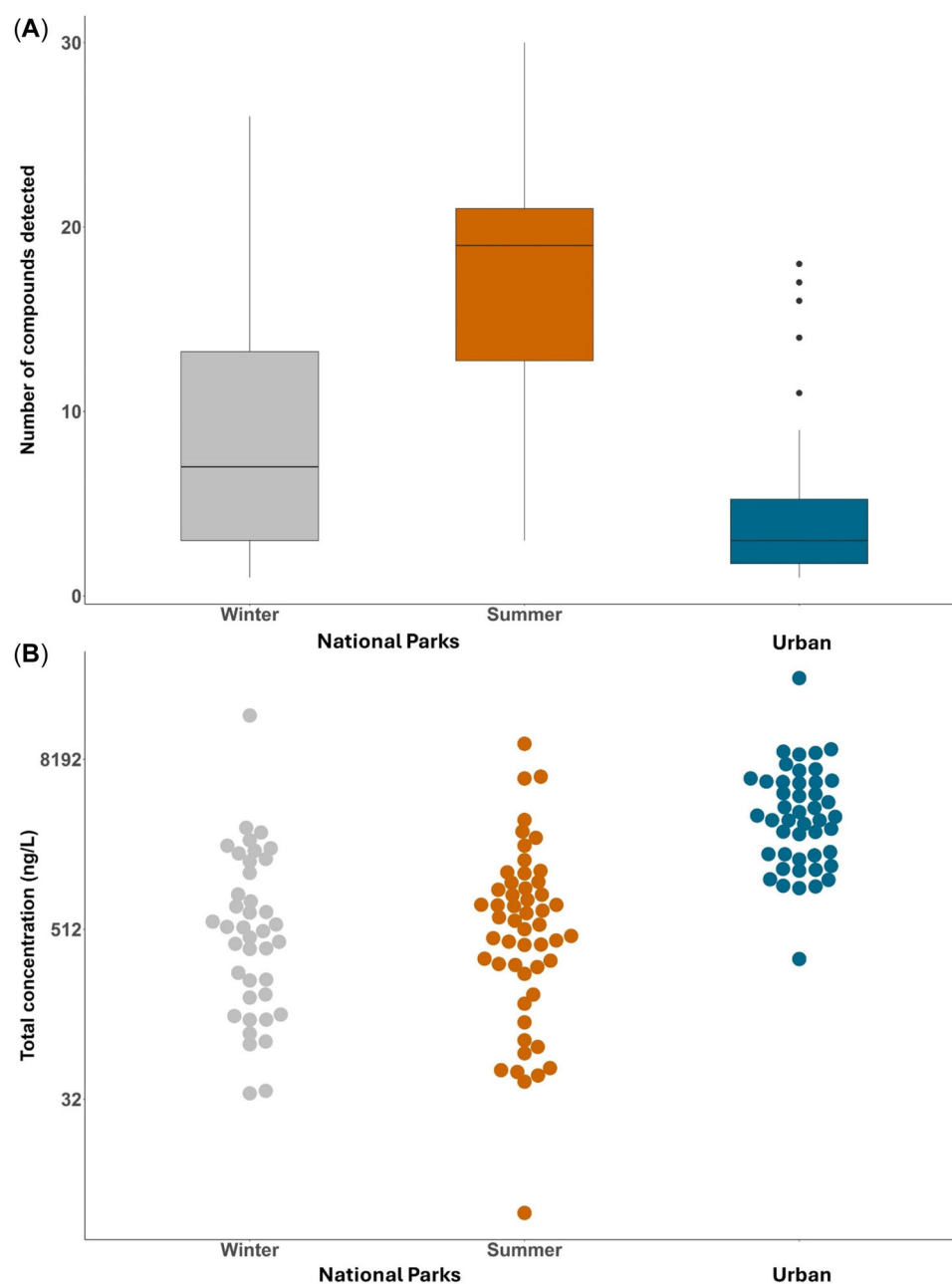
Seven locations had concentrations of at least one API above  $PNEC_{apical}$  or  $LOEC_{nonapical}$  values for aquatic organisms in the winter, while eight locations had concentrations of at least one API above these values in the summer (Figure 5). Seven APIs—amitriptyline, carbamazepine, clarithromycin, diltiazem, metformin, paracetamol, and propranolol—exceeded  $PNECs$  and/or  $LOECs$  for at least one location (Figure 5). In the summer, three locations, one in Exmoor and two in the Peak District, had concentrations of ciprofloxacin and/or

clarithromycin above the concentrations believed to be safe in terms of selection of antimicrobial resistance.

