Journal Pre-proofs

Full length article

A ONE-HEALTH ENVIRONMENTAL RISK ASSESSMENT OF CONTAMINANTS OF EMERGING CONCERN IN LONDON'S WATERWAYS THROUGHOUT THE SARS-CoV-2 PANDEMIC

Melanie Egli, Helena Rapp Wright, Olukemi Oloyede, William Francis, Rhys Preston-Allen, Stav Friedman, Guy Woodward, Frédéric B. Piel, Leon P. Barron

PII:	S0160-4120(23)00483-X
DOI:	https://doi.org/10.1016/j.envint.2023.108210
Reference:	EI 108210
To appear in:	*Environment International*
Received Date:	24 May 2023
Revised Date:	4 August 2023
Accepted Date:	12 September 2023

Please cite this article as: M. Egli, H. Rapp Wright, O. Oloyede, W. Francis, R. Preston-Allen, S. Friedman, G. Woodward, F.B. Piel, L.P. Barron, A ONE-HEALTH ENVIRONMENTAL RISK ASSESSMENT OF CONTAMINANTS OF EMERGING CONCERN IN LONDON'S WATERWAYS THROUGHOUT THE SARS-CoV-2 PANDEMIC, *Environment International* (2023), doi: https://doi.org/10.1016/j.envint.2023.108210

A ONE-HEALTH ENVIRONMENTAL RISK ASSESSMENT OF CONTAMINANTS OF EMERGING CONCERN IN LONDON'S WATERWAYS THROUGHOUT THE SARS-CoV-2 PANDEMIC

Melanie Egli,[a,e] Helena Rapp Wright[a,e], Olukemi Oloyede[a,e], William Francis[a,b], Rhys Preston-Allen[c], Stav Friedman[a,e], Guy Woodward[c], Frédéric B. Piel[b,e], Leon P. Barron[a,d,e]*

[a]Environmental Research Group, School of Public Health, Faculty of Medicine, Imperial College London, Sir Michael Uren Hub, 86 Wood Lane, London, W12 0BZ, UK

[b]UK Small Area Health Statistics Unit (SAHSU), Department of Epidemiology & Biostatistics, School of Public Health, Imperial College London, London, UK

[c]Georgina Mace Centre for the Living Planet, Dept. Life Sciences, Imperial College London, Silwood Park, Brackhurst Road SL5 7PY, UK

[d]Dept. Analytical & Environmental Sciences, King's College London, 150 Stamford St., London, SE1 9NH, UK

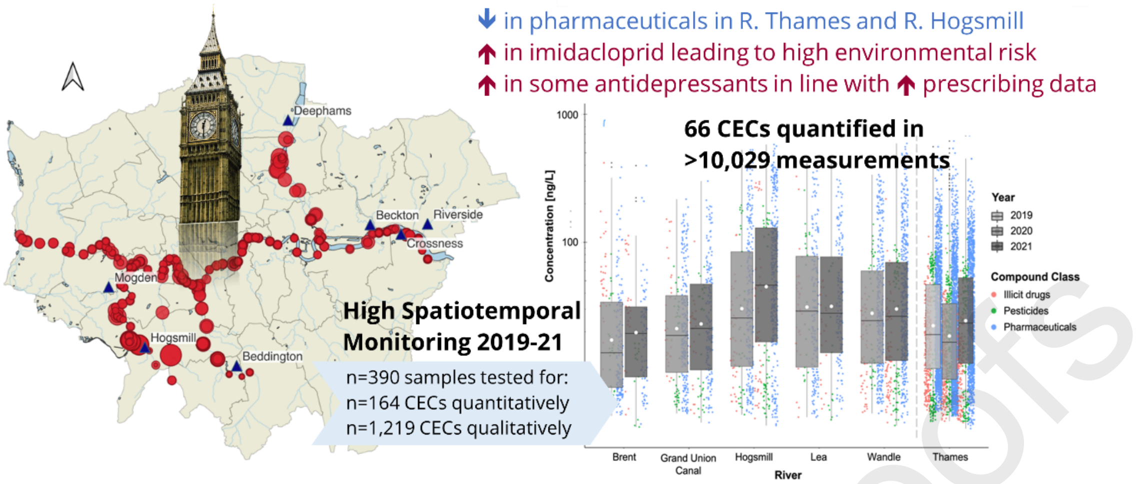
[e]MRC Centre for Environment and Health, Imperial College London, London, UK

*Corresponding Author: leon.barron@imperial.ac.uk

Highlights

- 98 contaminants of emerging concern detected in London's rivers (2019–21)
- Lower pharmaceutical concentrations during lockdown in Rivers Hogsmill and Thames
- 21 compounds had risk quotients >0.1 in seven of 14 water bodies tested
- Imidacloprid of highest and increasing urban risk despite ban in agriculture in 2018
- Low flow, wastewater-impacted waterways at higher risk from CECs

Graphical abstract



Abstract

The SARS-CoV-2 pandemic had huge impacts on global urban populations, activity and health, yet little is known about attendant consequences for urban river ecosystems. We detected significant changes in occurrence and risks from contaminants of emerging concern (CECs) in waterways across Greater London (UK) during the pandemic. We were able to rapidly identify and monitor large numbers of CECs in n=390 samples across 2019–2021 using novel direct-injection liquid chromatography-mass spectrometry methods for scalable targeted analysis, suspect screening and prioritisation of CEC risks. At total of 10,029 measured environmental concentrations (MECs) were obtained for 66 unique CECs. Pharmaceutical MECs decreased during lockdown in 2020 in the R. Thames ($p \leq 0.001$), but then increased significantly in 2021 ($p \leq 0.01$). For the tributary rivers, the R. Lee, Beverley Brook, R. Wandle and R. Hogsmill were the most impacted primarily via wastewater treatment plant effluent and combined sewer overflows. For the R. Hosgmill in particular, pharmaceutical MEC trends were generally correlated with NHS prescription statistics, likely reflecting limited wastewater dilution. Suspect screening of ~1,200 compounds tentatively identified 25 additional CECs at the five impacted sites, including metabolites such as O-desmethylvenlafaxine, an EU Watch List compound. Lastly, risk quotients (RQs) ≥0.1 were calculated for 21 compounds across the whole Greater London freshwater catchment, of which 7 were of medium risk (RQ ≥1.0) and three were in the high-risk category (RQ ≥10), including imidacloprid (RQ=19.6), azithromycin (15.7) and diclofenac (10.5). This is the largest spatiotemporal dataset of its kind for any major capital city globally and the first for Greater London, representing ~16 % of the population of England, and delivering a foundational One Health case study in the third largest city in Europe across a global pandemic.

Keywords

Pharmaceuticals, pesticides, illicit drugs, wastewater, combined sewer overflows, large-scale analysis

1. Introduction

To achieve sustainable urban ecosystems of healthy people, wildlife and environments - a concept commonly described as the ‘One Health’ approach - we need to improve our understanding of how they are altered by human activities, including the growing use of a diverse range of potentially toxic chemicals. Studying the effect of major perturbations, like the recent SARS-CoV-2 pandemic can provide valuable insights in this respect (Lefrançois et al., 2023). The impact of “novel entities”, including chemicals, was recently quantified as being of high risk on a global level (Steffen et al., 2015), and pollution is now considered the third greatest planetary crisis along with climate change and biodiversity loss (UN environment programme (UNEP), 2021). There are currently more than 204 million chemicals on the Chemical Abstracts Service (CAS) Registry, of which ~350,000 are currently licensed for manufacture and sale globally (Persson et al., 2022) and many are strongly associated with urban areas. Overall, little is known about the occurrence, effects and toxicity of these chemicals and their mixtures on human and environmental health. As much as chemicals enrich our lives, it is estimated that each year chemical pollution causes approximately 10 million excess deaths worldwide, representing more fatalities than war and murder (~1 million), alcohol use (~2 million), smoking (~7 million), and even severe illnesses such AIDS, malaria, and tuberculosis (~3 million) (Naidu et al., 2021). The European Union Water Framework Directive (EU WFD) includes fewer than a hundred chemical substances across two lists for regulation and/or monitoring: a “priority substances” list of 45 chemicals or chemical groups; and a “watch list” of 26 chemicals of emerging concern (CECs), which require more urgent understanding regarding their occurrence, fate and effects across multiple environmental compartments.

Globally, a growing proportion of the human population lives in urban environments which is expected to reach 68 % by 2050 (European Commission, 2020). Large cities are particularly complex systems due to the high-density of their resident population, the highly modified natural environment, and the heavy use of an array of chemical products. In many countries, the SARS-CoV-2 pandemic led to dramatic large-scale public health interventions which had a substantial impact on daily life, highlighting the complex interrelations between natural, chemical and societal systems. Although the surge in global demand for plastic (e.g., personal protective equipment) during the pandemic is well documented, such interventions also resulted in significant changes in the use of a wide range of chemicals (e.g., pharmaceuticals), particularly in urban areas. This changing population usage during the recent pandemic therefore had the potential to modulate the environmental risks of chemicals. London is the UK's largest city and, given its combined ~8.8 million residential population, its wider metropolitan area and conurbation, and its well-connected daily commuter belt, UNESCO ranks it as the third most populous megacity in Europe behind Istanbul and Moscow. It accounts for >13 % of the UK residential population and therefore its potential for CEC impacts in the Thames Basin is comparatively much larger than other areas of the country.

In 2019, the Environment Agency (EA) reported occurrence of 41 pharmaceuticals and two lifestyle products in a large-scale study of the R. Thames, from its source to the North Sea, in 37 samples spanning 33 sites (White et al., 2019) with the urbanised, tidal region within Central London being the most impacted by CECs. At the same time, the EA has also pioneered an ambitious programme of semi-quantitative chemical monitoring across England. Despite these new initiatives, arguably more spatiotemporal resolution is required to understand CECs and their risks within estuarine urban catchments like London. Firstly, as waters become saline, the risks of CECs to aquatic life are also predicted to be higher relative to fresh waters (e.g., predicted no-effect concentrations reported by the Norman Network Ecotoxicology Database are generally 10-fold lower in marine water), so the footprint of such a large port city like London demands particular attention. In addition, London's sewer network, like so many other European cities, is a combined system, with 57 overflow points discharging >39 million tonnes of raw sewage to the R. Thames annually (Ofwat, 2023). Currently, a major upgrade to London's sewer system is underway with the construction of a 'Super Sewer' which aims to reduce pollution in the Thames by >95 %, providing further impetus for obtaining high resolution baseline data against which projected improvements in water quality can be ground-truthed.

Identification and routine monitoring of so many chemicals is an enormous analytical challenge, but approaches to rapid monitoring at higher spatiotemporal resolution for larger numbers of CECs are improving at a rapidly accelerating rate. The vast majority of studies to date have required sample clean-up and analyte preconcentration to measure concentrations reliably at the low to sub ng/L concentration range (Menger et al., 2020). However, new direct-injection liquid chromatography-tandem mass spectrometry (LC-MS/MS) and liquid chromatography-high resolution accurate mass spectrometry methodologies (LC-HRMS) have emerged, which offer sufficient sensitivity to rapidly identify sources of large numbers of chemicals in complex environmental samples, such as river water and wastewater (Borrull et al., 2019; Egli et al., 2021; Ng et al., 2020; Ramos et al., 2017; Rapp-Wright et al., 2023; Reemtsma et al., 2013). They also bring several additional advantages, including the need for fewer solvents, reagents and consumables (reducing time and cost), lower sample volume requirements for analysis and cold storage, and reduced impacts from the selectivity of the extraction step in limiting the chemical space coverage. Taken together, these advances represent a step-change with enormous potential to scale up chemical monitoring programmes over both space and time, to help prioritise CEC risks in the environment far more rapidly and sustainably than was previously possible.

Our central hypothesis was that changing public health, chemical usage and activity during the SARS-CoV-2 pandemic resulted in a significant change in CECs in urbanised waterways, using London and the Thames catchment as a case study. Our objectives were: (a) to measure CECs spatiotemporally in waterways in Greater London in the last quarter of 2019, 2020 (during lockdown) and 2021, using both targeted analysis and suspect screening methods; (b) determine whether changes in measured environmental concentrations (MECs) between years were significant and which individual compounds, groups of compounds or classes gave the strongest signals; (c) to determine whether trends in MECs in rivers for pharmaceuticals was reflected in regional prescription statistics; (d) to locate likely sources of CECs in the urban watershed; and (e) to understand what impact changes in MECs had on the environmental risks of CECs and to prioritise them. To the best of our knowledge, this represents by far the most comprehensive environmental study of CEC occurrence and distribution in waterways in any major global city to date. It also acts as an important baseline before the major 'super-sewer' infrastructure upgrade. Most importantly, it is the first study to focus on how a global pandemic influenced CEC contamination and risk in urban waterways demonstrating the 'One Health' approach in practice.

2. Materials and methods

2.1 Materials and reagents

HPLC-MS-grade methanol, isopropanol, acetonitrile and formic acid (> 95 %, v/v) were bought from Sigma-Aldrich (Steinheim, Germany). Ultrapure water (UP) was generated with a resistivity of 18.2 mΩ at 25 °C using a Millipore Milli-Q water purification system (Bedford, MA, USA). A total of 164 reference materials were sourced mostly from Sigma Aldrich (except trimethoprim, Fluka, Buchs Switzerland) for quantitative analysis and were of 97 % purity or higher and in three broad classes: pharmaceuticals (n=97), pesticides (n=56) and illicit drugs (n=11), see the supplementary information for a full list of reference materials. In addition to this, a further 36 stable isotope-labelled internal standards (ILIS) were purchased from QMX (Essex, UK) for quality control and for quantification purposes (see SI (S1) for a complete list of reference materials and ILIS). Several standard mixtures covering all compounds and ILIS were prepared at 0.1, 0.01 or 0.001 µg/mL in methanol and stored at -20 °C to prevent degradation. All standards, prepared samples, matrix-matched standards, blanks and controls were kept in 1.5 mL silanised amber vials (Fisher Scientific, Loughborough, UK). Whatman^{TM} 0.2 µm PTFE membrane filters (GE Healthcare Life Science, Little Chalfont, UK) and 1 mL PlastipakTM syringes (BD, Berkshire, UK) were used for sample pre-filtering after preparation (i.e., adding appropriate standards and ILIS where necessary) and before LC-MS/MS analysis.

