Tracking changes in the occurrence and source of pharmaceuticals within the River Thames, UK; from source to sea

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Highlights

- Pharmaceutical contamination is linked to WWTW discharge and untreated wastewater
- Sucralose found to be an excellent proxy for pharmaceutical contamination
- Diclofenac was detected above a proposed EQS of 0.1µg/l
- Antimicrobials found in every site except the groundwater dominated Thames source

Keywords: Antimicrobials; diclofenac; micro-organic contaminants; sucralose; surface water watch list; wastewater tracers.

Abstract

There is a growing interest in the occurrence and sources of pharmaceutical substances in the environment. This paper reports the first detailed transect of pharmaceutical occurrence along the River Thames, UK, from source to sea, undertaken during a period of high flow in 2016. In 37 samples a total of 41 pharmaceuticals and 2 lifestyle compounds (cocaine and sucralose) were detected. Total concentration of pharmaceuticals ranged from 0.0012 µg/l to 10.24 µg/l with a median of 2.6 µg/l. Sucralose concentrations varied from <0.01 to 5.9 µg/l with a median concentration of 1.93 µg/l and was detected in every sample except the groundwater-dominated sources of the Thames. Antimicrobials, including those on the surface water watch list (erythromycin, clarithromycin and azithromycin) were detected in every site downstream of the

Thames source. Diclofenac, recently on the surface water watch list, was detected in 97% of Thames samples and above the proposed EQS of 0.1 μg/L in 12 samples. Distinct increases in concentration and number of pharmaceuticals were found downstream of the Oxford, Mogdon and Hogsmill wastewater treatment works (WWTW) but were more subdued downstream of the Crossness and Beckton WWTW due to the tidal nature of the Thames and combined sewer outflows. Sucralose was found to be an excellent tracer of wastewaters (treated and untreated) and can be used as a proxy for many pharmaceuticals. Paracetamol and ibuprofen were tracers of untreated wastewater inputs to the Thames due to their high biodegradation within WWTWs.

1. Introduction

Contamination of the aquatic environment from both legacy and emerging micro-organic pollutants (MOs) is a growing concern globally (Kasprzyk-Hordern et al. 2008; Pal et al. 2010; Lapworth et al. 2012; Loos et al. 2013; Lapworth et al. 2015; Kim et al. 2016). An ever increasing variety of substances are detected in environmental waters as analytical techniques evolve (Richardson and Ternes, 2014). Aquatic ecosystems and humans are exposed to a broad mixture of compounds from a variety of sources, major sources being effluent from WWTWs direct to surface waters or as run-off from land-applied biosolids, urban and rural runoff, drainage and accidental spills. MOs from land-applied WWTW biosolids can also become part of the riparian food chain (Richmond et al., 2018). MO's include contaminants such as pesticides, pharmaceuticals (human and veterinary), lifestyle products, and personal care products. The UK's Chief Medical Officer recognised the cocktail of pharmaceuticals found in the environment in a recent report (CMO 2017) and voiced the concern over antibacterial resistance in the environment and the transmission to humans.

Priority substances are regulated contaminants under the European Water Framework Directive (WFD, 2000/60/EC). There are currently 33 substances on the Priority substance list and an additional 8 substances for which quality standards were set in 2008 (annex II of Directive 2008/105 EC) and revised in 2013 (EU 2013). Additional substances without quality standards are included on a

47 dynamic surface water watch list (EU, 2015/495/EC) to be monitored in order to collect more data to
48 assess them for addition to the Priority substance list (JRC 2015; EC 2017). Recent activity by the
49 European Commission Strategic Coordination Group in 2017 proposed that 4 substances (including
50 diclofenac) were taken off the surface water watch list as enough information had been gathered to
51 assess them for Annex I and II (EC 2017).

52 WWTWs are the major source of pharmaceuticals in surface waters through treated wastewater
53 discharge (Kasprzyk-Hordern et al. 2008; Writer et al. 2013) and untreated discharge during high
54 flow periods (WWF-UK 2017). Sewage sludge and animal waste that is applied to land can contain
55 MOs such as antimicrobials and veterinary drugs which can be leached to surface waters and
56 groundwater (Lupo et al. 2012; Lapworth et al. 2012). Concentrations of MO's in rivers are dynamic
57 and controlled by a number of processes including changes in source loading, catchment rainfall-run-
58 off characteristics and base-flow controls (Burns et al., 2018).

59 Pharmaceuticals, including human and veterinary products, enter the environment via WWTWs due
60 to incomplete uptake and consequent excretion of pharmaceuticals by humans or animals, incorrect
61 disposal of medications and manufacturing discharge 'hotspots'. There is a strong correlation
62 between the amount of pharmaceuticals dispensed and their concentration in surface water
63 (Kasprzyk-Hordern et al. 2008). The large range of compounds in wastewaters, found typically at ng-
64 µg/l concentrations, are difficult and costly to remove though current treatment options
65 (Glassmeyer et al. 2005; Loos et al. 2013; Subedi et al. 2015) leading to discharge to surface waters
66 followed by dilution and dispersion. The proportion of MO compounds removed by WWTW and the
67 residual MO concentration in the WWTW effluent depends on the treatment processes used, its
68 effectiveness at removing the particular MO and the concentration in the influent, which can vary
69 seasonally (Golovko et al. 2014). Detection of pharmaceuticals in environmental waters has been
70 widely studied and their eco-toxicity is a growing area of research (CMO 2017, Richmond et al.,
71 2017).