## DISCUSSION

### What are the scale and nature of pharmaceutical pollution in the English national parks?

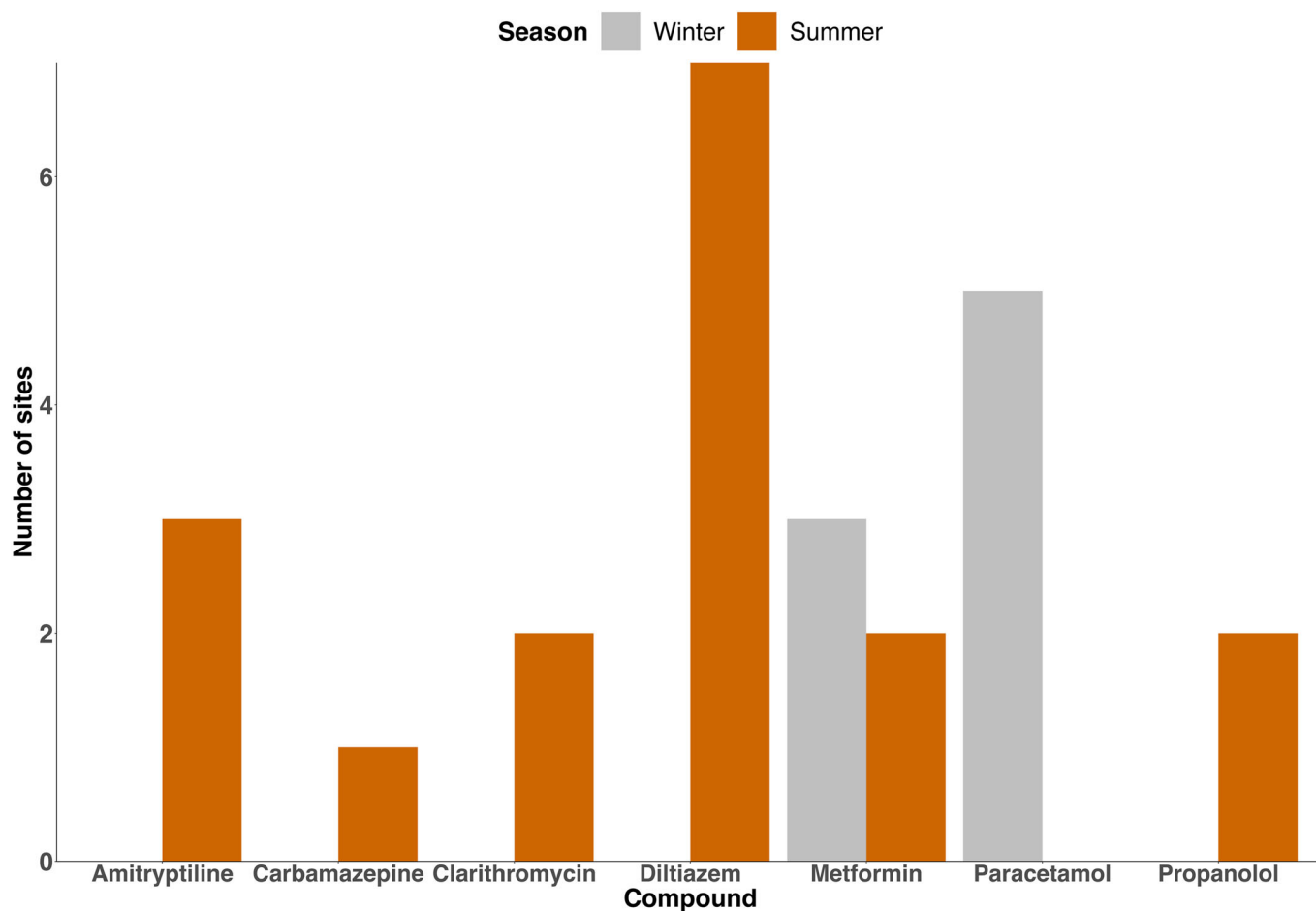
Although the presence and risks of pharmaceuticals in urban systems have received significant focus from the scientific community (see Hughes et al., 2013), the occurrence and impacts in less populated areas such as the English national parks have



**FIGURE 4:** Comparison of number of pharmaceuticals (A) and cumulative concentrations of pharmaceuticals measured (B) in surface water samples obtained from different locations in the 10 English national parks in either the winter or summer of 2022 with total concentrations and numbers of detections for samples obtained at different locations in urban environments in England in 2018 or 2019 (data for the urban environments taken from Wilkinson et al., 2022). Note the active pharmaceutical ingredients detected were common across both studies and, with the exception of amitriptyline, cetirizine, and cotinine, where the limits of quantification (LOQs) were subtly different, the LOQs were the same for both studies.

received limited attention. The present study was therefore performed to characterize the concentrations of 54 APIs in the 10 English national parks. While at two sites no APIs were detected (even though data from The Rivers Trust sewage map [Supporting Information S7] show that both of these locations have upstream inputs from multiple wastewater sources), at every other site we detected at least one API, demonstrating that contamination of rivers in the English national parks by APIs is widespread. Similar observations have been made from studies on national parks and reserves and other protected areas in the United States (Battaglin et al., 2018; Bradley et al., 2020, 2021).