2.2 Instrumentation

For all quantitative targeted analysis of trace CECs, a previously published 5.5-minute direct injection LC-MS/MS analytical method was used employing a Shimadzu LCMS-8060 instrument (Shimadzu Corp., Kyoto, Japan) with just 10 µL injection of the filtered water sample pre-spiked with ILIS (see Ng et al., (2020) for reference). For a summary of method performance characteristics, see Table S1. For suspect screening, a similar direct-injection LC-quadrupole-time-of-flight mass spectrometry (QTOF-MS)-based method was used on a Shimadzu LCMS-9030 using data-independent analysis (DIA). A slightly larger injection volume of 40 µL was used to achieve sufficient sensitivity and gradient separations ran over 17.0 minutes. Please see the SI (S2) for more details of both methods.

2.3 River water sampling locations and procedures

Building on our previous study of temporal CEC fluxes in the R. Thames in 2014 from CSOs and wastewater effluents (Munro et al., 2019), we conducted a highly spatially resolved study of the river in November 2019. Following the onset of the SARS-CoV-2 pandemic, an additional and unique opportunity arose to study how changing public health, chemical usage and activity resulted in any significant change in CECs in London's waterways over both space and time. As a result, we subsequently conducted more extensive sampling campaigns across Quarter 4 in both 2020 and 2021. Across all three years, n=390 samples were taken (Figure 1(a)). Campaign 1 (2019) focussed on the R. Thames only and comprised 84 samples taken across 29 sites spanning 60 km distance on a single day (27th November). Sampling direction was against the outgoing tide (from Erith in the east to Kingston in the west). Campaign 2 (2020) ran from 14th October to the 17th December, covering 14 separate sampling days. Water samples were collected again from the R. Thames, as well as detailed longitudinal transects of five auxiliary waterways (n = 133 sites/138 samples) including the Rivers Brent, Hogsmill, Lee/Lea, Wandle and the Grand Union Canal. Campaign 3 (2021) sampling took place from 5th November until 14th December, over 15 separate days (total = 150 sites/168 samples). Several additional single grab samples of other rivers were collected in 2020 and 2021, but these water bodies were not studied in detailed spatially resolved transects. These included the R. Crane, Fray's River, Paddington Arm, Pymmes Brook, Slough Arm, R. Lee, Channelsea River, as well as from the Low Maynard Reservoir near Tottenham Hale, which provides drinking water to London. In the latter two campaigns, selected sites were visited multiple times to investigate inter-day variation (see S3 for more details, and Figure S1 for all river locations).

Samples were collected in 10 L food-grade buckets each with a 10 m rope attached (Amazon.com Inc., London, UK). Buckets were cast into the river and sub-samples were taken in 30 mL Nalgene bottles (Sigma Aldrich, UK). Buckets and sample bottles were pre-washed with methanol and ultrapure water in the laboratory and rinsed with river water (each three times) at each site before taking a sample. Samples were taken in the river itself at safely accessible sites and ~5-10 m from the shoreline, or alternatively from embankments or bridges (see Table S2 for details for each sample). Sample bottles were stored under ice gel packs while in transit. The maximum period from sampling to freezing in the laboratory at -20 °C was 8 h (3-4 hours on average) and chemical analysis for each set was all performed within two weeks of sampling collection.

2.4 Procedures for quantification of target compounds and suspect screening

Quantification was performed using separate external 13-point matrix-matched calibration curves and quality control (QC) samples at two concentration levels for each river and/or date of sampling in line with recommendations proposed by Hernández et al. (2023). All MEC values were derived for each CEC substance in each sample individually and as the average of triplicate LC-MS/MS runs. Samples from the R. Thames were grouped into multiple river segments to prepare pooled matrix for separate calibrations. Freshwater sites were quantified separately from brackish sites. Quantification was performed in the same manner as in previous work (Egli et al., 2021) and more details including the number, concentrations, frequency and composition of matrix-matched calibration curves and QCs are provided in the SI (S3).

For suspect screening, Shimadzu Explorer Library Screening software v3.8 SP1 was used to search a list of n=1,219 compounds, which included the Shimadzu toxicology screening library, Shimadzu pesticide library and additional in-house reference materials data from Imperial College London. This library included compound specific retention time (t_R), MS1 and MS2 data and identification included four degrees of confirmation. i.e., t_R ±0.5 min, accurate m/z 5 ppm of the precursor ion in MS1, at least one fragment in MS2, a library similarity index >45 and an isotopic distribution score >20. In addition, a threshold of 5,000 minimum peak height intensity and signal-to-noise (S/N) of ≥3:1 were used for final shortlisting. Suspect screening was performed on 10 samples (i.e., two samples from each of five water bodies) which were selected based on (a) the occurrence of a relatively large number and concentration of CECs from the R. Brent, R. Hogsmill, R. Wandle, R. Lea and the Grand Union

Canal as part of Campaign 3 (2021) measured using targeted LC-MS/MS analysis as well as (b) a downstream site (see Table S3 for details) on each water body for comparison purposes. All samples for suspect screening derived from freshwater sites. Assignment of confidence levels for all compounds was performed as per the Schymanski framework (Schymanski et al., 2014).

2.5 Data analysis

All graphs were generated using R Studio (Boston, MA, USA, version 1.1.463), Orange (Bioinformatics Lab at University of Ljubljana, Slovenia, version 3.33.0) and Microsoft Office (Redmond, WA, USA, version 16.48). All statistical analyses were performed using R Studio. For comparison with river water measurements, monthly English Prescribing Datasets (EPDs) released by the National Health Service Business Services Authority (NHSBSA) were accessed for 2019-2021 (NHS, 2023) and aligned with Clinical Commissioning Groups (CCGs) whose catchment area overlapped the Greater London catchment area. Prescribed drug concentration was calculated for all detected substances in g/day using R (https://www.R-project.org/ version 3.5.1) by first extracting the quantity (mg) of drug within each medicine prescribed, then multiplying this value by the number of doses prescribed by each registered practice within a CCG. This was followed by summing the quantity of prescribed drug across each of the registered practices. Where the quantity of drug reported for a given medicine referred to a conjugated form of that drug (e.g., bisoprolol as bisoprolol fumarate) the quantity of drug in its unconjugated form was calculated by multiplying the quantity by the molecular weight ratio of drug-to-drug conjugate. The total quantity of each drug prescribed across all selected CCGs in each month was then converted from mg to g and divided by the corresponding number of days for that month.

2.6 Environmental risk assessment (ERA)

Risk calculations were based on Equation 1 where MEC is the measured environmental concentration of a compound from LC-MS/MS analysis (average of triplicate analyses), and $PNEC_{fw}$ represents the lowest predicted no effect concentration in freshwater of a compound sourced from the Norman Network Ecotoxicology database as of December 2022.

$$\text{Risk quotient (RQ)} = \frac{MEC}{PNEC_{fw}} \qquad (1)$$

Thresholds for the RQs were aligned with Palma et al. (2014), i.e., high environmental risk was defined as RQ ≥ 10.0, medium risk as 1.0 – 10.0, low risk as 0.1 – 1.0, and insignificant risk as < 0.1. No RQs were calculable for samples taken from the tidal component of the R. Thames estuary (i.e., brackish water). Interpretation of RQs was performed in two ways including: (a) the standard approach to classify environmental risk using the largest MEC at a particular site to calculate the 'worst case scenario' RQ for each compound for the Greater London catchment overall, a specific water body or timeframe; and (b) the average of all RQs obtained for each substance at all sites in the Greater London area, water body or specific timeframe to understand the spatial risks more generally, including its broad scale and variation across sites (RQ=0 assumed for instances of non-detection of a compound). In addition, and for each specific freshwater site, the total combined risk of the RQs of all compounds was calculated as the sum (ΣRQ).

3. Results and Discussion

3.1 CEC occurrence summary in Greater London's rivers: spatial patterns

Across all 390 samples taken at all sites over the three years (Figure 1(a)), a total of 98 compounds were detected at least once (73 from targeted analysis and 25 additional substances using suspect screening). Of these, 66 compounds were quantifiable (Table S2) with MECs ranging between 3 ng/L (clopidogrel, an anticoagulant) and 3,326 ng/L (salicylic acid, a widely used keratolytic treatment and an aspirin metabolite). The mean of the total combined MECs for all substances quantified at each site across all years was 1,181 ±905 ng/L (ranging from 87 to 5,505 ng/L at each site) and the mean concentration ±standard deviation for individual CECs was 46 ±86 ng/L. The top five compounds on average were pharmaceuticals and were highly variable (Figure 1(b)), i.e., salicylic acid (190 ±295 ng/L), carbamazepine (an antipsychotic/antiepileptic drug at 127 ±109 ng/L), clarithromycin (a macrolide antibiotic at 122 ±163 ng/L), tramadol (an opioid analgesic at 109 ±84 ng/L), and diclofenac (a non-steroidal anti-inflammatory drug at 100 ±88 ng/L). Of these, both diclofenac and clarithromycin have been included in previous EU WFD Watch Lists with negative environmental impacts on wildlife reported (Herrero-Villar et al., 2020) and/or promotion of antimicrobial resistance (Lee et al., 2021; Paulshus et al., 2019). In total, 11 substances had quantifiable level frequencies >90 %. The top five compounds by frequency were also all pharmaceuticals or metabolites, i.e., tramadol (positive in 98 % of all 390 samples), carbamazepine (97 %), venlafaxine (an antidepressant, 95 %), benzoylecgonine (cocaine metabolite, 95 %) and bisoprolol (a beta-blocker medication, 94 %). Of these, venlafaxine was recently included in the latest EU WFD Watch List along with its metabolite O-desmethylvenlafaxine (Official Journal of the European Union, 2022).

In comparison to other studies of the region for CECs, MECs were relatively similar for common substances overall, but the spatial resolution achieved was much larger than any previous study including the EA's semi-quantitative chemical monitoring programme running since 2005 (Environment Agency, 2022). Within Greater London, LC-MS data exists within this programme for just 19 sites (Figure S1) and this is insufficient for exact identification of CEC sources including regular wastewater and storm water discharges and combined sewer overflows (CSOs). In addition, a 3 % occurrence of sewer misconnections in London is estimated (Dunk et al., 2008; Ellis and Butler, 2015), but exact knowledge of where these are located is lacking. Lastly, agricultural and wastewater contamination is also likely carried into this region from upriver sites. Maximum total MECs from an EA study in 2019 were approximately double those reported in our work (10.24 µg/L), but the selection of compounds for monitoring was also somewhat different (19/43 compounds in common (White et al., 2019)). Within this, sucralose (an artificial sweetener) alone was estimated to constitute between ~13-33 % of the total CEC concentrations across all samples, but was not monitored herein as it likely presents a relatively lower risk to aquatic life (despite being a good marker of wastewater influx (Li et al., 2020)). The number of pharmaceuticals detected in the EA study was almost double that recently detected in the R. Thames as part of a global assessment of pharmaceutical contamination in rivers (n=26 detected out of 61 pharmaceuticals monitored across nine samples with a mean total concentration of 3,661 ng/L) (Wilkinson et al., 2022), showing again that there was high variation in CEC occurrence depending on where and when samples are taken and the number of analytes targeted.

3.2 Chemical signature analysis and identification of major contamination sites

3.2.1. Chemical signature analysis from targeted analysis data

Several CEC sources were identified and wastewater was identified as the dominant driver. Hierarchical cluster analysis (HCA) of all MEC data (Figure 2(a)) and across all campaigns revealed some clear groupings and these were considered in terms of (a) sites and (b) analytes detected to indicate potential sources of contamination (for full details of HCA for individual samples and examples of inter-/intra-day MEC variability in each year, see Figures S2 and S3, respectively). Firstly, in terms of site groupings in HCA, there were two major clusters, i.e., those with and without wastewater source contamination. For the former, this was dominated by sampling sites on tributary rivers downstream of major WWTPs or CSO discharge points and regardless of the year sampled (Figure S1). All nine WWTPs in the London area run at an average of 96 % of their population equivalent (PE) capacity, which is higher than the UK average (88 %) (Defra Data Services Platform, 2020) meaning that CSOs are potentially more likely sources of contamination, especially in smaller waterbodies. For example, a very small stream, the Beverley Brook, had the highest MECs across the whole study (maximum total MEC=5,505 ng/L for n=40 CECs) and it is regularly impacted by CSO discharges. Sampling points at confluences of these heavily impacted tributary rivers with the R. Thames also clustered together in this grouping and presented consistently higher MECs even than those at large WWTP discharge points in the estuary itself (e.g., Mogden, Crossness, Beckton, Riverside and Longreach WWTPs; combined population equivalent (PE): ~8.5 M (Defra, 2020)). The second grouping of sites contained mostly those from the rest of the R. Thames grouped together with auxiliary bodies that had no obvious wastewater treatment plant effluent or major CSO activity (i.e., Rivers Brent, Crane, Grand Union Canal, Fray's River, etc.). Some contamination was still evident in this grouping, but was likely to originate from other sources, such as surface run-off, leachate, storm/foul sewer misconnections, leakages and potentially direct dumping of materials.