A European study by Loos et al. (2013) detected sucralose in 88% of river samples with an average concentration of 2.6 µg/l and maximum concentration of 12.9 µg/l. MO's have been suggested as tracers of bacterial loads from wastewater (Glassmeyer et al. 2005) and septic tank systems (Subedi et al. 2015; James et al. 2016). For example, Subedi et al., (2015) suggested that concentrations of atenolol could be used as a proxy for *Escherichia coli* leaching from septic tank systems. Carbamazepine (Hai et al. 2018) and the widely used artificial sweeteners (Lange et al., 2012; Tran et al. 2014), have also been suggested as tracers for WWTW effluents in rivers.

Sucralose has been on the European market since 2004 (Loos et al. 2009) and has been in industrial use since the 1990s (Neset et al. 2010). Sucralose is a stable compound that is poorly absorbed and rapidly removed from the body with a lack of bioaccumulation and minor metabolites occurring in the urine (Roberts et al. 2000; Batchu et al. 2013). Degradation of sucralose during WWT is minimal (Torres et al. 2011; Scheurer et al., 2009), and as such is a highly suitable tracer for wastewater sources of pollution (Oppenheimer et al. 2011; Scheurer et al., 2009; Loos et al. 2013; Yang et al. 2017).

Antimicrobial (AM) compounds detected in the aquatic environment are of increasing global concern due to antimicrobial resistance (Amos et al. 2015; Hawkey 2008; Lupo et al. 2012; Szmolka and Nagy 2013). The World Health Organization (WHO) developed a list of critically important AMs for human medicine in response to the increasing evidence of adverse human health consequences due to resistant organisms resulting from non-human use of AMs (WHO CIA list 2017). Guidelines have been produced (WHO 2017) on the use of medically important AMs in food production to try and tackle this problem. WWTW effluents are a major source of AMs as there is often minimal removal by most treatment processes (Roberts and Thomas 2006). A UK study showed that erythromycin concentrations actually increased by 89% between the influent and effluent of a major WWTWs due to recombination of transformation products (Roberts and Thomas 2006). AM resistance is naturally present in the environment, however, low concentrations of antimicrobials in the environment may

97 accelerate development of antimicrobial resistance (Amos et al. 2015; Lupo et al., 2012; Martinez et
98 al. 2009). Agricultural run-off from sewage sludge and animal manure spread onto arable land is an
99 additional source of AMs to surface waters (Kay et al., 2005; Kim et al., 2016; Watanabe et al. 2010).
100 Studies have found hotspots of AM residues from large scale intensive swine and poultry feeding
101 operations in animal waste, surface waters and groundwater (Campagnolo et al. 2002). Industry has
102 shown a commitment to reduce environmental pollution from AMs by tackling inappropriate use
103 and reducing the release of antibiotics in manufacturing effluent to reduce antimicrobial resistance
104 in the environment (AMR industry alliance 2018).

105 The objective of this paper is to assess for the first time the changes in pharmaceutical pollution
106 along the whole length of the River Thames from source to sea. Specifically we investigate the
107 changes in pharmaceutical concentration and number within the non-tidal and tidal Thames and
108 along the rural to urban gradient of this large European River. An assessment is made of the impact
109 of a number of WWTWs along the Thames as point sources of pharmaceuticals. The occurrence of a
110 broad range of pharmaceuticals is assessed against the established WW tracer sucralose to
111 understand the source and fate of pharmaceuticals in the Thames. This study has a wide relevance
112 to similar global settings where treated and untreated WW is discharged into surface waters.

113 ### 1.1. Study area

114 The River Thames rises as groundwater-fed streams in the Cotswolds, initially flowing through rural
115 agriculturally dominated areas, through a series of towns and cities before flowing through London
116 and out to sea via the tidal Thames estuary. The Thames, the second longest river in the UK, has a
117 total length of 215 miles (Figure 1) and 45 locks. St Johns lock near Lechlade in Gloucestershire is the
118 first lock and Teddington Lock in south west London is the last full lock (Figure 1), the river is tidal
119 from Teddington lock at Ham in south west London (Figure 1). The Thames is impacted by
120 agricultural runoff, small WWTWs and septic tanks in the headwaters and then urban inputs from
121 industry and larger wastewater treatments works further downstream (WWF-UK 2017). The

122 Thames has a total catchment area of c. 12900 km^2 and is a crucial water source for London
123 (population of Greater London approximately 14 million). Major WWTWs mentioned in this paper
124 that ultimately discharge into the Thames include Oxford (>250,000 people, inputs before sample
125 site 8), Reading (c. 282,000 people inputs before site 11), Slough (c. 250,000 people inputs before
126 site 16), Hogsmill (c. 400,000 people, inputs before site 18), Mogdon (c. 1.4 million people inputs
127 before site 19), Beckton (over 3.5 million people, inputs before site 28) and Crossness (c. 2 million
128 people, inputs before site 28).