Twenty-three of the 54 APIs monitored were not detected in any of the English national parks. This is likely due to a range of factors, including low use levels, low human dosage, a high degree of metabolism by humans, a high degree of removal in wastewater treatment, high analytical detection limits, or a combination of these. The most frequently detected compounds were the Type 2 diabetes treatment metformin, the lifestyle compound caffeine, the antihistamines cetirizine and fexofenadine, and the antiepileptic treatment carbamazepine. The findings for caffeine, metformin, and carbamazepine are similar to a recent global reconnaissance study of APIs in rivers,



**FIGURE 5:** Number of sampling locations where measured concentrations of active pharmaceutical ingredients exceeded a predicted-no-effect concentration (PNEC) based on apical aquatic ecotoxicity endpoints and/or a lowest-observed-effect concentration (LOEC) from nonapical aquatic ecotoxicity tests. Only active pharmaceuticals that exceeded one of these concentrations for at least one location are shown. The PNEC and LOEC were obtained from Bouzas-Monroy et al. (2022).

where these three substances were the top three most frequently detected APIs (Wilkinson et al., 2022). Metformin and carbamazepine are prescription-only molecules. Even though metformin is well removed by wastewater-treatment systems (Burns, Carter, Kolpin, et al., 2018), the high frequency of detection is likely explained by the high incidence rates of Type 2 diabetes (6.3%; Whicher et al., 2020) relative to other chronic diseases in the UK population and the high treatment dose of metformin, meaning that it is the second most prescribed synthetic medicine in the United Kingdom after paracetamol. While the incidence of epilepsy (0.94%; Wigglesworth et al., 2023) and the consequent use of carbamazepine in the UK population (21st most used API) are lower than for metformin, this molecule is resistant to removal by wastewater-treatment systems (Burns, Carter, Kolpin, et al., 2018). The high incidence of caffeine is likely due to beverage consumption rather than its use as an API. Caffeine was also one of the most commonly substances detected in a study into the occurrence of bioactive substances in a US national park (Battaglin et al., 2018). Cetirizine and fexofenadine can both be obtained over the counter in the United Kingdom for the treatment of allergies. Their high detection likely results from the high

prevalence of hay fever in the United Kingdom, which affects 26% of adults (Bauchau & Durham, 2004). Cetirizine is the fifth most used over-the-counter API by mass (Guo et al., 2016).

We observed differences in the numbers of APIs detected and concentrations of individual APIs between the two sampling periods. Generally, highest concentrations of APIs were observed in samples collected in the summer. Differences in flow conditions might be one explanation for these seasonal differences. The weather in February in England was dominated by the storms Dudley, Eunice, and Franklin; and rainfall levels across England were higher than the long-term average for the month (Environment Agency, 2022a). In contrast, August sampling followed 5 months of below-average rainfall across England (Environment Agency, 2022b); and during this period, monthly rainfall totals and river flows across the country were classed as below average for the time of year (Environment Agency, 2022b). River flow data for the study rivers, where available (UK Centre for Ecology & Hydrology, 2024; Table 1), showed river flows to be 0.5 (River Lune, Yorkshire Dales) to 61 (River Seven, North York Moors) times higher during the time of winter sampling compared to the time of summer sampling (median difference 11 times). Comparison of

differences in flow at the times of sampling with differences in total API concentrations (Supporting Information, Figure in SI9) showed a nonsignificant and weak positive relationship, indicating that flow differences alone do not explain the observed differences in cumulative API concentration.

Observed seasonal differences in API numbers and concentrations might also be explained by the large influx of tourists to the English national parks that occurs in the summer months and which will result in higher API loadings. Visitor influxes have been shown to contribute to API loadings in US national parks (Bradley et al., 2021). For the antihistamines, such as cetirizine and fexofenadine, the higher concentrations might also be influenced by the higher incidence of hay fever during August compared to February—with the hay fever season in the United Kingdom running from late March to September (Met Office, 2024). Higher concentrations of paracetamol and nicotine were observed in samples taken from February compared to August. Both paracetamol and nicotine are extensively removed in wastewater treatment (Burns, Carter, Kolpin, et al., 2018; Ekpeghere et al., 2018), so their presence in English national park rivers might be explained by the influence of combined sewer overflows on the system. Combined sewer overflows, which are designed to release untreated wastewater to the environment during periods of extreme rainfall, have previously been shown to be an important source of some pharmaceuticals in surface waters (Kay et al., 2017).

### **How do pollution patterns and levels compare to urban environments in the United Kingdom?**

The overall number of APIs detected in the national parks was slightly lower than detected in the UK urban systems (31 vs. 34), with norethisterone, salbutamol, and ranitidine being detected in the urban settings but not the national parks. Norethisterone and salbutamol were only detected in single samples in the urban monitoring work, so their occurrence in urban settings appears not to be widespread. On the other hand, ranitidine, which is a treatment for stomach acid, was widely detected in UK urban settings. The mismatch between our results for ranitidine and the urban data is likely explained by the fact that this molecule was removed from the market in 2020 prior to the commencement of our study but after sampling had been done for the global study. The removal of ranitidine from the market was due to the presence of *N*-nitrosodimethyl amine, a suspected carcinogen, in the product (European Medicines Agency, 2020).