With respect to chemical clustering, two main CEC groupings existed following HCA, across all data, which enabled further interpretation for elucidating chemical signatures of wastewater contamination (Figure 3(a)). The first major grouping of 27 compounds represented signatures of treated wastewater effluent, such as diclofenac, temazepam and tramadol (Munro et al., 2019). Other compounds within this cluster have been shown to be removed only in part or not at all during wastewater treatment (e.g., trimethoprim and carbamazepine) and were more indicative of general wastewater influx (both treated and untreated). Within the second larger grouping of 39 compounds, 31 were drug-related and eight were pesticides. Most compounds were generally lower in concentration than those in the first group and/or detected at lower frequency. However, those CECs measured at higher concentration in this second grouping were indicative of raw wastewater influx, either from CSOs, foul sewer misconnections and/or runoff. The most obvious example was salicylic acid, which has been shown to be efficiently removed during treatment (Camacho-Muñoz et al., 2012; Martín et al., 2012). Other recognised markers of CSOs included benzoylecgonine, cocaine, sulfapyridine, bezafibrate, diazepam, caffeine and furosemide, many of which also fell within this grouping and occurred together with salicylic acid at some sites, especially where CSOs were more prevalent (e.g., the Beverley Brook and R. Hogsmill sites). However, sulfapyridine did not follow this trend and lay in the first grouping of 27 compounds. Additionally, caffeine was not included in the targeted analysis method due to low retention on the short analytical column. Similarly high-use polar compounds indicative of wastewater influx, such as metformin, eluted too close to the void and therefore these data were also excluded.

3.2.2 Suspect screening for additional substances

Based on the criteria set for compound identification, suspect screening of the most impacted sites in five water bodies each with a sample from a downstream site for comparison resulted in detection of 32 compounds at Confidence Level 2(a) (Schymanski et al., 2014). Of these, 25 were additional to the targeted analysis using LC-MS/MS (Table S3). All but three compounds were related to pharmaceuticals, and these were pesticides. Only one compound was detected in every sample (i.e., amisulpride, an antipsychotic medication). Seven compounds were transformation products/metabolites, and four of these had their parent compound present in the same samples detected using either of the two analytical methodologies (i.e., O-desmethylcitalopram and O-desmethylvenlafaxine, benzoylecgonine and O-desmethyltramadol). HCA based on the normalised peak areas of all 32 compounds resulted in clear groupings of samples from the same water body (Figure 2(b)). The R. Lea samples contained the most compounds (n=32) and at generally higher signal intensity, followed by the R. Hogsmill (n=31), R. Wandle (n=22), Grand Union Canal (n=12) and R. Brent (n=7). However, as this is a direct-injection LC-HRMS method, the number of compounds detected is expected to be lower than if pre-concentration was used for samples. Water bodies showed particularly high intensity signals for lamotrigine, O-desmethylvenlafaxine (also an EU WFD Watch List pharmaceutical metabolite) and carbamazepine. Suspect screening of the R. Thames in 2014 identified lamotrigine and carbamazepine as being more prevalent in wastewater effluent than influent and most of these samples were close to outfalls of major WWTPs (Munro et al., 2019). Conversely, caffeine and benzoylecgonine were detected in the R. Brent site, indicating a predominance of untreated wastewater influx, and aligned with targeted analysis data.

3.3 Spatiotemporal variation in CECs across the SARS-CoV-2 pandemic

3.3.1 Greater London pandemic timeline, population and impact of CSO events

The UK entered its first national lockdown on 23rd March 2020 for four months (Brown and Kirk-Wade, 2021) when non-essential business was closed and strict public restrictions were applied. A second national lockdown occurred in November 2020. In the 2021 census, the recorded population of Greater London was 8,799,800. London's weekday population was previously estimated to increase by 20 % over the residential population (~1.8 million people (London datastore, 2015)), including mainly the commuting workforce. Examination of measured ammonia concentrations in influent from the largest WWTP (Beckton, which serves most of Central and East London) revealed a ~15 % population equivalent reduction during lockdown (Figure S4(a)). In addition, a drop in total journeys within London of ~60 % occurred between Campaign 1 and 2, and remained ~30 % lower than pre-pandemic levels by Campaign 3 (Figure S4(b)) (London datastore, 2023). Regional rail statistics indicated that 340 million fewer journeys (>77 %) were made to/from London from April to March 2020-2021 (Office of Rail and Road, 2022, 2021). Therefore, this drop in daily transitory population was likely to significantly contribute to lower sewer loadings, particularly of pharmaceuticals and lifestyle chemicals such as illicit drugs.

In London, even a small rainfall event can trigger CSOs, but dates and volumes were not publicly available, only the number of spill hours and duration. Rainfall (Table S4) compared across each of the last three months of each year (Q4) were not statistically different (2.7 ±3.8, 3.0 ±6.0 and 1.9 ±4.5 mm/day in 2019, 2020 and 2021, respectively). In 2019, where R. Thames sampling occurred on one single day, no CSOs were reported to fall within 48-h of samples being taken. In 2020, 11 CSOs occurred from October – December in this region and of these, only one CSO occurred within 48-hours of sampling (14th Nov). No formal R. Thames CSO notifications existed for 2021.

3.3.2 CECs in the R. Thames across the pandemic, from 2019-2021

Figure 3 shows spatial CEC occurrence across all locations on the R. Thames by compound class during lockdown in 2020 (for all years, see Figure S5). For the 64 CECs quantifiable in the R. Thames, the median and interquartile range of MECs decreased slightly in 2020 during the SARS-CoV-2 lockdown period (Figure 4), and then returned to statistically higher concentrations in 2021 ($p \leq 0.05$). Relevant river flow data in the non-tidal region at Kingston were only available for 2019 and 2020 and no significant difference was observed (UK Centre for Ecology & Hydrology, 2023), respectively (Figure S6). However, a deeper assessment of MECs by compound class revealed important statistical differences, particularly for pharmaceuticals. The most significant MEC decreases during the 2020 lockdown period were attributable to three medicinal compounds: (temazepam - an antidepressant and treated effluent marker; lidocaine - an anaesthetic and cocaine cutting agent; and clopidrogel - an antiplatelet medication) and a neonicotinoid insecticide (acetamiprid). Each of these MECs rose again by Campaign 3 in 2021 (Figures 5). There were also significant increases in MECs just in 2020, including bisoprolol and propranolol (both beta-blockers), bezafibrate (an antilipemic and CSO marker), diclofenac (a non-steroidal anti-inflammatory and treated effluent marker), salicylic acid (an analgesic and CSO marker) and cocaine (illicit drug and also a CSO marker). For all MECs across all years please see Figure S7. Despite matching the trends in some cases, comparison of MECs across all compounds in the R. Thames across all three years with NHS prescription data for Greater London revealed no consistent or reliable associations even for prescription-only medications. This was also the case for illicit drugs like cocaine and its metabolite benzoylecgonine, whose trends did not match as expected, likely due to varying and complex sources of direct disposal and wastewater influx points to the river. Analysis of untreated wastewater influent is currently a better approach to track drug use trends in a catchment and for epidemiology-type studies (González-Mariño et al., 2020). The UK Chemicals Investigation Programme (CIP) has provided residue measurements in monthly grab influent/effluent wastewater and river water samples since 2010 in England and Wales (UK Water Industry Research, 2022). This dataset unfortunately did not cover contamination in Greater London waterways comprehensively (data available for just four sites in 2020 and 2021 and mostly for only one to two grab samples per month per site, with mostly fewer than five analytes each). No CIP data existed for any common pharmaceuticals to this study WWTP influent to help further interpret trends.

The temporal trends for pesticide occurrence were mixed. In contrast to acetamiprid, imidacloprid MECs increased across the three campaigns. CIP data was available for wastewater for Mogden WWTP (PE=1.96 million) (Defra Data Services Platform, 2020) in West London between September 2020 and September 2021 which discharges to the R. Thames. Imidacloprid concentrations increased in this period (i.e., from 62 ng/L, n=12 from Sept 2020-June 2021 to 154 ng/L, n=6 in Aug-Sept 2021) which may explain some of this riverine MEC increase. Across all 390 samples, including auxiliary water bodies, it was quantifiable a total of 162 times (41 %), despite being banned in the EU/UK for all outdoor use in 2018 (Official Journal of the European Union, 2018) and along with two other neonicotinoids, thiamethoxam and clothianidin, due to their toxicity to invertebrates (Goulson, 2013; Official Journal of the European Union, 2009). Imidacloprid's permitted uses now include indoor gardening/greenhouses and as a veterinary parasiticide, mainly for companion animals. Other pesticides such as terbutryn, simazine (both now priority hazardous substances under the EU WFD) and piperophos were quantified for the first time and in statistically higher concentrations during the lockdown period than in 2021. Apart from any remaining occurrence from CSOs that year, it remains unclear why this was the case.

3.3.3. Comparison with CEC occurrence in tributaries and auxiliary water bodies, 2020-2021

To assess changes in these smaller water bodies, we focused only on those where detailed spatiotemporal data were available (i.e., five auxiliary waterways which had detailed longitudinal transect sampling performed, as Figure 4). On average, decreased MECs overall were statistically significant only in the R. Hogsmill ($p \leq 0.001$). This river is heavily impacted from wastewater influx including a major WWTP discharge site and multiple CSOs. Lower MECs during lockdown were dominated by lower pharmaceutical contamination ($p \leq 0.001$) overall (Figure S8). It was not possible to distinguish MEC changes overall with respect to contributions from either CSO or treated wastewater markers, with the exception of a few individual compounds such as benzoylecgonine and diclofenac. Overall however, MECs in this river followed NHS prescribed medication trends more than any other river studied (see Figures S9 and S10). This was likely for several reasons: (a) it received treated effluent from a major WWTP as well as CSOs within the South London area; (b) it had the lowest recorded flow of the three wastewater-impacted tributaries and likely resulting in lower dilution (1.2 ±1.8 m^3/s across 2019-21, Figure S6); and (c) the R. Hogsmill, as well as the R. Wandle and R. Brent all rise within the Greater London catchment area and therefore are unlikely to be influenced by much transport of chemical residues into the sampling zone from beyond the city. Regarding increases in some anti-depressant MECs (particularly for amitriptyline and citalopram), prescriptions for antidepressants have generally increased over recent years, and monthly data peaked during lockdown periods (The Official Journal of the Royal Pharmaceutical Society, 2021)). Similar peaks were also recorded during the second and third lockdowns in December 2020 and January 2021. In addition, in the UK, there are about 600,000 people living with epilepsy (~1 in 100 people) (Epilepsy action, 2019). Young Epilepsy UK conducted a study with nearly 300 young people whereby 23 % of participants reported difficulties to access medication during lockdown (Young Epilepsy, 2020). The higher use and MECs for carbamazepine were consistent with findings of increased seizure occurrence of epilepsy patients following the pandemic. It is important to highlight the limitations of NHS-prescribing data that might apply to the time-span of this study: as data originate from reimbursement claims (e.g., from pharmacies), they do not always perfectly align with the date of prescription and can differ by several months. Secondly, data represent items prescribed by practices in England, but these can be dispensed in the wider UK. By extension, if the daily migrant population resides outside of London, their prescriptions may be dispensed in different locations that might not be included in the Greater London dataset and the latter was therefore potentially susceptible to mismatches in space and time during the pandemic. Among the pesticides, both imidacloprid and terbutryn MECs increased in the R. Hogsmill from 2020-21 ($p \leq 0.05$).

Like the R. Hogsmill, changes in MECs in the R. Wandle were also significant for pharmaceuticals ($p \leq 0.05$) and similar general trends were evident for citalopram, ketamine, lidocaine, diphenhydramine and carbamazepine (Figure S11). In contrast, significant decreases in MECs for the sulfonamides and diclofenac occurred in the R. Wandle. Associations of MECs with NHS data for this river were less obvious. In the R. Lee/Lea, the only overall statistical changes in MECs by class between 2020-21 were for pesticides (driven by an increase in atrazine, and a decrease in imidacloprid and terbutryn) and an illicit drug (cocaine, which increased). At the specific compound level however, statistical MEC changes were observed in the R. Lee/Lea for several pharmaceuticals too, including atorvastatin, bezafibrate and salicylic acid (which both increased) and sulfamethoxazole and verapamil (which decreased). The R. Lea passes through ~50 km of rural area before entering Greater London and so pandemic impacts within the city itself would be unlikely to be the only source of such changes. No major changes in MECs for any overall compound class were observed in either the Grand Union Canal or the R. Brent. Some statistical changes were observed for individual compounds, but generally concentrations were much lower overall and <50 ng/L in total (Figures S13 and S14). Further interpretations of MECs in all rivers studied are given in S4 in the Supplementary Information.