129 Below Teddington, London has a combined sewerage network which takes sewage and surface
130 runoff. The system has 34 Combined Sewer Overflows (CSOs) which, even following light rain,
131 discharge untreated sewage to the Thames to reduce sewage flooding the city (DEFRA 2015). The
132 untreated sewage will then flow up and down the river with the tide. The European Commission
133 found that the tidal Thames contravened the European Commission Urban Waste Water Treatment
134 Directive (UWWTD 91/271/EEC). In January 2016 the Lee Tunnel began operation to take extra
135 wastewater from the Abbey Mills pumping station to the Beckton WWTWs to be treated and several
136 of the WWTWs in London were updated to handle more waste (Beckton, Crossness, Long Reach,
137 Riverside and Mogden) (DEFRA 2015). This was estimated to reduce the flow of raw sewage into the
138 Thames from 39 million tonnes a year to 18 million tonnes a year (DEFRA 2015). The UK government
139 has recently recommended increased environmental monitoring of pharmaceuticals and further
140 research into associated wastewater engineering targets and treatment systems (CMO 2017). The
141 Environment Agency, England, has identified two pharmaceuticals (clarithromycin and diclofenac) as
142 substances of emerging concern (EA 2018).

143 # 2. Methods

144 ## 2.1. Sampling

145 A total of 33 sites were sampled along the length of the Thames from the source to the sea (Figure
146 1) in January and February 2016, during a period of high flow conditions (Figure S1). The Thames was

147 sampled on three separate days, with sites 1 to 8 on 11/02/16, sites 8 to 18 on 26/01/16 and sites 19
148 to 33 on 04/02/16, and with an additional sample taken from the Littlemore Brook on 11/02/16
149 (figure S1). Sampling locations on the non-tidal Thames were selected upstream and downstream of
150 major towns and cities, downstream of likely WWTW discharge, and/or downstream of the
151 confluence with tributaries. Samples were either collected directly from the surface water or
152 sampled using a submersible pump where access to the River was difficult. Due to river conditions
153 and safety considerations the non-tidal Thames was sampled from the bank.

154 Fifteen samples from the tidal Thames were sampled from a boat with the Environment Agency's
155 Estuarine & Coastal Monitoring and Assessment Service (ECMAS) from a selection of their routine
156 sampling sites. All tidal Thames samples were taken from the centre of the river using a peristaltic
157 pump and from 1 m below the water's surface to avoid localised surface contamination. A Solinst
158 410 peristaltic pump was used together with pump tubing and rigid high-density polyethylene
159 (HDPE) tubing that had previously been washed in a solution of Virkon and rinsed with deionised
160 water. All sample tubing was rinsed thoroughly with sample water prior to sampling. From sample
161 collection to pre-concentration on solid-phase extraction (SPE) cartridges all precautions were taken
162 to reduce the possibility of contaminating the samples. Specific electrical conductance (SEC) was
163 measured using a Metler-toledo meter, however, for the tidal Thames portion the ECMAS's on board
164 Idronaut Ocean Seven 305 multi-parameter probe was used. Additional samples were filtered using
165 Whatman 0.45 µm cellulose nitrate filters for Cl concentration by IC at the BGS Keyworth
166 laboratories.

167 MO samples were collected in clean glass bottles supplied by the National Laboratory Services (NLS).
168 No bottles were re-used, and sample bottles were stored away from potential sources of
169 contamination. Sampling occurred during winter when ambient temperatures were low. All samples
170 were refrigerated at 4 °C at the end of the sampling day on return to the laboratory, left to stand for
171 particulate matter to settle and processed within 2 to 5 days of sampling.

River flow data was later obtained from the Environment Agency's gauging station at Ewen, Kingston and Reading (Figure 1, Figure S1) to assess river flow during the sampling period but water travel times were not estimated.

2.3 Solid phase extraction and field QA methods

The SPE of dissolved MOs was undertaken using pre-conditioned sorbent Oasis® HLB cartridges supplied by NLS and carried out using the method laid down in White et al. (2017). The system was run to minimise possible contamination from within the laboratory environment. A sample volume of 492 ml ± 5.37% was passed through the SPE cartridge and the cartridge was stored refrigerated in Corning centristar centrifuge tubes to protect them and stop them drying out prior to dispatch to NLS. Sample handling in the laboratory was carried out using nitrile gloves.

Field duplicate and blank samples were run to validate the field procedures and information for this can be found in supplementary information 'Blank and duplicate field samples for QA'

2.3 Analysis

Broad screening for MOs was carried out using pre-concentrated SPE followed by target based Ultra-High-Definition (UHD) Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) liquid chromatography/mass spectrometry (LC/MS) screening at the UK Environment Agency's laboratories at Starcross using a semi-quantitative method (see supplementary information 'Analysis'). A blank and a single point calibration standard is used to establish a response factor and quantify target substances. Over 750 compounds are screened for using this method including pesticides and industrial compounds which are not discussed in this paper, only pharmaceuticals and lifestyle products were selected for interpretation. Prior to reviewing the data, all results were corrected for compounds (n=2) that were detected in the blank. Compounds without a limit of detection (LoD) value were removed (see supplementary information 'Blank and duplicate samples for QA'). Statistical analysis was carried out on duplicate data to look at repeatability of results (see supplementary information 'Statistical analysis').