One API, sulfadiazine, was detected in the present study but not in any of the urban samples. This substance was only detected in the winter at two locations (one in the Lake District and the other on Exmoor). The antibiotic did not co-occur with many other APIs—at the Exmoor site, caffeine was the only other API detected, while at the Lake District site, no other APIs were detected. These data may suggest that the use of the antibiotic in veterinary medicine is the likely cause of the detections, given its utilization in a number of oral and injection treatments for cattle, horses, pigs, and poultry (National Office of Animal Health, 2024). While overall numbers of APIs for the

individual samples obtained in the national parks were typically lower than seen at the urban monitoring locations, there were instances where the numbers of APIs detected were greater than seen in urban environments. For example, the number of compounds detected in the Peak District (29) was greater than the numbers detected in many of the UK cities (York, 15; Leeds, 21; Belfast, 23; London, 26) monitored in our recent global monitoring study (Wilkinson et al., 2022). This likely results from the apparent influence of a combined sewer overflow in the winter and the low degree of dilution at Brook Head stream in the Peak District in both the winter and the summer.

In general, total API concentrations for samples obtained from the national parks were lower than concentrations observed in urban systems. However, there were exceptions to this, with concentrations observed in samples obtained from Tideswell in the Peak District and Exford on Exmoor being ranked as the second and third most polluted sites of all the locations monitored across the two studies. These two sites were located <500 m downstream of WWTP discharge points, so the high levels of detection were likely due to emissions from the sewerage system. The populations of Exford (389) and Tideswell (1760) are lower than the Urban Wastewater Treatment Directive (European Commission, 2023) threshold for secondary treatment, so the level of treatment at these two plants may be limited compared to larger urban treatment systems. A storm overflow is also located upstream of the sampling point at Tideswell, which discharged on 92 occasions in 2022 for a total of 1166 h (Rivers Trust, 2023), probably explaining the high concentration of paracetamol in the sample taken from this point in the winter.

Overall, comparison of national park API data with the urban API data indicates that while, in general, the level of pharmaceutical pollution in rivers in the national parks is lower than in urbanized settings, there are instances where concentrations are similar to or greater than those seen in urban settings. This could have implications in terms of impacts.

### **Could APIs be impacting ecological and human health in our national parks?**

Given that national parks are hotspots for biodiversity, the widespread occurrence of APIs in the national parks and the relatively high concentrations of APIs detected at some locations are concerning in terms of potential impacts of these molecules on ecological health. The most contaminated site, for example, was Brook Head Stream in Tideswell Dale, a short, largely dry limestone valley which is a nature reserve and designated as a Site of Special Scientific Interest (SSSI). It is part of the Wye Valley SSSI, which is one of the most important areas of carboniferous limestone in Britain (Natural England, 2022). The limestone is cut by valleys, the “dales,” which both expose areas of high geological and geomorphological interest and support a range of important seminatural woodland, scrub, grassland, and stream habitats (Natural England, 2022).

Comparison of API concentration data with ecotoxicological data (taken from Bouzas-Monroy et al. 2022) for the detected

APIs shows that 14 of the locations monitored had concentrations of at least one API of ecological concern. Locations in the Peak District, the Lake District, Exmoor, South Downs, and the New Forest had concentrations of either amitriptyline, carbamazepine, diltiazem, or metformin where effects on fish or invertebrate biochemistry have been demonstrated (Crago & Klaper, 2018; Yang et al., 2014). The concentrations of paracetamol at five locations in the Peak District in the winter were at levels that have been shown to affect fish behavior (Erhunmwunse et al., 2021). Water samples taken from Brook Head stream in the Peak District in the summer had concentrations of propranolol of concern for fish reproduction and growth (Gunnarsson et al., 2019) and concentrations of clarithromycin higher than those of concern for growth of algae (Watanabe et al., 2016). Impacts on aquatic organisms might therefore be expected. It is also important to recognize that at many locations monitored a complex mixture of APIs was detected, which raises the potential for toxic interactions of the mixtures that might exacerbate the impacts (Kortenkamp et al., 2019).

Annual average environmental quality standards (AA EQS) have recently been proposed for some of the study molecules (carbamazepine, clarithromycin, and erythromycin) by the European Commission (2022a). Comparison of our data with these proposed EQS values shows that concentrations of carbamazepine at Exford on Exmoor were 1.8 times greater than the proposed AA EQS values and that concentrations of clarithromycin at Tideswell in the Peak District were 2.8 times higher than the AA EQS. Therefore, in the future, if the EQS proposals are adopted, pharmaceutical pollution could be a cause for EQS failures for rivers in the national parks. Other APIs (sulfamethoxazole, trimethoprim, venlafaxine, metformin) are included on the European Water Framework Directive Watch List for union-wide monitoring (European Commission, 2022b), so it is possible that these could also be more tightly regulated in the future.