3.4 Environmental risk assessment in freshwaters

Aside from MECs, any changes in environmental risk were evaluated across all 151 freshwater samples. A total of 21 CECs presented a minimum of ‘low risk’ at least once (from a total of n=963 instances where RQs were ≥0.1). All remaining substances with RQ <0.1 were considered of negligible environmental risk. The risk assessment performed here utilised PNEC data from the Norman ecotoxicology database. Therefore, RQ calculations may be subject to change if PNECs either become obsolete or are measured more accurately in the future. With the benefit of hindsight, a limitation of this study was the lack of inclusion of some antiviral and antibiotic medications used to treat SARS-CoV-2 in the analytical method to enable an environmental risk assessment to be performed like in other works (Cappelli et al., 2022; Domínguez-García et al., 2023; Galani et al., 2021; Kumari and Kumar, 2022; Reinstadler et al., 2021). However, several monitored substances were used for the treatment of symptoms, including other antibiotics (e.g., trimethoprim and macrolides), analgesics/anti-inflammatories (e.g., morphine and ibuprofen) and several treatments to combat depression/anxiety (e.g., benzodiazepines and haloperidol (Almeida et al., 2023; National Institute for Health and Care Excellence (NICE), 2023)). In terms of maximum risk across the whole Greater London catchment, and across all years, the top five compounds were imidacloprid (RQ=19.6, R. Lea close to a WWTP outlet, 2020), azithromycin (RQ=15.7, Beverley Brook close to a CSO vent, 2021), diclofenac (RQ=10.5, R. Hogsmill close to a WWTP outlet, 2020), acetamiprid (RQ=8.0, R. Hogsmill close to the same WWTP outlet, 2020) and clarithromycin (RQ=5.9, Beverley Brook close to the same CSO vent as for azithromycin, 2021) (Figure 6(a)-(c)). Taking the average RQ calculated for all compounds across all freshwater sites (setting RQ=0 for cases of non-detection), the same top five compounds were shortlisted and all peaked in 2020. When examining all calculated RQ data combined across all 151 samples, no statistical difference was observed between 2020 and 2021 across all waterways. However, on an individual compound level, some differences were significant (Figure S15). Among the top five highest risk compounds, significantly higher RQs for imidacloprid ($p \leq 0.001$) and diclofenac ($p \leq 0.01$) were observed on average during lockdown in freshwaters. Conversely, lower RQs on average were calculated for azithromycin ($p \leq 0.01$). Upon closer inspection of multiple sites along the auxiliary waterways (Figure 7), high RQs were especially associated with WWTP outlets and sites with strong CSO impacts. For the Grand Union Canal and the R. Brent, clear signals for similarly large sources of wastewater influx were not apparent (Figure S16).

The RQs calculated for imidacloprid were of particular concern. It has also been detected in aquatic invertebrates and recently high concentrations have been reported in urban catchments in the UK, despite its agricultural ban (Miller et al., 2021, 2019). Sources of this compound in domestic wastewater have been ascribed both directly and indirectly to pet treatment activities, with possible sources including wash-off from pet bathing at home, washing of owner hands following treatment application, washing of bedding and clothing with contact to treated animals, direct disposal of litter material to sewerage systems, and surface run-off to shores (Perkins and Goulson, 2023; Preston-Allen et al., 2023). Despite an estimated 22.1 million pets (10.2 million dogs, 11.1 million cats, 1 million rabbits) living in UK households (PDSA, 2022), no data is currently available to support anecdotal claims of markedly increased pet ownership across the pandemic, although the individual rate of treatment of animals has increased in recent years (PDSA, 2019). For any indoor greenhouse usage, some direct introduction to wastewater networks seems feasible, but this is considered unlikely to be the major source in comparison to pet applications.

Of the other medium-to-high risk compounds, the decreased risks observed for the two macrolide antibiotics, azithromycin and clarithromycin, during lockdown were interesting. This finding was not consistent with other studies which monitored these and other substances used for SARS-CoV-2 treatment elsewhere (Cappelli et al., 2022; Domínguez-García et al., 2023; Galani et al., 2021; Kumari and Kumar, 2022; Reinstadler et al., 2021). In the UK, the use of antimicrobials was especially high in hospitalised SARS-CoV-2 patients to treat secondary or co-infections (Russell et al., 2021) and also in dental treatment, but, perhaps surprisingly, not in general healthcare practice in London (Palmer and Seoudi, 2021). As a possible explanation or the latter it has been suggested that ‘social distancing’ and home working reduced transmissibility of other infectious diseases and that this was evident also in the number of emergency room presentations and (remote) consultations with general practitioners in London during lockdowns (Zhu et al., 2021). However, prescribing remained lower even after restrictions were relaxed and the evaluation of clinical outcomes regarding infections, hospital admissions and deaths due to potential delayed treatment is needed. NHS prescribing data for both clarithromycin and azithromycin decreased generally across Greater London to its lowest level in 2020 over the period studied (Figure S9). Diclofenac has been the focus of many published environmental occurrence studies (Sathishkumar et al., 2020), including in the UK for nearly two decades (Ashton et al., 2004; Johnson et al., 2007; White et al., 2019). It can be harmful to aquatic organisms and has proposed environmental quality standards (EQS) of 100 ng/L and 10 ng/L for freshwater and saltwater, respectively. Using the freshwater EQS alone, MECs here were higher than this in 31 % of all samples taken in the catchment (i.e., 109 of 351 samples where diclofenac was quantifiable). The MECs for some antidepressants and antipsychotics in freshwaters resulted in potential risks to aquatic life. For the serotonin reuptake inhibitors (SSRIs) for example, 18 samples yielded RQs>1.0 for citalopram (maximum RQ =1.7 in the Beverley Brook near a CSO vent, of n=127 MECs) and 10 for sertraline (maximum RQ = 7.0 in the R. Hogsmill at a WWTP outfall) even though detection frequency was low for this compound. There has been an increasing focus on these compounds and their varied effects on aquatic life, including reduced locomotion, feeding, and decreased body size in fish (Bertram et al., 2018; Kellner et al., 2018; Ziegler et al., 2020) and premature larval release in freshwater mussels (Hazelton et al., 2013). Recent work in our group showed that citalopram and sertraline both represented the highest single-contaminant concentrations measured in the mudsnail *Peringia ulvae* sampled downstream of an urban WWTP in the UK (Miller et al., 2021). Other antidepressants amitriptyline and venlafaxine showed a maximum RQ of 0.8 and 0.4, showing that they still both posed low risks overall despite an increase in prescriptions in Greater London across the pandemic. Lastly, thousands of houseboats are moored across the entire catchment and such sites generally showed few obviously increased risks. However, a cluster of houseboats existed at one particular site on the R. Brent downstream of the confluence with the canal and which coincided with a relatively larger risk in lockdown in 2020 (Figure S16). A CSO located nearby however could be the source given the similar general chemical signature obtained. On the R. Thames a similar cluster of houseboats and a CSO were located near Twickenham and Teddington Lock (Figure 3) with higher MECs for analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) again during lockdown in 2020, but RQs could not be reliably calculated due to its brackish nature. Boat owners are legally required to dispose of onboard waste through approved services (Port of London Authority, 2014) and, despite these two instances, this source of CEC exposure was considered minor overall. Further interpretation of risks from specific compounds are given in S4.

5. Conclusion

Large-scale watercourse monitoring at exceptionally high spatial resolution in the Greater London area across the SARS-CoV-2 pandemic resulted in detection of 98 CECs, with two-thirds of these being quantifiable. In the R. Thames, pharmaceutical MECs decreased significantly during the 2020 lockdown period, with riverine concentrations exceeding pre-pandemic levels the following year. Potential reasons for this include a large reduction (by >77 %) in daily migration to and from the city during lockdowns, as well as reduced movement within the city itself (by >60 %), which was also reflected in reduced ammonia measurements in WWTP influent. The chemical signatures of treated wastewater (34 compounds) and CSOs/raw wastewater discharges (27 compounds) were differentiable using HCA, with the Beverley Brook and the River Hogsmill being the most impacted sites by both wastewater source types overall. For R. Hogsmill in particular, temporal trends in MECs reflected NHS prescribing data, including for substances used to treat the symptoms of SARS-CoV-2 (e.g., anti-inflammatories, analgesics and antibiotics). Antiviral drugs were not included in the study. Daily prescribed mass of antidepressant and antipsychotic medications in Greater London rose across the pandemic, but only some of these were represented in matched trends in riverine MECs, likely as a result of extensive metabolism. These generally represented low-insignificant risk to aquatic life, except for two SSRIs and one antipsychotic (citalopram, sertraline and clozapine, where RQs lay between 1.0 and 10 (i.e., moderate risk)). Of all CECs measured in freshwaters, high risk to aquatic life was evident, in decreasing order, for imidacloprid, azithromycin and diclofenac (all RQs ≥10). This study delivers a foundational baseline to assess not just the historical impact of the SARS-CoV-2 pandemic in near real-time, but also to gauge future changes in their occurrence and sources at high spatiotemporal resolution, including the impacts of a major sewer upgrade in London that is planned to reduce aquatic wastewater pollution by 95 %.

Acknowledgments Melanie Egli thanks the Medical Research Council for financial support. Leon Barron and Frédéric Piel thank the National Institute for Health and Care Research (NIHR) for funding under the Health Protection Research Units in Environmental Exposures and Health and Chemical and Radiation Threats and Hazards, both partnerships between the UK Health Security Agency and Imperial College London. The views expressed are those of the authors and not necessarily those of the NIHR, UK Health Security Agency or the Department of Health and Social Care. Guy Woodward thanks the Natural Environment Research Council (NE/S000348/1) for support. In addition to the authors involvement, special thanks are extended to those who assisted with grab sampling including Luc Barron Hein, Keng Tiong Ng, Rachel Irlam, Alicia Hartmann, Lucy Birkitt and Alex Richardson. Thanks are also extended to Martin Whitehead and Annalisa Sheehan for their assistance with supporting data.

CRediT Statement: Melanie Egli: Conceptualisation, Methodology, Software, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – Review & Editing; Visualisation; **Helena Rapp Wright:** Conceptualisation, Methodology, Validation, Formal Analysis, Investigation, Resources, Data Curation, Writing – Review & Editing; **Olukemi Oloyede:** Investigation, Review & Editing; **William Francis:** Software, Formal Analysis, Data Curation, Review & Editing, Visualisation; **Rhys Preston-Allen:** Software, Data Curation, Review & Editing, Visualisation; **Stav Friedman:** Writing – Review & Editing; **Guy Woodward:** Conceptualisation, Writing – Review & Editing; **Frederic B. Piel:** Conceptualisation, Writing – Review & Editing, Supervision, Project Administration, Funding Acquisition; **Leon P. Barron:** Conceptualisation, Methodology, Formal Analysis, Resources, Data Curation, Writing - Original & Draft, Writing – Review & Editing; Visualisation, Supervision, Project Administration, Funding Acquisition.

References

Almeida, A., De Mello-Sampayo, C., Lopes, A., Carvalho Da Silva, R., Viana, P., Meisel, L., 2023. Predicted Environmental Risk Assessment of Antimicrobials with Increased Consumption in Portugal during the COVID-19 Pandemic; The Groundwork for the Forthcoming Water Quality Survey. Antibiotics 12, 652. https://doi.org/10.3390/antibiotics12040652

Ashton, D., Hilton, M., Thomas, K.V., 2004. Investigating the environmental transport of human pharmaceuticals to streams in the United Kingdom. Science of The Total Environment 333, 167–184. https://doi.org/10.1016/j.scitotenv.2004.04.062

Bertram, M.G., Ecker, T.E., Wong, B.B.M., O'Bryan, M.K., Baumgartner, J.B., Martin, J.M., Saaristo, M., 2018. The antidepressant fluoxetine alters mechanisms of pre- and post-copulatory sexual selection in the eastern mosquitofish (Gambusia holbrooki). Environmental Pollution 238, 238–247. https://doi.org/10.1016/j.envpol.2018.03.006

Borrull, J., Colom, A., Fabregas, J., Pocurull, E., Borrull, F., 2019. A simple, fast method for the analysis of 20 contaminants of emerging concern in river water using large-volume direct injection liquid chromatography-tandem mass spectrometry. Analytical and Bioanalytical Chemistry 411, 1601–1610. https://doi.org/10.1007/s00216-019-01602-x

Brown, J., Kirk-Wade, E., 2021. Coronavirus: A history of "Lockdown laws" in England.

Camacho-Muñoz, D., Martín, J., Santos, J.L., Aparicio, I., Alonso, E., 2012. Effectiveness of Conventional and Low-Cost Wastewater Treatments in the Removal of Pharmaceutically Active Compounds. Water Air Soil Pollut 223, 2611–2621. https://doi.org/10.1007/s11270-011-1053-9

Cappelli, F., Longoni, O., Rigato, J., Rusconi, M., Sala, A., Fochi, I., Palumbo, M.T., Polesello, S., Roscioli, C., Salerno, F., Stefani, F., Bettinetti, R., Valsecchi, S., 2022. Suspect screening of wastewaters to trace anti-COVID-19 drugs: Potential adverse effects on aquatic environment. Science of The Total Environment 824, 153756. https://doi.org/10.1016/j.scitotenv.2022.153756

Defra, 2020. Defra Data Services Platform [WWW Document]. URL https://environment.data.gov.uk/portalstg/home/item.html?id=9428644c0fec4ffa95c9422354649b24 (accessed 5.7.23).

Defra Data Services Platform, 2020. Urban Waste Water Treatment Directive Treatment Plants [WWW Document]. URL https://environment.data.gov.uk/portalstg/sharing/rest/content/items/9428644c0fec4ffa95c9422354649b24 (accessed 10.31.22).