3. Results

A total of 44 pharmaceutical and 2 lifestyle compounds were detected and quantified within the 37 samples representing 33 sites along the Thames (including 4 duplicates) and one site from the Littlemore Brook (n=2). Table 1 shows the compounds detected in the River Thames, the number of times they were detected (n) above their LoD, frequency of detection and concentration range. Substances highlighted in red italics are on, or were recently on in the case of diclofenac, the surface water watch list.

The total concentration and number of pharmaceuticals, grouped by type, are shown in Figures 2a and 2b, sites can be referenced using Figure 1. Sucralose was found in high concentrations with large variations along the Thames transect (Figure S6 and Table 1) and above the LoD in every sample except the source (site 1). Chloride concentrations and SEC are used to investigate changes in salinity and MOs within the river (Figure S3) due to tidal mixing.

An assessment of the association between concentrations of the WWTW tracer sucralose with selected pharmaceuticals and pharmaceutical subgroups was undertaken using Spearman's rank correlation coefficient and the results checked for statistical significance (see supplementary information 'Statistical analysis') . Only pharmaceutical or subgroups were selected that had <25% of data <LoD for each compound. There is a high positive correlation for sucralose with most of the pharmaceuticals, and all of the pharmaceutical subgroups tested but a low correlation with paracetamol (Table S2). This shows that sucralose is a good tracer for the selected pharmaceuticals and pharmaceutical subgroups detected but not for paracetamol.

4. Discussion

4.1. Occurrence of pharmaceuticals from source to sea

Sampling took place in the winter when river levels and flow were high corresponding to high potential discharge of untreated WW and also high potential dilution of contaminants in the Thames

221 downstream of point sources. The variation in river flow during the three sampling events was
222 marked (Figure S1) with the highest flows occurring during sampling the source to Stanford on
223 Thames (11/02/16). There were noticeably lower concentrations of pharmaceuticals towards the
224 source of the Thames, likely due to larger baseflow inputs, higher than average flows and lower
225 WWTW inputs in this section of the Thames. The occurrence of pharmaceuticals at the source
226 indicates that groundwater is a potential pathway and source of contamination as point sources
227 such as septic tanks may contribute to low level contamination of groundwater (Subedi et al. 2015;
228 Carrara et al. 2008).

229 In this study the median total pharmaceutical concentration in the Thames was 2.6 µg/l and the
230 maximum total concentration was 10.2 µg/l. Total concentrations and number of pharmaceuticals
231 are relatively low from the source to site 7 (0.0012 to 0.64 µg/l), then rise sharply after the input
232 from the main Oxford WWTW at site 8 (Figure 2). Overall concentration of pharmaceuticals is below
233 human therapeutic dose (CMO 2017), however, detection of AMs within the river is of concern, as is
234 the potential effect on dependant ecosystems of individual pharmaceuticals or chemical mixtures.
235 Concentration of contaminants was only measured in the river water, further study should be done
236 on sediment concentrations for the long term health of the aquatic ecosystem.

237 4.2. Antimicrobial compounds

238 Antimicrobials were detected above the LoD in every sample except the Thames source (site 1),
239 highlighting the widespread occurrence of these compounds in the environment (Figure S2). The
240 increase in concentration of AMs after Hogsmill WWTWs input (site 18, Figure S2) is significant and is
241 the highest concentration seen within the study (1.78 µg/l), higher even than within the Littlemore
242 Brook which receives direct discharge from a WWTWs (Figure S5). A total of 11 AMs including three
243 critically important ones were detected which are also surface water watch list compounds
244 (erythromycin, clarithromycin, azithromycin) (Table 1 and Figure S2). Clarithromycin was the most
245 frequently detected AM, however erythromycin was often seen at higher concentrations (Figure S2,

246 Table 1). It must be noted that the screen used does not contain an exhaustive list of AMs or their
247 degradation products and this represents a subset of potential AMs in the Thames.

248 Antibiotics are the most important drugs in human and veterinary medicine to treat infectious
249 diseases, but their widespread use and release into the environment, even at low concentrations,
250 from WWTW, surface runoff and agricultural activities is of increasing concern (e.g. (Rodriguez-
251 Mozaz et al. 2015; WHO 2017; CMO 2017). Unlike other contaminants, the concentration of an AM
252 is not the only concern, it is the fact that it is *in* the environment and able to interact with
253 microorganisms that could lead to antimicrobial resistance and interfere with natural microbial
254 functions within the environment that is of the greatest concern. Antibiotic resistance is a major
255 global health concern (WHO 2014; CMO 2017) and that results in AMs becoming ineffective against
256 the microorganism (WHO 2017). The Thames study was carried out during the winter when it has
257 been found that antibiotic use and WWTW influent concentration is higher (Golovko et al. 2014);
258 concentrations of erythromycin actually increasing within WWTWs due to recombination of
259 breakdown products (Roberts and Thomas 2006). Our results corroborate a recent study showing
260 the widespread distribution of AM resistant bacteria in the Thames (Song et al. 2017). By
261 comparison, maximum concentrations of sulfamethoxazole in the Thames were around 30% of those
262 detected using the same methods in a recent study of the highly polluted Ganges River at Varanasi,
263 India (Lapworth et al. 2018).