Measured concentrations of some APIs at some locations were also at levels of concern for human health, with concentrations of ciprofloxacin and clarithromycin observed at Exford and Tideswell, respectively, exceeding concentrations believed to be safe for selection of antimicrobial resistance in microorganisms (Tell et al., 2019). Given that these national parks are important areas for freshwater recreation, humans could come into contact with water contaminated by resistant bacteria through activities like swimming. The implications of resistance selection could therefore be greater than in urban settings, where human connectivity to the natural environment is likely to be lower.

The APIs we detected will likely co-occur with other APIs in use that we did not monitor and other down-the-drain chemicals such as chemicals used in personal care and cleaning products. Transformation products of these chemicals formed from human metabolism and wastewater treatment will also likely be present, many of which will pose a threat to aquatic organisms (Boxall et al., 2004). Ecological and health impacts of the complex mixture of these chemicals could therefore be even greater than we predict. Given the predicted increases in the frequency and severity of droughts in the United Kingdom (Hanlon et al., 2021)

which will decrease river flows and the reduced dilution capacity of national park rivers receiving treated wastewater, risks to human and ecological health could become more prevalent in the future. Attention should therefore be given to improved monitoring and management of chemical contaminants, such as pharmaceuticals, in the national parks.

### **Implications for monitoring and management of chemicals in the national parks**

The current degree of regulatory monitoring and regulation of pollution in the rivers that we monitored is highly variable and likely not fit for purpose. For the Brook Head Stream at Tideswell, for example, since 2016, only 61 samples have been taken for monitoring by the Environment Agency of England, with only seven parameters (pH,  $Mg^{2+}$ ,  $Ca^{2+}$ , dissolved organic carbon, iron, dissolved, and bioavailable Mn) measured (Environment Agency, 2024). In contrast, the second most contaminated location on the River Exe at Exford has been extensively monitored, with 240 samples taken between 2018 and 2020 and measurements made for 111 parameters including general water parameters and metals, pesticides, polycyclic hydrocarbons, and biocides (Environment Agency, 2024). In terms of the WWTPs that are likely the cause of the high concentrations of APIs in Brook Head Stream and the River Exe, no monitoring is required because the population equivalents of these sites falls below the 2000 population equivalents threshold. Our results, therefore, highlight the need for improved monitoring of smaller WWTPs and more regular sampling of riverine systems in the national parks and a move away from monitoring only general water quality parameters to monitoring a range of potentially hazardous chemicals such as APIs that could be affecting ecological health. Exposure and risk modeling work, which to date has focused on inputs from larger WWTPs, should be extended to considering exposure resulting from smaller plants.

The substantial number of small to medium-sized WWTPs discharging to receiving waters located both within the national parks themselves and outside the park boundary but to rivers flowing in indicates that they are likely to be a significant pathway for APIs into river systems of the national parks. Each of the English national parks also has discharges of sewage unconnected to the sewer network through the use of septic tanks and “package” treatment works (self-contained wastewater-treatment tanks which provide a modern alternative to septic tank systems for areas not serviced by a sewer network). In the case of the South Downs and the Broads, tens of these discharges are located upstream of each API sampling point. Such features are known to pollute watercourses through pathogen and nutrient loadings (Richards et al., 2016) and, although evidence is limited, pharmaceuticals (Phillips et al., 2015), so these are probably also contributing to the contamination observed in the present study.

Improved removal of APIs by connected and unconnected treatment systems would help to lower API concentrations and therefore reduce the level of risk to aquatic ecosystems.



Greater use of nature-based solutions, such as wetlands, which are known to be able to attenuate APIs and other micro-pollutants (Ilyas et al., 2020; Zhang et al., 2019), could be one solution. The rural location of many of the WWTPs in the national parks means that, unlike many urban settings, there is the physical space available to implement these more natural treatment technologies, which also provide other benefits including flood prevention, improved aesthetics, increased biodiversity, and habitat formation (Agaton & Guila, 2023). The extension of recent UK government rules for newer septic tank systems (Gov.UK, 2023) to older systems and better maintenance and management of septic tanks to optimize treatment would also be beneficial in reducing API loadings.

The results of the present study show that if we are to protect these ecologically and societally important areas, much more needs to be done to understand the emissions and impacts of chemical pollutants in our national parks. While our focus has been on national parks in England, similar environments exist across the world which are likely experiencing similar pressures from chemical pollution. Moving forward we need more thorough regulatory monitoring and tighter control of wastewater emissions in national parks in England, the United Kingdom, and more widely to reduce contamination to safe levels so that we can continue to enjoy the benefits of these areas and protect biodiversity into the future.

**Supporting Information**—The Supporting Information is available on the Wiley Online Library at <https://doi.org/10.1002/etc.5973>.