Domínguez-García, P., Rodríguez, R.R., Barata, C., Gómez-Canela, C., 2023. Presence and toxicity of drugs used to treat SARS-CoV-2 in Llobregat River, Catalonia, Spain. Environ Sci Pollut Res 30, 49487–49497. https://doi.org/10.1007/s11356-023-25512-9

Dunk, M.J., McMath, S.M., Arikans, J., 2008. A new management approach for the remediation of polluted surface water outfalls to improve river water quality. Water & Environment J 22, 32–41. https://doi.org/10.1111/j.1747-6593.2007.00083.x

Egli, M., Hartmann, A., Rapp Wright, H., Ng, K.T., Piel, F.B., Barron, L.P., 2021. Quantitative Determination and Environmental Risk Assessment of 102 Chemicals of Emerging

Concern in Wastewater-Impacted Rivers Using Rapid Direct-Injection Liquid Chromatography—Tandem Mass Spectrometry. Molecules 26, 5431. https://doi.org/10.3390/molecules26185431

Ellis, J.B., Butler, D., 2015. Surface water sewer misconnections in England and Wales: Pollution sources and impacts. Science of The Total Environment 526, 98–109. https://doi.org/10.1016/j.scitotenv.2015.04.042

Environment Agency, 2022. Water quality monitoring data GC-MS and LC-MS semi-quantitative screen [WWW Document]. URL https://www.data.gov.uk/dataset/0c63b33e-0e34-45bb-a779-16a8c3a4b3f7/water-quality-monitoring-data-gc-ms-and-lc-ms-semi-quantitative-screen

Epilepsy action, 2019. Epilepsy facts and terminology [WWW Document]. URL https://www.epilepsy.org.uk/press/facts (accessed 9.2.22).

European Commission, 2020. Developments and Forecasts on Continuing Urbanisation [WWW Document]. URL https://knowledge4policy.ec.europa.eu/foresight/topic/continuing-urbanisation/developments-and-forecasts-on-continuing-urbanisation_en#:~:text=Based%20on%20previously%20accepted%20definitions,urban%20population%20will%20nearly%20double. (accessed 5.11.23).

Galani, A., Alygizakis, N., Aalizadeh, R., Kastritis, E., Dimopoulos, M.-A., Thomaidis, N.S., 2021. Patterns of pharmaceuticals use during the first wave of COVID-19 pandemic in Athens, Greece as revealed by wastewater-based epidemiology. Science of The Total Environment 798, 149014. https://doi.org/10.1016/j.scitotenv.2021.149014

González-Mariño, I., Baz-Lomba, J.A., Alygizakis, N.A., Andrés-Costa, M.J., Bade, R., Bannwarth, A., Barron, L.P., Been, F., Benaglia, L., Berset, J., Bijlsma, L., Bodík, I., Brenner, A., Brock, A.L., Burgard, D.A., Castrignanò, E., Celma, A., Christophoridis, C.E., Covaci, A., Delémont, O., Voogt, P., Devault, D.A., Dias, M.J., Emke, E., Esseiva, P., Fatta-Kassinos, D., Fedorova, G., Fytianos, K., Gerber, C., Grabic, R., Gracia-Lor, E., Grüner, S., Gunnar, T., Hapeshi, E., Heath, E., Helm, B., Hernández, F., Kankaanpaa, A., Karolak, S., Kasprzyk-Hordern, B., Krizman-Matasic, I., Lai, F.Y., Lechowicz, W., Lopes, A., López de Alda, M., López-García, E., Löve, A.S.C., Mastroianni, N., McEneff, G.L., Montes, R., Munro, K., Nefau, T., Oberacher, H., O'Brien, J.W., Oertel, R., Olafsdottir, K., Picó, Y., Plósz, B.G., Polesel, F., Postigo, C., Quintana, J.B., Ramin, P., Reid, M.J., Rice, J., Rodil, R., Salgueiro-González, N., Schubert, S., Senta, I., Simões, S.M., Sremacki, M.M., Styszko, K., Terzic, S., Thomaidis, N.S., Thomas, K.V., Tscharke, B.J., Udrisard, R., Nuijs, A.L.N., Yargeau, V., Zuccato, E., Castiglioni, S., Ort, C., 2020. Spatio-temporal assessment of illicit drug use at large scale: evidence from 7 years of international wastewater monitoring. Addiction 115, 109–120. https://doi.org/10.1111/add.14767

Goulson, D., 2013. REVIEW: An overview of the environmental risks posed by neonicotinoid insecticides. J Appl Ecol 50, 977–987. https://doi.org/10.1111/1365-2664.12111

Hazelton, P.D., Cope, W.G., Mosher, S., Pandolfo, T.J., Belden, J.B., Barnhart, M.C., Bringolf, R.B., 2013. Fluoxetine alters adult freshwater mussel behavior and larval metamorphosis. Science of The Total Environment 445–446, 94–100. https://doi.org/10.1016/j.scitotenv.2012.12.026

Hernández, F., Fabregat-Safont, D., Campos-Mañas, M., Quintana, J.B., 2023. Efficient Validation Strategies in Environmental Analytical Chemistry: A Focus on Organic Micropollutants in Water Samples. Annual Rev. Anal. Chem. 16, 401–428. https://doi.org/10.1146/annurev-anchem-091222-112115

Herrero-Villar, M., Velarde, R., Camarero, P.R., Taggart, M.A., Bandeira, V., Fonseca, C., Marco, I., Mateo, R., 2020. NSAIDs detected in Iberian avian scavengers and carrion after diclofenac registration for veterinary use in Spain. Environmental Pollution 266, 115157. https://doi.org/10.1016/j.envpol.2020.115157

Johnson, A.C., Keller, V., Williams, R.J., Young, A., 2007. A practical demonstration in modelling diclofenac and propranolol river water concentrations using a GIS hydrology model in a rural UK catchment. Environmental Pollution 146, 155–165. https://doi.org/10.1016/j.envpol.2006.05.037

Kellner, M., Porseryd, T., Porsch-Hällström, I., Borg, B., Roufidou, C., Olsén, K.H., 2018. Developmental exposure to the SSRI citalopram causes long-lasting behavioural effects in the three-spined stickleback (Gasterosteus aculeatus). Ecotoxicology 27, 12–22. https://doi.org/10.1007/s10646-017-1866-4

Kumari, M., Kumar, A., 2022. Environmental and human health risk assessment of mixture of Covid-19 treating pharmaceutical drugs in environmental waters. Science of The Total Environment 812, 152485. https://doi.org/10.1016/j.scitotenv.2021.152485

Lee, J., Ju, F., Maile-Moskowitz, A., Beck, K., Maccagnan, A., McArdell, C.S., Dal Molin, M., Fenicia, F., Vikesland, P.J., Pruden, A., Stamm, C., Bürgmann, H., 2021. Unraveling the riverine antibiotic resistome: The downstream fate of anthropogenic inputs. Water Research 197, 117050. https://doi.org/10.1016/j.watres.2021.117050

Lefrançois, T., Malvy, D., Atlani-Duault, L., Benamouzig, D., Druais, P.-L., Yazdanpanah, Y., Delfraissy, J.-F., Lina, B., 2023. After 2 years of the COVID-19 pandemic, translating One Health into action is urgent. The Lancet 401, 789–794. https://doi.org/10.1016/S0140-6736(22)01840-2

Li, D., O'Brien, J.W., Tscharke, B.J., Choi, P.M., Zheng, Q., Ahmed, F., Thompson, J., Li, J., Mueller, J.F., Sun, H., Thomas, K.V., 2020. National wastewater reconnaissance of artificial sweetener consumption and emission in Australia. Environment International 143, 105963. https://doi.org/10.1016/j.envint.2020.105963

London datastore, 2023. Public Transport Journeys by Type of Transport [WWW Document]. URL https://data.london.gov.uk/dataset/public-transport-journeys-type-transport

London datastore, 2015. Daytime Population of London 2014 [WWW Document]. URL https://data.london.gov.uk/blog/daytime-population-of-london-2014/ (accessed 8.26.22).

Martín, J., Camacho-Muñoz, D., Santos, J.L., Aparicio, I., Alonso, E., 2012. Occurrence of pharmaceutical compounds in wastewater and sludge from wastewater treatment plants: Removal and ecotoxicological impact of wastewater discharges and sludge disposal. Journal of Hazardous Materials 239–240, 40–47. https://doi.org/10.1016/j.jhazmat.2012.04.068

Menger, F., Gago-Ferrero, P., Wiberg, K., Ahrens, L., 2020. Wide-scope screening of polar contaminants of concern in water: A critical review of liquid chromatography-high resolution mass spectrometry-based strategies. Trends in Environmental Analytical Chemistry 28, e00102. https://doi.org/10.1016/j.teac.2020.e00102

Miller, T.H., Ng, K.T., Bury, S.T., Bury, S.E., Bury, N.R., Barron, L.P., 2019. Biomonitoring of pesticides, pharmaceuticals and illicit drugs in a freshwater invertebrate to estimate toxic or effect pressure. Environment International 129, 595–606. https://doi.org/10.1016/j.envint.2019.04.038

Miller, T.H., Ng, K.T., Lamphiere, A., Cameron, T.C., Bury, N.R., Barron, L.P., 2021. Multicompartment and cross-species monitoring of contaminants of emerging concern in an estuarine habitat. Environmental Pollution 270, 116300. https://doi.org/10.1016/j.envpol.2020.116300

Munro, K., Martins, C.P.B., Loewenthal, M., Comber, S., Cowan, D.A., Pereira, L., Barron, L.P., 2019. Evaluation of combined sewer overflow impacts on short-term pharmaceutical and illicit drug occurrence in a heavily urbanised tidal river catchment (London, UK). Science of The Total Environment 657, 1099–1111. https://doi.org/10.1016/j.scitotenv.2018.12.108

Naidu, R., Biswas, B., Willett, I.R., Cribb, J., Kumar Singh, B., Paul Nathanail, C., Coulon, F., Semple, K.T., Jones, K.C., Barclay, A., Aitken, R.J., 2021. Chemical pollution: A growing peril and potential catastrophic risk to humanity. Environment International 156, 106616. https://doi.org/10.1016/j.envint.2021.106616

National Institute for Health and Care Excellence (NICE), 2023. COVID-19 rapid guideline: Managing COVID-19.

Ng, K.T., Rapp-Wright, H., Egli, M., Hartmann, A., Steele, J.C., Sosa-Hernández, J.E., Melchor-Martínez, E.M., Jacobs, M., White, B., Regan, F., Parra-Saldivar, R., Couchman, L., Halden, R.U., Barron, L.P., 2020. High-throughput multi-residue quantification of contaminants of emerging concern in wastewaters enabled using direct injection liquid chromatography-tandem mass spectrometry. Journal of Hazardous Materials 398, 122933. https://doi.org/10.1016/j.jhazmat.2020.122933

NHS, 2023. English prescribing data (EPD) [WWW Document]. URL https://www.nhsbsa.nhs.uk/prescription-data/prescribing-data/english-prescribing-data-epd

Office of Rail and Road, 2022. Regional Rail Usage 2020-21.

Office of Rail and Road, 2021. Regional Rail Usage 2019-20.

Official Journal of the European Union, 2022. 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 Union, 2018. Commission Implementing Regulation (EU) 2018/783 of 29 May 2018 amending Implementing Regulation (EU) No 540/2011 as regards the conditions of approval of the active substance imidacloprid (Text with EEA relevance.).

Official Journal of the European Union, 2009. Commission Regulation (EC) No 1179/2009 of 26 November 2009 amending or repealing certain regulations on the classification of goods in the Combined Nomenclature.

Ofwat, 2023. Thames Tideway [WWW Document]. URL https://www.ofwat.gov.uk/households/supply-and-standards/thames-tideway/

Palma, P., Köck-Schulmeyer, M., Alvarenga, P., Ledo, L., Barbosa, I.R., López de Alda, M., Barceló, D., 2014. Risk assessment of pesticides detected in surface water of the Alqueva reservoir (Guadiana basin, southern of Portugal). Science of The Total Environment 488–489, 208–219. https://doi.org/10.1016/j.scitotenv.2014.04.088

Palmer, N.O.A., Seoudi, N., 2021. The effect of SARS-CoV-2 on the prescribing of antimicrobials and analgesics by NHS general dental practitioners in England. Br Dent J. https://doi.org/10.1038/s41415-020-2595-2

Paulshus, E., Kühn, I., Möllby, R., Colque, P., O'Sullivan, K., Midtvedt, T., Lingaas, E., Holmstad, R., Sørum, H., 2019. Diversity and antibiotic resistance among Escherichia coli populations in hospital and community wastewater compared to wastewater at the receiving urban treatment plant. Water Research 161, 232–241. https://doi.org/10.1016/j.watres.2019.05.102

PDSA, 2022. PDSA Animal Wellbeing (PAW) Report.

PDSA, 2019. PDSA Animal Wellbeing (PAW) Report.

Perkins, R., Goulson, D., 2023. To flea or not to flea: survey of UK companion animal ectoparasiticide usage and activities affecting pathways to the environment. PeerJ 11, e15561. https://doi.org/10.7717/peerj.15561. In Press

Persson, L., Carney Almroth, B.M., Collins, C.D., Cornell, S., de Wit, C.A., Diamond, M.L., Fantke, P., Hassellöv, M., MacLeod, M., Ryberg, M.W., Søgaard Jørgensen, P., Villarrubia-Gómez, P., Wang, Z., Hauschild, M.Z., 2022. Outside the Safe Operating Space of the Planetary Boundary for Novel Entities. Environ. Sci. Technol. 56, 1510–1521. https://doi.org/10.1021/acs.est.1c04158

Port of London Authority, 2014. Guidance to Boat Owners on Compliance with Byelaw 49 – Prohibiting Discharge of Sewage into the Thames.

Preston-Allen, R.G.G., Albini, D.D., Barron, D.L., Collins, D.T., Alex, P., Duncalf-Youngson, H., Jackson, D.M., Johnson, P.A., Perkins, D.R., Prentis, D.A., Spurgeon, D.D., Stasik, N., Wells, C., Woodward, P.G., 2023. Are urban areas hotspots for pollution from pet parasiticides? Grantham Institute Briefing note No 15.