264 ### 4.3. Analgesics and cough suppressants

265 Non-steroidal anti-inflammatory drugs (NSAID) are widely used for pain relief. The NSAID diclofenac,
266 ibuprofen and naproxen were all detected in the Thames above the LoD. Diclofenac was detected in
267 97% of the Thames samples with 12 samples above the proposed freshwater EQS of 0.1 µg/l and a
268 proposed EQS of 0.01 µg/l for saltwater (EU 2011) (Figure S4a). Diclofenac is harmful to aquatic
269 organisms (EU 2011). Concentrations within the river after the input from two major WWTWs (site
270 18 and 19) was over 3 times higher than the proposed freshwater EQS. However, after the main

271 Oxford WWTW input (site 8) there is a disparity with 1 of the 2 samples lower than the EQS due to
272 dilution from high flows within the river on that day (see section 4.7.1). The last estuarine sample on
273 the Thames has a concentration of 0.04 µg/l, well above the proposed saline EQS. Ibuprofen was not
274 seen above the proposed EQS in the Thames. The highest concentrations within the main river are
275 again seen after the effluent input from WWTWs (site 8, 18, 19, Figure S4b) and concentrations are
276 high after the Beckton and Crossness WWTWs (site 28).

277 Roberts and Thomas (2006) showed that diclofenac, ibuprofen and paracetamol were reduced in
278 concentration by 71%, 89% and 100% respectively from the influent stream to the effluent in a
279 major UK WWTWs (using LoDs 0.02 µg/l, 0.008 µg/l, 0.02 µg/l respectively). Paracetamol is
280 biodegradable and typically removed by WWTWs (Roberts and Thomas 2006; Sidhu et al. 2013; Yang
281 et al. 2017).It has been suggested as a tracer for untreated wastewater (Yang et al. 2017) especially
282 recent releases (Sidhu et al. 2013). A freshwater EQS for Ibuprofen of 1 µg/l (WCA 2014) has been
283 proposed from limited available research. It has been shown that NSAIDs (including diclofenac and
284 ibuprofen) are toxic to birds either through direct administration (Cuthbert et al. 2007) or through
285 scavenging on treated livestock (Prakash et al. 2012; Oaks et al. 2004; Green et al. 2007). This raises
286 concerns for increasing NSAID concentrations in the environment and the effect this may have on
287 birds feeding and living in the aquatic environment.

288 Concentrations of paracetamol within the Thames are above the LoD (0.005 µg/l) in 78% of Thames
289 samples. Concentrations of paracetamol after the major London WWTW (site 18 and 19) do not
290 show the increase in concentration seen with other pharmaceuticals, suggesting preferential
291 removal, indeed it is below the LoD after the Beckton and Crossness WWTWs inputs to the Thames
292 (site 28 to 30). The highest concentrations of paracetamol within the Thames occurs during the
293 highest flows corresponding to sampling of sites 1 to 8 when the Thames was visibly flooded, the
294 sewerage system would have been stressed and it is likely that untreated or partially treated
295 wastewaters were released (Figure S1). Site 8, after the input of Oxford WWTWs, was sampled on

two separate days with concentrations of paracetamol and ibuprofen greater during higher river flow (11/02/16) than lower river flow (26/01/16) (Figure S4b); all other pharmaceuticals had reduced concentrations during high flow (Figure 2 and section 4.9.1).

4.4. Anticonvulsants

Lamotrigine is present in all of the samples from the Thames and, together with the 3 other anticonvulsants detected (Table 1), make up a significant proportion of total pharmaceutical load within the samples (between 9 and 100% with a median of 27% Figure 2). Gabapentin is consistently seen at the highest concentrations and the anticonvulsants are seen to significantly increase after three major WWTW inputs. Lamotrigine (an anticonvulsant of which 10% is excreted unaltered and a further 76−90% is excreted as lamotrigine-N^2-glucuronid) is resistant to degradation in conventional biological WWTWs and photodegradation (Zonja, Pérez, and Barceló 2015). Carbamazepine (detected above LoD in all samples except the source of the Thames) has been proposed as an anthropogenic tracer as it is similarly difficult and costly to remove from wastewaters (Hai et al., 2018).