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## REFERENCES

- Agaton, C. B., & Guila, P. M. C. (2023). Ecosystem services valuation of constructed wetland as a nature-based solution to wastewater treatment. *Earth*, 4(1), 78–92.
- Aus der Beek, T., Weber, F. A., Bergmann, A., Hickmann, S., Ebert, I., Hein, A., & Küster, A. (2016). Pharmaceuticals in the environment—Global occurrences and perspectives. *Environmental Toxicology and Chemistry*, 35(4), 823–835.
- Battaglin, W. A., Bradley, P. M., Iwanowicz, L., Journey, C. A., Walsh, H. L., & Blazer, V. S. (2018). Pharmaceuticals, hormones, pesticides, and other bioactive contaminants in water, sediment, and tissue from Rocky Mountain National Park, 2012–2013. *Science of the Total Environment*, 643, 651–673.
- Bauchau, V., & Durham, S. R. (2004). Prevalence and rate of diagnosis of allergic rhinitis in Europe. *European Respiratory Journal*, 24(5), 758–764.
- Bouzas-Monroy, A., Wilkinson, J. L., Melling, M., & Boxall, A. B. A. (2022). Assessment of the potential ecotoxicological effects of pharmaceuticals in the world's rivers. *Environmental Toxicology and Chemistry*, 41(8), 2008–2020.
- Boxall, A. B. A. (2004). The environmental side effects of medication: How are human and veterinary medicines in soils and water bodies affecting human and environmental health? *EMBO Reports*, 5(12), 1110–1116.
- Boxall, A. B. A., Sinclair, C. J., Fenner, K., Kolpin, D., & Maund, S. J. (2004). When synthetic chemicals degrade in the environment. *Environmental Science & Technology*, 38(19), 368A–375A.
- Boxall, A. B. A., Wilkinson, J. L., & Bouzas-Monroy, A. (2022). Medicating nature: Are human-use pharmaceuticals poisoning the environment? *One Earth*, 5, 1080–1084.
- Bradley, P. M., Kulp, M. A., Huffman, B. J., Romanok, K. M., Smalling, K. L., Breitmeyer, S. E., Clark, J. M., & Journey, C. A. (2021). Reconnaissance of cumulative risk of pesticides and pharmaceuticals in Great Smoky Mountains National Park streams. *Science of the Total Environment*, 781, Article 146711.
- Bradley, P. M., Romanok, K. M., Duncan, J. R., Battaglin, W. A., Clark, J. M., Hladik, M. L., Huffman, B. J., Iwanowicz, L. R., Journey, C. A., & Smalling, K. L. (2020). Exposure and potential effects of pesticides and pharmaceuticals in protected streams of the US National Park Service southeast region. *Science of the Total Environment*, 704, Article 135431.
- Burns, E. E., Carter, L. J., Kolpin, D. W., Thomas-Oates, J., & Boxall, A. B. A. (2018). Temporal and spatial variation in pharmaceutical concentrations in an urban river system. *Water Research*, 137, 72–85.
- Burns, E. E., Carter, L. J., Snape, J., Thomas-Oates, J., & Boxall, A. B. A. (2018). Application of prioritization approaches to optimize environmental monitoring and testing of pharmaceuticals. *Journal of Toxicology and Environmental Health—Part B: Critical Reviews*, 21(3), 115–141.
- Crago, J., & Klaper, R. (2018). Place-based screening of mixtures of dominant emerging contaminants measured in Lake Michigan using zebrafish embryo gene expression assay. *Chemosphere*, 193, 1226–1234.
- Defra. (2016). *Policy paper: National parks: 8-point plan for England (2016–2020)*. Accessed July 31, 2024 from: <https://www.gov.uk/government/publications/national-parks-8-point-plan-for-england-2016-to-2020/title#:~:text=There%20are%20currently%20an%20estimated,to%20National%20Parks%20per%20year>
- Ekpeghere, K. I., Sim, W.-J., Lee, H.-J., & Oh, J.-E. (2018). Occurrence and distribution of carbamazepine, nicotine, estrogenic compounds, and their transformation products in wastewater from various treatment plants and the aquatic environment. *Science of the Total Environment*, 640–641, 1015–1023.
- Environment Agency. (2019). *Waste water treatment works: Treatment monitoring and compliance limits*. [https://www.gov.uk/government/publications/waste-water-treatment-works-treatment-monitoring-and-compliance-limits](https://www.gov.uk/government/publications/waste-water-treatment-works-treatment-monitoring-and-compliance-limits/waste-water-treatment-works-treatment-monitoring-and-compliance-limits)
- Environment Agency. (2022a). *Monthly water situation report for England: February*. [https://assets.publishing.service.gov.uk/media/622f2dd1d3bf7f5a88fa8243/Water\\_situation\\_report\\_for\\_England\\_February\\_2022.pdf](https://assets.publishing.service.gov.uk/media/622f2dd1d3bf7f5a88fa8243/Water_situation_report_for_England_February_2022.pdf)
- Environment Agency. (2022b). *Monthly water situation report for England: August*. [https://assets.publishing.service.gov.uk/media/633476dc8fa8f506587dd149/Water\\_Situation\\_Report\\_for\\_England\\_August\\_2022.pdf](https://assets.publishing.service.gov.uk/media/633476dc8fa8f506587dd149/Water_Situation_Report_for_England_August_2022.pdf)
- Environment Agency. (2024). *Water quality data archive*. <https://environment.data.gov.uk/water-quality/view/landing>