Ramos, A.M., Whelan, M.J., Cosgrove, S., Villa, R., Jefferson, B., Campo, P., Jarvis, P., Guymer, I., 2017. A multi-component method to determine pesticides in surface water by liquid-chromatography tandem quadrupole mass spectrometry: A multi-component method. Water and Environment Journal 31, 380–387. https://doi.org/10.1111/wej.12254

Rapp-Wright, H., Regan, F., White, B., Barron, L.P., 2023. 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. Science of The Total Environment 860, 160379. https://doi.org/10.1016/j.scitotenv.2022.160379

Reemtsma, T., Alder, L., Banasiak, U., 2013. A multimethod for the determination of 150 pesticide metabolites in surface water and groundwater using direct injection liquid chromatography–mass spectrometry. Journal of Chromatography A 1271, 95–104. https://doi.org/10.1016/j.chroma.2012.11.023

Reinstadler, V., Ausweger, V., Grabher, A.-L., Kreidl, M., Huber, S., Grander, J., Haslacher, S., Singer, K., Schlapp-Hackl, M., Sorg, M., Erber, H., Oberacher, H., 2021. Monitoring drug consumption in Innsbruck during coronavirus disease 2019 (COVID-19) lockdown by wastewater analysis. Science of The Total Environment 757, 144006. https://doi.org/10.1016/j.scitotenv.2020.144006

Russell, C.D., Fairfield, C.J., Drake, T.M., Turtle, L., Seaton, R.A., Wootton, Dan G, Sigfrid, L., Harrison, E.M., Docherty, A.B., De Silva, T.I., Egan, C., Pius, R., Hardwick, H.E., Merson, L., Girvan, M., Dunning, J., Nguyen-Van-Tam, J.S., Openshaw, P.J.M., Baillie, J.K., Semple, M.G., Ho, A., Baillie, J.K., Semple, M.G., Openshaw, P.J., Carson, G., Alex, B., Bach, B., Barclay, W.S., Bogaert, D., Chand, M., Cooke, G.S., Docherty, A.B., Dunning, J., Da Silva Filipe, A., Fletcher, T., Green, C.A., Harrison, E.M., Hiscox, J.A., Ho, A.Y., Horby, P.W., Ijaz, S., Khoo, S., Klenerman, P., Law, A., Lim, W.S., Mentzer, A.J., Merson, L., Meynert, A.M., Noursadeghi, M., Moore, S.C., Palmarini, M., Paxton, W.A., Pollakis, G., Price, N., Rambaut, A., Robertson, D.L., Russell, C.D., Sancho-Shimizu, V., Scott, J.T., De Silva, T., Sigfrid, L., Solomon, T., Sriskandan, S., Stuart, D., Summers, C., Tedder, R.S., Thomson, E.C., Thompson, A.R., Thwaites, R.S., Turtle, L.C., Gupta, R.K., Palmieri, C., Zambon, M., Hardwick, H., Donohue, C., Lyons, R., Griffiths, F., Oosthuyzen, W., Norman, L., Pius, R., Drake, T.M., Fairfield, C.J., Knight, S.R., Mclean, K.A., Murphy, D., Shaw, C.A., Dalton, J., Girvan, M., Saviciute, E., Roberts, S., Harrison, J., Marsh, L., Connor, M., Halpin, S., Jackson, C., Gamble, C., Leeming, G., Law, A., Wham, M., Clohisey, S., Hendry, R., Scott-Brown, J., Greenhalf, W., Shaw, V., McDonald, S.E., Keating, S., Ahmed, K.A., Armstrong, J.A., Ashworth, M., Asiimwe, I.G., Bakshi, S., Barlow, S.L., Booth, L., Brennan, B., Bullock, K., Catterall, B.W., Clark, J.J., Clarke, E.A., Cole, S., Cooper, L., Cox, H., Davis, C., Dincarslan, O., Dunn, C., Dyer, P., Elliott, A., Evans, A., Finch, L., Fisher, L.W., Foster, T., Garcia-Dorival, I., Greenhalf, W., Gunning, P., Hartley, C., Jensen, R.L., Jones, C.B., Jones, T.R., Khandaker, S., King, K., Kiy, R.T., Koukorava, C., Lake, A., Lant, S., Latawiec, D., Lavelle-Langham, L., Lefteri, D., Lett, L., Livoti, L.A., Mancini, M., McDonald, S., McEvoy, L., McLauchlan, J., Metelmann, S., Miah, N.S., Middleton, J., Mitchell, J., Moore, S.C., Murphy, E.G., Penrice-Randal, R., Pilgrim, J., Prince, T., Reynolds, W., Ridley, P.M., Sales, D., Shaw, V.E., Shears, R.K., Small, B., Subramaniam, K.S., Szemiel, A., Taggart, A., Tanianis-Hughes, J., Thomas, Jordan, Trochu, E., Van Tonder, L., Wilcock, E., Zhang, J.E., Flaherty, L., Maziere, N., Cass, E., Doce Carracedo, A., Carlucci, N., Holmes, A., Massey, H., Murphy, L., Wrobel, N., McCafferty, S., Morrice, K., MacLean, A., Adeniji, K., Agranoff, D., Agwuh, K., Ail, D., Aldera, E.L., Alegria, A., Angus, B., Ashish, A., Atkinson, D., Bari, S., Barlow, G., Barnass, S., Barrett, N., Bassford, C., Basude, S., Baxter, D., Beadsworth, M., Bernatoniene, J., Berridge, J., Best, N., Bothma, P., Chadwick, D., Brittain-Long, R., Bulteel, N., Burden, T., Burtenshaw, A., Caruth, V., Chadwick, D., Chambler, D., Chee, N., Child, J., Chukkambotla, S., Clark, T., Collini, P., Cosgrove, C., Cupitt, J., Cutino-Moguel, M.-T., Dark, P., Dawson, C., Dervisevic, S., Donnison, P., Douthwaite, S., DuRand, I., Dushianthan, A., Dyer, T., Evans, C., Eziefula, C., Fegan, C., Finn, A., Fullerton, D., Garg, S., Garg, S., Garg, A., Gkrania-Klotsas, E., Godden, J., Goldsmith, A., Graham, C., Hardy, E., Hartshorn, S., Harvey, D., Havalda, P., Hawcutt, D.B., Hobrok, M., Hodgson, L., Hormis, A., Jacobs, M., Jain, S., Jennings, P., Kaliappan, A., Kasipandian, V., Kegg, S., Kelsey, M., Kendall, J., Kerrison, C., Kerslake, I., Koch, O., Koduri, G., Koshy, G., Laha, S., Laird, S., Larkin, S., Leiner, T., Lillie, P., Limb, J., Linnett, V., Little, J., Lyttle, M., MacMahon, M., MacNaughton, E., Mankregod, R., Masson, H., Matovu, E., McCullough, K., McEwen, R., Meda, M., Mills, G., Minton, J., Mirfenderesky, M., Mohandas, K., Mok, Q., Moon, J., Moore, E., Morgan, P., Morris, C., Mortimore, K., Moses, S., Mpenge, M., Mulla, R., Murphy, M., Nagel, M., Nagarajan, T., Nelson, M., O'Shea, M.K., Otahal, I., Ostermann, M., Pais, M., Panchatsharam, S., Papakonstantino, D., Paraiso, H., Patel, B., Pattison, N., Pepperell, J., Peters, M., Phull, M., Pintus, S., Singh Pooni, J., Post, F., Price, D., Prout, R., Rae, N., Reschreiter, H., Reynolds, T., Richardson, N., Roberts, M., Roberts, D., Rose, A., Rousseau, G., Ryan, B., Saluja, T., Shah, A., Shanmuga, P., Sharma, A., Shawcross, A., Sizer, J., Shankar-Hari, M., Smith, R., Snelson, C., Spittle, N., Staines, N., Stambach, T., Stewart, R., Subudhi, P., Szakmany, T., Tatham, K., Thomas, Jo, Thompson, C., Thompson, R., Tridente, A., Tupper-Carey, D., Twagira, M., Ustianowski, A., Vallotton, N., Vincent-Smith, L., Visuvanathan, S., Vuylsteke, A., Waddy, S., Wake, R., Walden, A., Welters, I., Whitehouse, T., Whittaker, P., Whittington, A., Papineni, P., Wijesinghe, M., Williams, M., Wilson, L., Sarah, S., Winchester, S., Wiselka, M., Wolverson, A., Wootton, Daniel G, Workman, A., Yates, B., Young, P., 2021. Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study. The Lancet Microbe 2, e354–e365. https://doi.org/10.1016/S2666-5247(21)00090-2

Sathishkumar, P., Meena, R.A.A., Palanisami, T., Ashokkumar, V., Palvannan, T., Gu, F.L., 2020. Occurrence, interactive effects and ecological risk of diclofenac in environmental compartments and biota - a review. Science of The Total Environment 698, 134057. https://doi.org/10.1016/j.scitotenv.2019.134057

Schymanski, E.L., Jeon, J., Gulde, R., Fenner, K., Ruff, M., Singer, H.P., Hollender, J., 2014. Identifying Small Molecules via High Resolution Mass Spectrometry: Communicating Confidence. Environ. Sci. Technol. 48, 2097–2098. https://doi.org/10.1021/es5002105

Steffen, W., Richardson, K., Rockström, J., Cornell, S.E., Fetzer, I., Bennett, E.M., Biggs, R., Carpenter, S.R., de Vries, W., de Wit, C.A., Folke, C., Gerten, D., Heinke, J., Mace, G.M., Persson, L.M., Ramanathan, V., Reyers, B., Sörlin, S., 2015. Planetary boundaries: Guiding human development on a changing planet. Science 347, 1259855. https://doi.org/10.1126/science.1259855

The Official Journal of the Royal Pharmaceutical Society, 2021. A perfect storm: the impact of COVID-19 on the mental health of young people [WWW Document]. URL https://pharmaceutical-journal.com/article/feature/a-perfect-storm-the-impact-of-covid-19-on-the-mental-health-of-young-people (accessed 9.2.22).

UK Centre for Ecology & Hydrology, 2023. National River Flow Archive [WWW Document]. URL https://nrfa.ceh.ac.uk/data/station/meanflow/39001 (accessed 11.9.22).

UK Water Industry Research, 2022. Chemical Investigations Programme - Data access Portal [WWW Document]. URL https://ukwir.org/chemical-investigations-programme-EIR-Database (accessed 12.7.22).

UN environment programme (UNEP), 2021. The triple planetary crisis and public health [WWW Document]. URL https://www.unep.org/news-and-stories/speech/triple-planetary-crisis-and-public-health (accessed 8.3.23).

White, D., Lapworth, D.J., Civil, W., Williams, P., 2019. Tracking changes in the occurrence and source of pharmaceuticals within the River Thames, UK; from source to sea. Environmental Pollution 249, 257–266. https://doi.org/10.1016/j.envpol.2019.03.015

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., Petrosyan, V., Perikhanyan, Y., Mahon, C.S., McGurk, C.J., Hofmann, T., Kormoker, T., Iniguez, V., Guzman-Otazo, J., Tavares, J.L., Gildasio De Figueiredo, F., Razzolini, M.T.P., Dougnon, V., Gbaguidi, G., Traoré, O., Blais, J.M., Kimpe, L.E., Wong, M., Wong, D., Ntchantcho, R., Pizarro, J., Ying, G.-G., Chen, C.-E., Páez, M., Martínez-Lara, J., Otamonga, J.-P., Poté, J., Ifo, S.A., Wilson, P., Echeverría-Sáenz, S., Udikovic-Kolic, N., Milakovic, M., Fatta-Kassinos, D., Ioannou-Ttofa, L., Belušová, V., Vymazal, J., Cárdenas-Bustamante, M., Kassa, B.A., Garric, J., Chaumot, A., Gibba, P., Kunchulia, I., Seidensticker, S., Lyberatos, G., Halldórsson, H.P., Melling, M., Shashidhar, T., Lamba, M., Nastiti, A., Supriatin, A., Pourang, N., Abedini, A., Abdullah, O., Gharbia, S.S., Pilla, F., Chefetz, B., Topaz, T., Yao, K.M., Aubakirova, B., Beisenova, R., Olaka, L., Mulu, J.K., Chatanga, P., Ntuli, V., Blama, N.T., Sherif, S., Aris, A.Z., Looi, L.J., Niang, M., Traore, S.T., Oldenkamp, R., Ogunbanwo, O., Ashfaq, M., Iqbal, M., Abdeen, Z., O'Dea, A., Morales-Saldaña, J.M., Custodio, M., de la Cruz, H., Navarrete, I., Carvalho, F., Gogra, A.B., Koroma, B.M., Cerkvenik-Flajs, V., Gombač, M., Thwala, M., Choi, K., Kang, H., Ladu, J.L.C., Rico, A., Amerasinghe, P., Sobek, A., Horlitz, G., Zenker, A.K., King, A.C., Jiang, J.-J., Kariuki, R., Tumbo, M., Tezel, U., Onay, T.T., Lejju, J.B., Vystavna, Y., Vergeles, Y., Heinzen, H., Pérez-Parada, A., Sims, D.B., Figy, M., Good, D., Teta, C., 2022. Pharmaceutical pollution of the world's rivers. Proc. Natl. Acad. Sci. U.S.A. 119, e2113947119. https://doi.org/10.1073/pnas.2113947119

Young Epilepsy, 2020. Increase in epilepsy seizures in young people during lockdown [WWW Document]. URL https://www.youngepilepsy.org.uk/news-and-events/news/increase-in-epilepsy-seizures-in-young-people-during-lockdown.html (accessed 9.1.22).