4.5. Antihistamines

Only 3 antihistamines are included in the LCMS scan used (alizapride, cetirizine and diphenhydramine), of these only 2 were detected in this study (Table 1). No antihistamines were detected within the Thames above the LoD until after the major Oxford WWTWs at Sandford on Thames (site 8) and diphenhydramine was only detected above the LoD at sites 18 and 19 directly after input from WWTWs, strongly suggesting that WWTW effluent is a major source of antihistamines within the river. Concentration of antihistamines at site 8 increases to 1.9 µg/l after the input. Although antihistamines make up a small proportion of the number of compounds (n=2) they make up a proportionally large percentage of total concentration of pharmaceuticals, most of which is due to cetirizine (median 36% and a maximum of 44%). Cetirizine is the most commonly quantified antihistamine, found in every sample downstream of site 8.

Antihistamines present a potential risk to aquatic ecosystems (Berninger and Brooks 2010; Kristofco and Brooks 2017). Golovko et al. (2014) found lower concentrations within WWTW effluent during winter compared to the summer, in line with therapeutic use. Increased summer antihistamine concentration in WWTW effluent and reduced summer river flows (Figure S1) will lead to decreased dilution and further elevated antihistamine concentrations within the Thames.

4.6. Beta-blockers

Three beta blockers were detected above the LoD during the study with concentrations seen to increases after the input of the main WWTW (sites 8, 18 and 19). Atenolol was seen above the LoD at every site except the source (site 1), sotalol is above the LoD in every site except the first 2 and propranolol detected at all sites downstream of site 8.

Under laboratory conditions propranolol is hydrolytically stable with a half-life of >1 year (Maszkowska et al. 2014a). A multigenerational *Daphnia* test using environmentally relevant concentrations of propranolol (0.0015, 0.2 and 26 µg/l) showed effects in heart rates, abdominal appendage movements, and somatic growth (Jeong et al., 2015). Propranolol was seen to be harmful to aquatic organisms during a green algae test (*Scenedesmus vacuolatus*), however, sorption inhibits the hazardous effects reducing concentrations in the environments therefore the risks are of minor importance to the environment (Maszkowska et al. 2014b). Atenolol was found to be non-toxic to *Daphnia* and algae (Cleuvers 2005).

4.7. Tracing WW input to the River Thames

Many specific MO's have been suggested as WWTW effluent tracers, such as sucralose, carbamazepine and the AM subgroup (Hai et al. 2018; Oppenheimer et al. 2011; Scheurer et al. 2009; Loos et al. 2013; Yang et al. 2017). More specifically, increased sucralose, carbamazepine, total AM concentration and pharmaceutical load (concentration and/ or number) are seen within the Thames after the input of WWTW effluent, especially after Oxford (site 8), Hogsmill (site 18), and Mogdon (site 19), followed by evidence of down-stream dilution (Figures 2, S6) showing they are

346 good WW tracers. However the effect is more subtle after the Reading (site 11), Slough (site 16),
347 Beckton and Crossness WWTWs (both site 28) see below.

348 #### 4.7.1. Non-tidal Thames

349 On 11/02/16 samples were taken upstream (site 7) and downstream (site 8) of the confluence with
350 the Littlemore Brook which receives the discharge of the Oxford WWTW (WWTW 1) in order to look
351 in more details at the effect of a major WWTW and a city (Figures 1 and S5c). Wolvercote (Site 7,
352 Figure S5c) is in the peri-urban area upstream of the City of Oxford, inputs will be from agricultural
353 run-off and smaller WWTWs prior to this point. Site 8 is downstream of Oxford and approximately
354 0.5 km downstream of the confluence of the Littlemore Brook and the Thames (Figure S5c). A
355 sample was also taken from Site 8 on 26/01/16 which has been used as a comparison. Two samples
356 were taken from the Littlemore Brook on 11/02/16 after the input from the Oxford WWTWs.

357 The temperature and conductivity of the Littlemore Brook was anomalously high and consistent with
358 most of the flow within the brook coming from the WWTW outflow. The MO data for the Littlemore
359 Brook and site 8 show spikes consistent with the input from WW (Figure S5). A total of 2 lifestyle
360 compounds (sucralose and cocaine) and 33 pharmaceuticals were detected in the Littlemore Brook
361 (Figure S5), of these 3 pharmaceuticals (clozapine, cimetidine, and quinidine) were only detected in
362 this sample. Conversely, 7 pharmaceuticals (clopidol, dihydromorphine and the AMs erythromycin,
363 ketoconazole, lincomycin, sulfadiazine and sulphanilamide) were detected in at least 10 Thames
364 samples (Table 1) but not in the Littlemore Brook. The lack of detection of erythromycin within the
365 brook could point to untreated WW discharge as its break down products are re-combined in
366 WWTWs (Roberts and Thomas 2006).

367 Paracetamol was detected in high concentration within site 8 (11/02/16) and the Littlemore Brook
368 constituting about half the total concentration of analgesics within the samples. Ibuprofen was also
369 high (3 and 2.5 µg/l) within the Littlemore Brook and the 11/02/16 sample at site 8 was over 3 times
370 higher than the sample taken at the lower flow (26/01/16).

371 Cocaine was detected above the LoD in the Littlemore Brook and site 8 on 11/02/16 but nowhere
372 else during the study. Research suggests a >93% removal of cocaine by WWTW's (van Nuijs et al.
373 2009). The appearance of cocaine, the high concentration of paracetamol and ibuprofen, and the
374 lack of erythromycin within this sample suggests that untreated or partially treated WW was
375 discharged into the Littlemore Brook and ultimately the Thames on 11/02/16.