- Erhunmwunse, N. O., Tongo, I., & Ezemonye, L. I. (2021). Acute effects of acetaminophen on the developmental, swimming performance and cardiovascular activities of the African catfish embryos/larvae (*Clarias gariepinus*). *Ecotoxicology and Environmental Safety*, 208, Article 111482.
- European Commission. (2022a). *Proposal for a Directive amending the Water Framework Directive, the Groundwater Directive and the Environmental Quality Standards Directive*. [https://environment.ec.europa.eu/publications/proposal-amending-water-directives\\_en](https://environment.ec.europa.eu/publications/proposal-amending-water-directives_en)
- European Commission. (2022b). 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. *Official Journal of the European Commission*, L197, 117–120.
- European Commission. (2023). *Urban wastewater*. [https://environment.ec.europa.eu/topics/water/urban-wastewater\\_en](https://environment.ec.europa.eu/topics/water/urban-wastewater_en)
- European Medicines Agency. (2020). *Suspension of ranitidine medicines in the EU*. <https://www.ema.europa.eu/en/news/suspension-ranitidine-medicines-eu>
- Furlong, E. T., Noriega, M. C., Kanagy, C. J., Kanagy, L. K., Coffey, L. J., & Burkhardt, M. R. (2014). Determination of human-use pharmaceuticals in filtered water by direct aqueous injection: High-performance liquid chromatography/tandem mass spectrometry. In *Techniques and methods* (5-B10). US Geological Survey. <https://pubs.usgs.gov/tm/5b10/pdf/tm10-b5.pdf>
- Gov.UK. (2023). *Septic tanks and sewage treatment plants: What you need to do*. <https://www.gov.uk/permits-you-need-for-septic-tanks>
- Gunnarsson, L., Jauhainen, A., Kristiansson, E., Nerman, O., & Larsson, D. G. J. (2008). Evolutionary conservation of human drug targets in organisms used for environmental risk assessments. *Environmental Science & Technology*, 42(15), 5807–5813.
- Gunnarsson, L., Snape, J. R., Verbruggen, B., Owen, S. F., Kristiansson, E., Margiotta-Casaluci, L., Österlund, T., Hutchinson, K., Leverett, D., Marks, B., & Tyler, C. R. (2019). Pharmacology beyond the patient—The environmental risks of human drugs. *Environment International*, 129, 320–332.
- Guo, J., Sinclair, C. J., Selby, K., & Boxall, A. B. A. (2016). Toxicological and ecotoxicological risk-based prioritization of pharmaceuticals in the natural environment. *Environmental Toxicology and Chemistry*, 35(6), 1550–1559.
- Hanlon, H. M., Bernie, D., Carigi, G., & Lowe, J. A. (2021). Future changes to high impact weather in the UK. *Climatic Change*, 166(3–4). <https://doi.org/10.1007/s10584-021-03100-5>
- Hughes, S. R., Kay, P., & Brown, L. E. (2013). Global synthesis and critical evaluation of pharmaceutical data sets collected from river systems. *Environmental Science & Technology*, 47(2), 661–677.
- Ilyas, H., Masih, I., & van Hullebusch, E. D. (2020). Pharmaceuticals' removal by constructed wetlands: A critical evaluation and meta-analysis on performance, risk reduction, and role of physicochemical properties on removal mechanisms. *Journal of Water and Health*, 18(3), 253–291.
- Johnson, A. C., Dumont, E., Williams, R. J., Oldenkamp, R., Cisowska, I., & Sumpter, J. P. (2013). Do concentrations of ethinylestradiol, estradiol, and diclofenac in European rivers exceed proposed EU environmental quality standards? *Environmental Science & Technology*, 47(21), 12297–12304. <https://doi.org/10.1021/es4030035>
- Kay, P., Hughes, S. R., Ault, J. R., Ashcroft, A. E., & Brown, L. E. (2017). Widespread, routine occurrence of pharmaceuticals in sewage effluent, combined sewer overflows and receiving waters. *Environmental Pollution*, 220(Pt B), 1447–1455.
- Kortenkamp, A., Faust, M., Backhaus, T., Altenburger, R., Scholze, M., Müller, C., Ermler, S., Posthuma, L., & Brack, W. (2019). Mixture risks threaten water quality: The European Collaborative Project SOLUTIONS recommends changes to the WFD and better coordination across all pieces of European chemicals legislation to improve protection from exposure of the aquatic environment to multiple pollutants. *Environmental Sciences Europe*, 31(1), Article 69.
- Met Office. (2024). *When is hay fever season in the UK?* <https://www.metoffice.gov.uk/weather/warnings-and-advice/seasonal-advice/health-wellbeing/pollen/when-is-hayfever-season#:~:text=Tree%20pollen%20occurs%20first%2C%20typically,affects%20around%2025%25%20of%20people>