Zhu, N., Aylin, P., Rawson, T., Gilchrist, M., Majeed, A., Holmes, A., 2021. Investigating the impact of COVID-19 on primary care antibiotic prescribing in North West London across two epidemic waves. Clinical Microbiology and Infection 27, 762–768. https://doi.org/10.1016/j.cmi.2021.02.007

Ziegler, M., Knoll, S., Köhler, H.-R., Tisler, S., Huhn, C., Zwiener, C., Triebskorn, R., 2020. Impact of the antidepressant citalopram on the behaviour of two different life stages of brown trout. PeerJ 8, e8765. https://doi.org/10.7717/peerj.8765

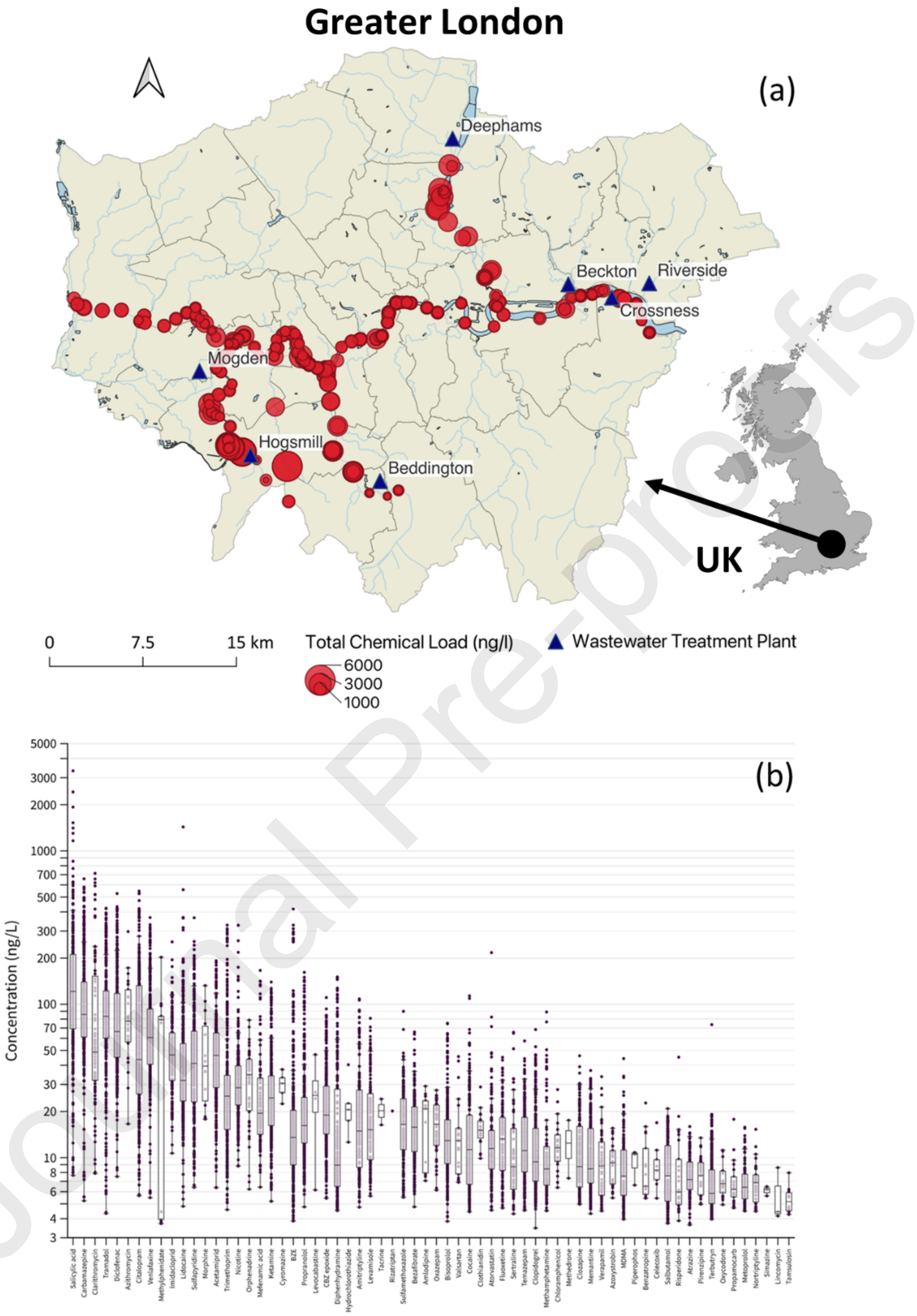


Figure 1. (a) Cumulative MECs at each site monitored in Greater London, UK, 2019-2021 (size of the red circles denote relative total chemical load and triangles represent locations of major WWTPs); and (b) box plot of ranked individual chemical MECs by average and interquartile range in the Greater London area, 2019-2021. Locations of all relevant waterbodies are given in Figure S1.

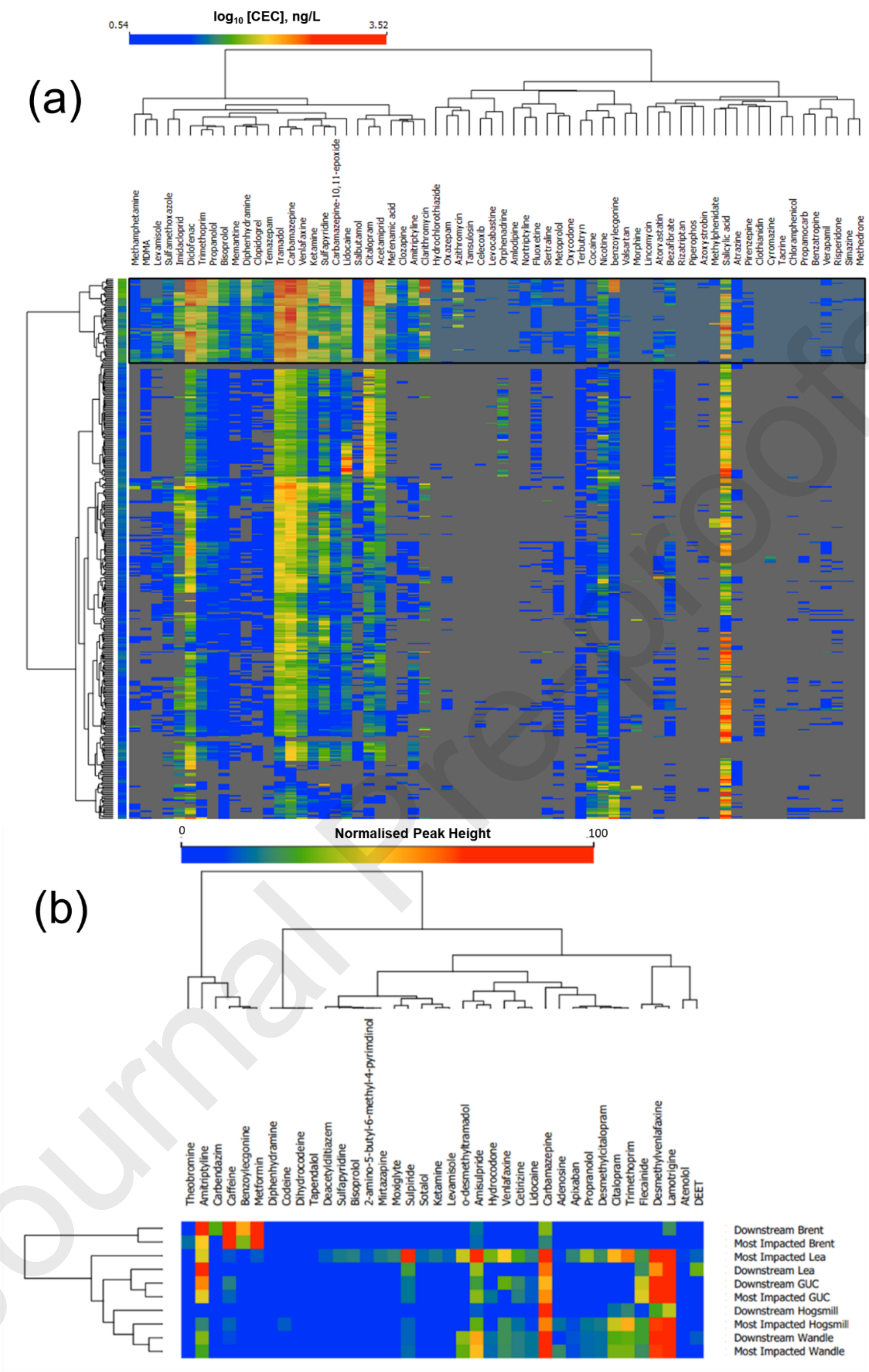


Figure 2. (a) HCA for all 66 MECs across all 390 water samples (data is log_{10} transformed). The black box in the top section highlights clustered samples that were predominantly impacted by wastewater sources. Average MEC at each site is shown in the first coloured column. Individual sample identifier details in HCA are given in Figure S2; (b) HCA of suspect screening data for the most impacted site on five water bodies tested and downstream sites for comparison. Peak area data normalised between 1-100 by compound at each site. No k-means clustering was applied.

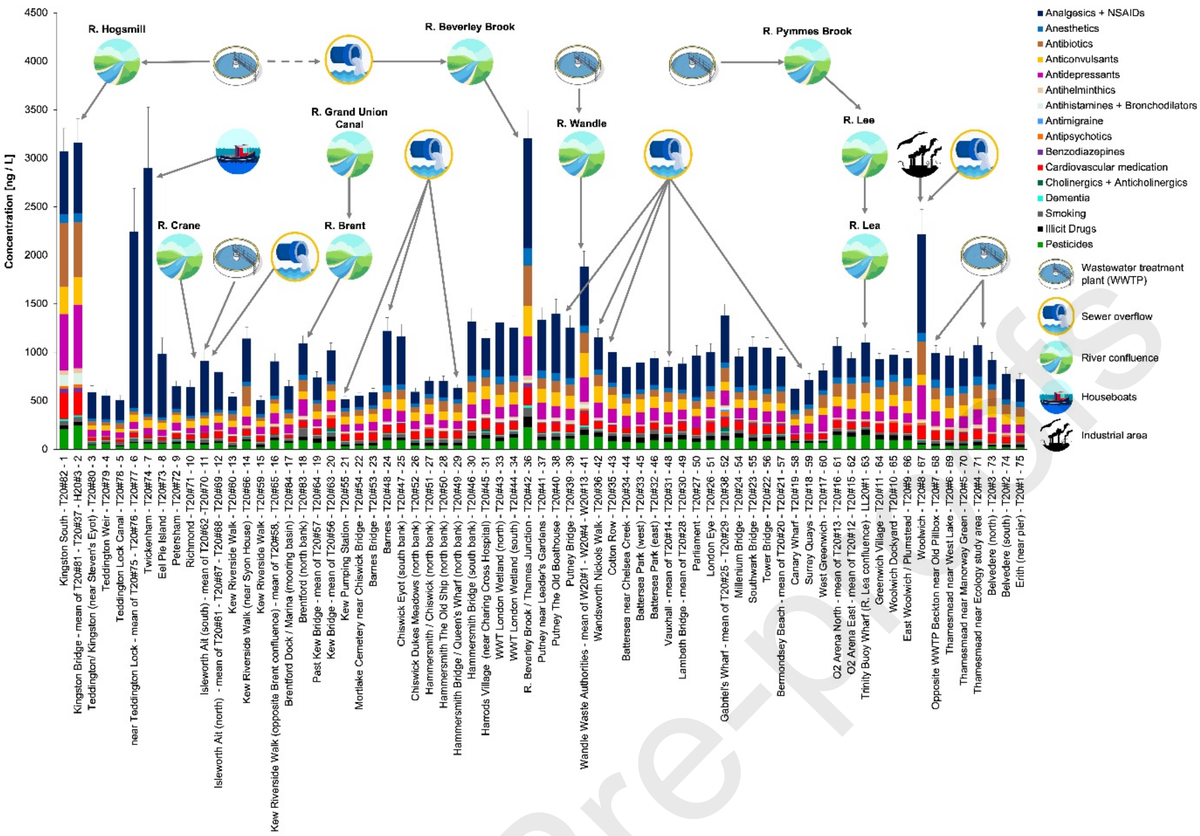
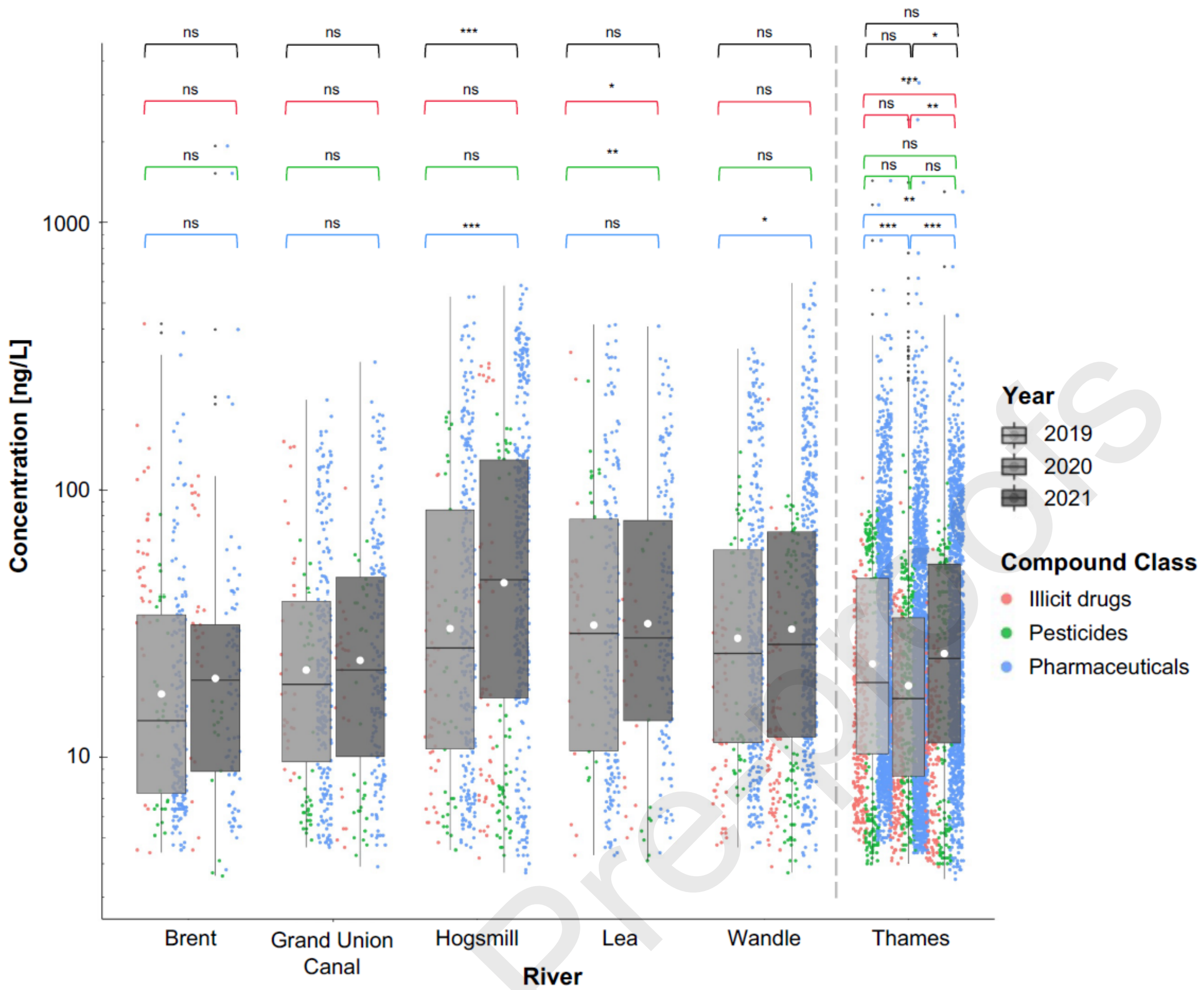