376 A significant variation of concentration can be seen within the different contaminant groups and
377 pharmaceutical subgroups between site 7, the Littlemore Brook and site 8 (Figure S5).
378 Concentrations of all groups were elevated within the Littlemore Brook but evidence of in-stream
379 attenuation/dilution can be seen once they flow into the Thames (Figure S5). Concentration of
380 potential tracers for wastewater such as AMs, carbamazepine, cetirizine, gabapentin and sucralose
381 are all elevated but this would have been similar if the sample was treated or untreated. The
382 concentration of total AMs decreases by an order of magnitude from the Littlemore Brook sample to
383 site 8 and concentrations within the river above Oxford at site 7 are an order of magnitude less than
384 at site 8 (Figure S5). This shows that WWTWs effluent are a major source of antimicrobials but there
385 is rapid attenuation/dilution within the Thames (Figure 2). Recent studies have shown that antibiotic
386 resistant genes are associated with AM contamination in rivers from WWTW, leading to the
387 conclusion that WWTW technology has the ability to effect antimicrobial resistance within surface
388 waters (Amos et al. 2015).

389 Similar sized WWTWs to Oxford can be found at Reading and Slough however the distance from
390 effluent input to sample point (Site 11 and 16 Figure 2) was much greater, the effects are still visible
391 but so is attenuation and dilution.

392 4.7.2. Tidal Thames

393 The Thames is tidal from Teddington lock (figure 1) and as such the surface water flows up and
394 down this section and mixes with seawater with the changing tides, this contrasts with the more
395 linear flow and mixing processes in the non-tidal Thames. CSOs discharging to the tidal Thames

release untreated sewage even in light rain. During the winter months the untreated wastewater will wash up and down the river and it will take approximately a month for the non-biodegradable waste to get from Teddington to the sea but up to 3 months during the lower flows in summer (DEFRA 2015). The MOs will similarly be retarded within the Thames and the motion of tides will mix MOs from treated and untreated wastewater sources making it less easy to highlight the exact source. The Tidal Thames sampling occurred less than a month after the Lee Tunnel came into operation and hence the full impacts of the improvements had not been felt. The tidal Thames was sampled on an ebb tide and it has been shown from salinity tracers (SEC and Cl Figure S3) that site 19 reflects the impact of the Mogden WWTW.

Increases in SEC and Cl are often caused by the input of WWTW effluent to the river but far greater increases are produced by saline water mixing within the tidal Thames (Figure S3). The last full lock on the Thames is before site 19 (Figure 1) therefore site 19 to 33 are within the tidal section of the Thames. However, increases in Cl and SEC start at Victoria Dock (site 25) but are marked at Erith (site 28) and beyond here there is a sharp rise (Figure S3) as the Thames becomes brackish (SEC >1 mS/cm) between sites 28 and 29. .

The wastewater system within London and most of the UK is a combined system that takes run-off as well as wastewater, increased rain during the winter increases water volume and hence dilution. The major London WWTWs at Crossness and Beckton WWTWs both input to the Thames between site 27 and 28. At site 28 ibuprofen increases and paracetamol is below the LoD and there is a slight increase in sucralose (Figure 2 and S6). The marked increases have been smoothed out by the already high pharmaceutical loads within the river from other WWTWs and other inputs such as untreated wastewater discharged via CSOs, leaking sewers and septic tanks and dilution due to greater flows in this section of the Thames.

The concentration of sucralose and total concentration of pharmaceuticals follow a similar pattern along the tidal Thames. There is a reduction at London Bridge (site 24) and a similar reduction after

Erith (28) where the Beckton and Crossness WWTWs input into the river (Figure 2). The decrease in concentration at London Bridge (24) may be due to dilution from tributaries downstream of Hammersmith Bridge (22) such as the Beverly Brook, Bell Lane Creek, Chelsea Creek and the River Fleet. To check for a correlation between concentrations of pharmaceutical or pharmaceutical subgroup with salinity (SEC and Cl), a Spearman's rank correlation coefficient was conducted for all sites (Table S2) and the tidal Thames subset (Table S3 site 19 to 33) using pharmaceuticals that had <25% detection below LoD. Using the whole data set naproxen and paracetamol showed a statistically significant negative correlation with SEC and sulfamethoxazole showed a statistically significant positive correlation with SEC. However 25 of the 27 showed a positive correlation with Cl. Using the smaller tidal Thames dataset, 11 of the 27 showed a statistically significant negative correlation with both Cl and SEC. It appears the effect of salinity on pharmaceuticals needs further investigation especially as WW will also cause an increase in SEC and Cl.