- Murray, C. J., Ikuta, K. S., Sharara, F., Swetschinski, L., Aguilar, G. R., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., & Johnson, S. C. (2022). Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *Lancet*, 399, 629–655.
- National Health Service. (2017). *Health survey for England 2017: Prescribed medicines*. Accessed July 31, 2024 from: <https://files.digital.nhs.uk/pdf/3/c/hse2016-pres-med.pdf>
- National Office of Animal Health. (2024). *Welcome to the NOAH compendium*. <https://www.noahcompendium.co.uk/?id=-312863>
- National Parks UK. (2024). *Key facts and figures for all 15 UK national parks*. <https://www.nationalparks.uk/app/uploads/2020/10/Key-Facts-and-Figures-for-the-15-UK-National-Parks.pdf>
- Natural England. (2022). *Designated sites view*. <https://designatedsites.naturalengland.org.uk/>
- Office for National Statistics. (2023). *National park residents, England and Wales: Census 2021*. <https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/nationalparkresidentsenglandandwales/census2021>
- Oldenkamp, R., Hoeks, S., Čengić, M., Barbarossa, V., Burns, E. E., Boxall, A. B. A., & Ragas, A. M. J. (2018). A high-resolution spatial model to predict exposure to pharmaceuticals in European surface waters: ePiE. *Environmental Science & Technology*, 52(21), 12494–12503.
- Phillips, P. J., Schubert, C., Argue, D., Fisher, I., Furlong, E. T., Foreman, W., Gray, J., & Chalmers, A. (2015). Concentrations of hormones, pharmaceuticals and other micropollutants in groundwater affected by septic systems in New England and New York. *Science of the Total Environment*, 15(512–513), 43–54.
- Richards, S., Paterson, E., Withers, P. J., & Stutter, M. (2016). Septic tank discharges as multi-pollutant hotspots in catchments. *Science of the Total Environment*, 542(Pt A), 854–863.
- Rivers Trust. (2023). *Sewage map*. <https://theriverstrust.org/sewage-map>
- RStudio (Version 2024.04.1) [Computer software]. (2024). Posit.
- Schaider, L. A., Ackerman, J. M., & Rudel, R. A. (2016). Septic systems as sources of organic wastewater compounds in domestic drinking water wells in a shallow sand and gravel aquifer. *Science of the Total Environment*, 547, 470–481.
- Tell, J., Caldwell, D. J., Häner, A., Hellstern, J., Hoeger, B., Journal, R., Mastrocco, F., Ryan, J. J., Snape, J., Straub, J. O., & Vestel, J. (2019). Science-based targets for antibiotics in receiving waters from pharmaceutical manufacturing operations. *Integrated Environmental Assessment and Management*, 15(3), 312–319.
- UK Centre for Ecology & Hydrology. (2024). *National river flow archive*. <https://nrfa.ceh.ac.uk/>
- Watanabe, H., Tamura, I., Abe, R., Takanobu, H., Nakamura, A., Suzuki, T., Hirose, A., Nishimura, T., & Tatarazako, N. (2016). Chronic toxicity of an environmentally relevant mixture of pharmaceuticals to three aquatic organisms (alga, daphnid, and fish). *Environmental Toxicology and Chemistry*, 35(4), 996–1006.
- Whicher, C. A., O'Neill, S., & Holt, R. I. G. (2020). Diabetes in the UK: 2019. *Diabetic Medicine*, 37(2), 242–247.
- Wigglesworth, S., Neligan, A., Dickson, J. M., Pullen, A., Yelland, E., Anjuman, T., & Reuber, M. (2023). The incidence and prevalence of epilepsy in the United Kingdom 2013–2018: A retrospective cohort study of UK primary care data. *Seizure: European Journal of Epilepsy*, 105, 37–42.
- Wilkinson, J. L., Boxall, A. B. A., & Kolpin, D. W. (2019). A novel method to characterise levels of pharmaceutical pollution in large-scale aquatic monitoring campaigns. *Applied Sciences*, 9(7), Article 1368. <https://doi.org/10.3390/app9071368>
- Wilkinson, J. L., Boxall, A. B. A., Kolpin, D. W., Leung, K. M. Y., Lai, R. W. S., Galbán-Malagón, C., Adell, A. D., Mondon, J., Metian, M., Marchant, R. A., Bouzas-Monroy, A., Cuni-Sanchez, A., Coors, A., Carriquiriborde, P., Rojo, M., Gordon, C., Cara, M., Moermond, M., Luarte, T., & Teta, C. (2022). Pharmaceutical pollution of the world's rivers. *Proceedings of the National Academy of Sciences of the United States of America*, 119(8), Article e2113947119.
- Yang, M., Qiu, W., Chen, J., Zhan, J., Pan, C., Lei, X., & Wu, M. (2014). Growth inhibition and coordinated physiological regulation of zebrafish (*Danio rerio*) embryos upon sublethal exposure to antidepressant amitriptyline. *Aquatic Toxicology*, 151, 68–76.
- Zhang, Y., Lyu, T., Zhang, L., Button, M., Arias, C. A., Weber, K. P., Shi, J., Chen, Z., Brix, H., & Carvalho, P. N. (2019). Microbial community metabolic profiles in saturated constructed wetlands treating iohexol and ibuprofen. *Science of the Total Environment*, 651(2), 1926–1934.