Figure 3. Cumulative CEC MECs across all locations monitored along the R. Thames during lockdown from October to December 2020, and proximity to potential contamination sources and confluences with other watercourses. Arrows represent connectivity between sources and/or discharge sites on the river. Each sample is annotated with its corresponding sample code and bars are sub divided into CEC class. Similar plots for sampling campaigns 2019 and 2021 across all 75 locations along the R. Thames are shown in the SI, as Figure S5.



1022

1023

1024 **Figure 4.** Changes in CEC concentrations by class for selected river catchments across the SARS-
1025 CoV-2 pandemic. Sampling on auxiliary waterways only occurred in 2020 and 2021. Statistical
1026 significance is represented as *, **, and ***, as p ≤0.05, ≤0.01 and ≤0.001, respectively (ns = not
1027 statistically different, significance notation in black is for the combined dataset). All individual CEC
1028 measurements are given in Table S2.

1029

Figure 5. Box plots showing the significant changes in MECs in the R. Thames, 2019-2021. Boxes represent the interquartile range of all data for that year from the longitudinal transect sampling, whiskers represent the 5th-95th centile, black dots represent outliers, black lines represent the median and blue dots represent the mean. Statistical differences marked with *, **, and *** represent p ≤0.05, 0.01 and 0.001 respectively and NS is non-significant. Where boxes do not exist for selected compounds in any year, this means that substance was not detected but samples were analysed. Box plots for all 64 CECs quantified over this period in the R. Thames specifically are given in Figure S7.

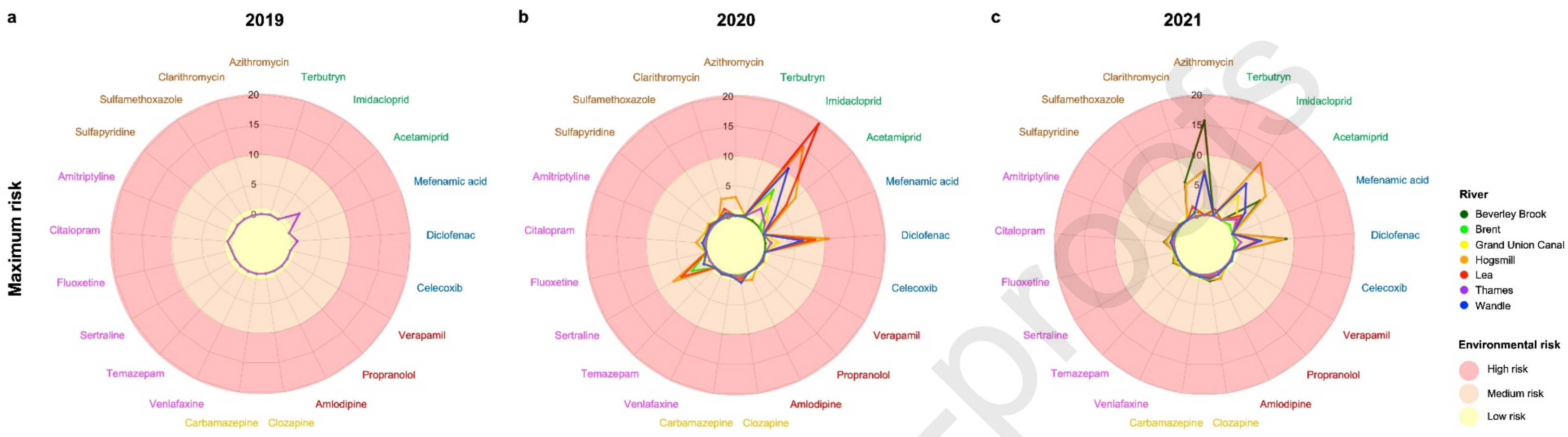


Figure 6. Risk assessment of 21 compounds with RQ ≥0.1 (using the highest MEC measured on that water body) in 2019 (a), 2020 (during lockdown) (b) and 2021 (c). Compounds (and rivers) carrying compounds where RQs < 0.1 were excluded. For 2019, RQ data only represents freshwater samples from the R. Thames (no other rivers sampled that year). Compounds are grouped in colour-coded substance types, i.e., brown for antibiotics, pink for antidepressants, yellow for antipsychotics, red for cardiovascular medication, blue for NSAIDs and analgesics, and green for pesticides. Similar spider charts using average risk are shown in Figure S16 and all RQ data is given in Table S5.

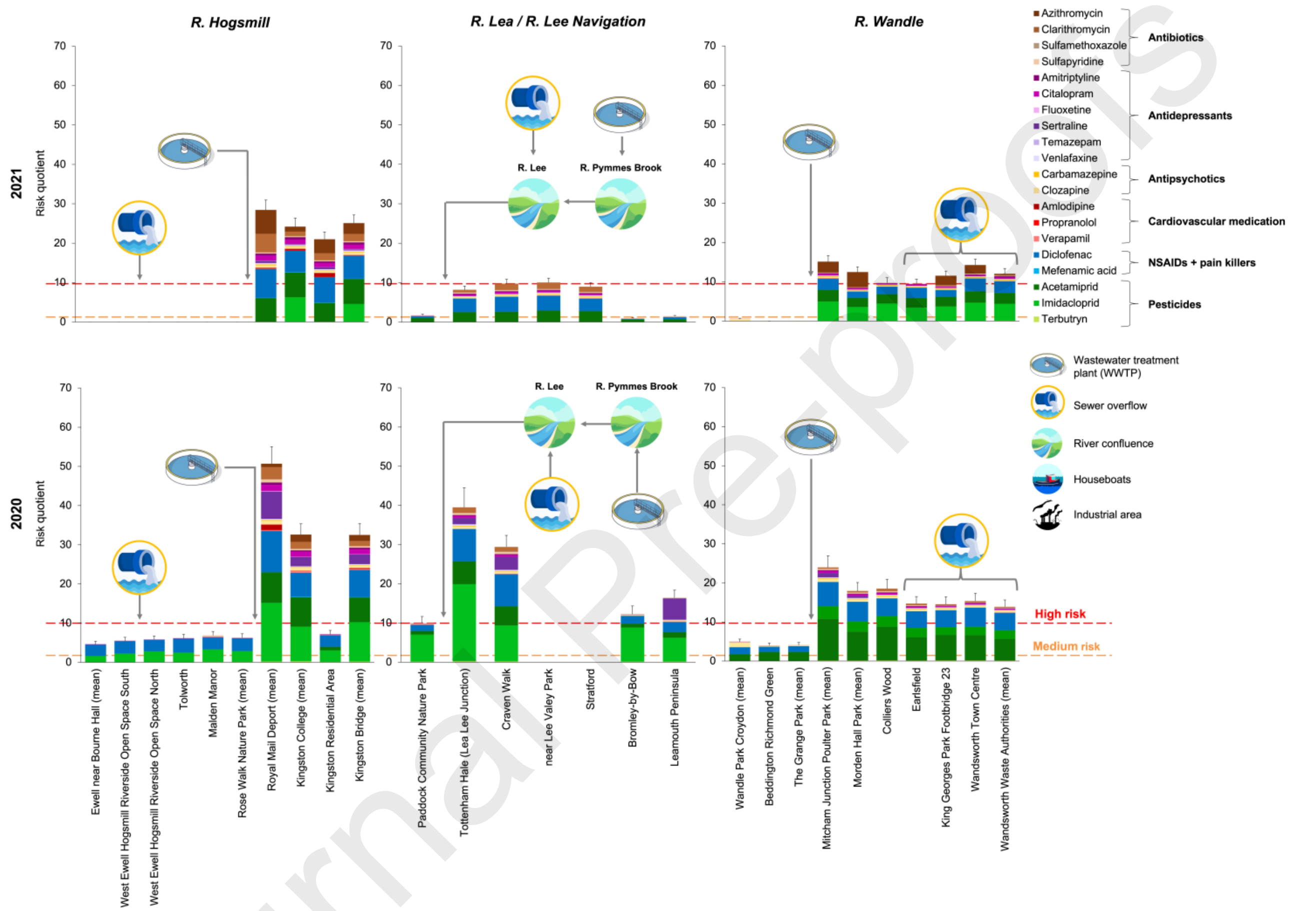
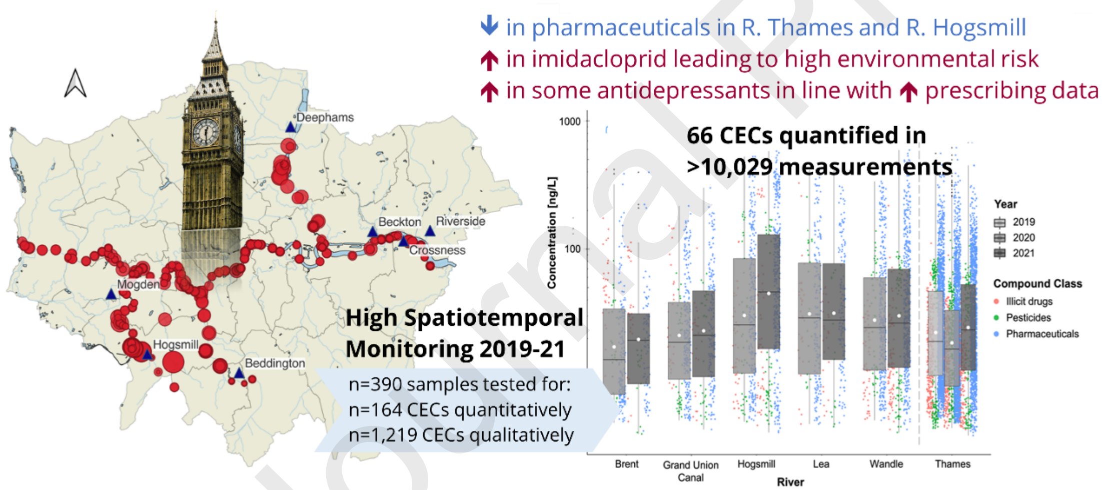


Figure 7: Total environmental risk (as ΣRQ) for all CECs monitored at individual sites on three selected wastewater-impacted tributaries in 2020 (during lockdown) and 2021. Potential sources are indicated with respective icons (e.g., WWTP, sewer/storm overflow, clusters of houseboat moorings and industrial areas). Thresholds for high and medium risk (as the risk quotient, RQ) are indicated at RQ≥1 (medium risk) and ≥10 (high risk threshold), respectively. Where replicate samples exist for overlapping sites, the mean MEC has been taken. Error bars represent the standard deviation.

Highlights

- 98 contaminants of emerging concern detected in London's rivers (2019–21)
- Lower pharmaceutical concentrations during lockdown in Rivers Hogsmill and Thames
- 21 compounds had risk quotients >0.1 in seven of 14 water bodies tested
- Imidacloprid of highest and increasing urban risk despite ban in agriculture in 2018
- Low flow, wastewater-impacted waterways at higher risk from CECs

Graphical Abstract



Author Agreement Statement

03/08/2023

We the undersigned declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We understand that the Corresponding Author is the sole contact for the Editorial process. He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Signed by all authors as follows:

- Melanie Egli
- Helena Rapp Wright
- Olukemi Oloyede
- William Francis
- Rhys Preston-Allen
- Stav Friedman

- Guy Woodward
- Frédéric B. Piel
- Leon P. Barron (corresponding author)

Declaration of interests

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

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Leon Barron reports financial support was provided by Imperial College London.