4.7.3. Sucralose as a tracer of WWTW inputs

In this study sucralose is consistently found to be the highest concentration MO in all samples except the source (site 1, Figure S6). Studies have shown that sucralose increases in a surface water after input of WWTW effluent (Amy-Sagers et al. 2017, Scheurer et al. 2009). Sucralose was below detection at the groundwater dominated site 1 (Figure 1) but was between 0.17 and 5.9 µg/l within the rest of the river (Figure S6). The mean concentration of sucralose found in the Thames study (1.8 µg/l) is comparable to that found in an EU wide study looking at WWTWs effluent concentrations in 18 EU countries which had a medium of 1.7 µg/l (Loos et al. 2013) indicating how high concentration are within the river. However, sucralose was only detected in 88% (LoD 0.1 µg/l) of EU effluents, possibly due to the higher LoD (Loos et al., 2013), whereas it was detected in 95% of samples from the Thames study.

A statistically significant positive relationship between sucralose and selected pharmaceuticals and groups of pharmaceuticals (<25% sample sites <LoD) was found within the Thames dataset (Table

S2). The strong correlation with total AMs (ρ = 0.93, p = <0.05) and total pharmaceuticals (ρ = 0.95, p= <0.05) (Table S2) leads to the conclusion that the major contribution of AMs and pharmaceuticals to the river is from WW and WWTW effluent. The best statistically significant correlation is seen with the anticonvulsants carbamazepine (ρ = 0.98), and all compounds tested have a positive correlations with sucralose (p<0.05, Table S2) except paracetamol. This leads to the conclusion that sucralose could potentially be used to estimate pharmaceutical load within the Thames or be used as a proxy for other pharmaceuticals. In sharp contrast, there is no correlation (ρ= -0.17, p = 0.31) between paracetamol and sucralose (Table S2), leading to the conclusion that these two are not related as paracetamol is biodegraded within WWTWs.

5. Conclusions

This is the first systematic study to report results from broad screening for micro-organics along the entire length of the River Thames, providing a snap-shot of the occurrence of a large range of substances of emerging concern in the environment. Pharmaceuticals are found to be ubiquitous in the Thames and were also detected at its source, which is groundwater dominated. A total of 41 pharmaceuticals and 2 lifestyle compounds (cocaine and sucralose) were detected within the Thames. Eleven antimicrobial substances (including 3 on the surface water watch list) were detected above the LoD in every sample except the Thames source highlighting the widespread occurrence and persistence of these substances. Diclofenac was detected above the proposed freshwater EQS in 12 Thames River samples.

Sucralose was found to be an excellent tracer for most pharmaceutics from WWTW and could be used as a proxy to estimate total pharmaceutical loads within surface water. Due to its biodegradability and high removal rates during treatment paracetamol was found to be suitable as a qualitative tracer for untreated or partially treated fresh sewage. The results of this study are applicable to many rivers worldwide which have similar marked land use gradients (rural agriculture-urban) from source to sea and receive treated and/or untreated wastewater inputs.

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7. Declaration of interest

None.

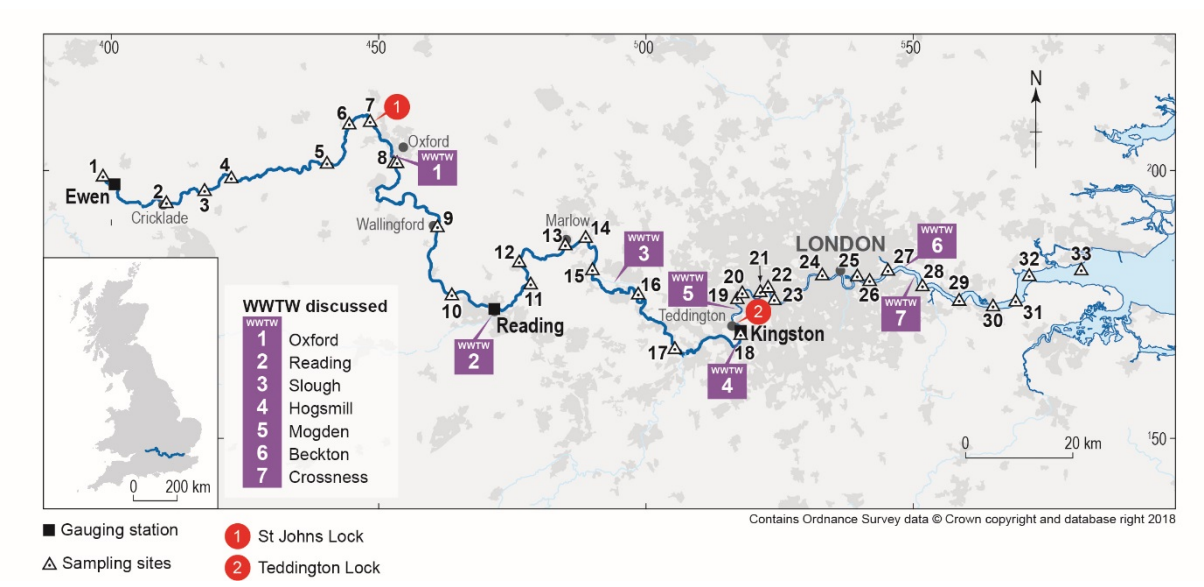

Figure 1. River Thames extent within Great Britain. Sampling points and gauging stations used to produce Figure S1 are included for future reference.

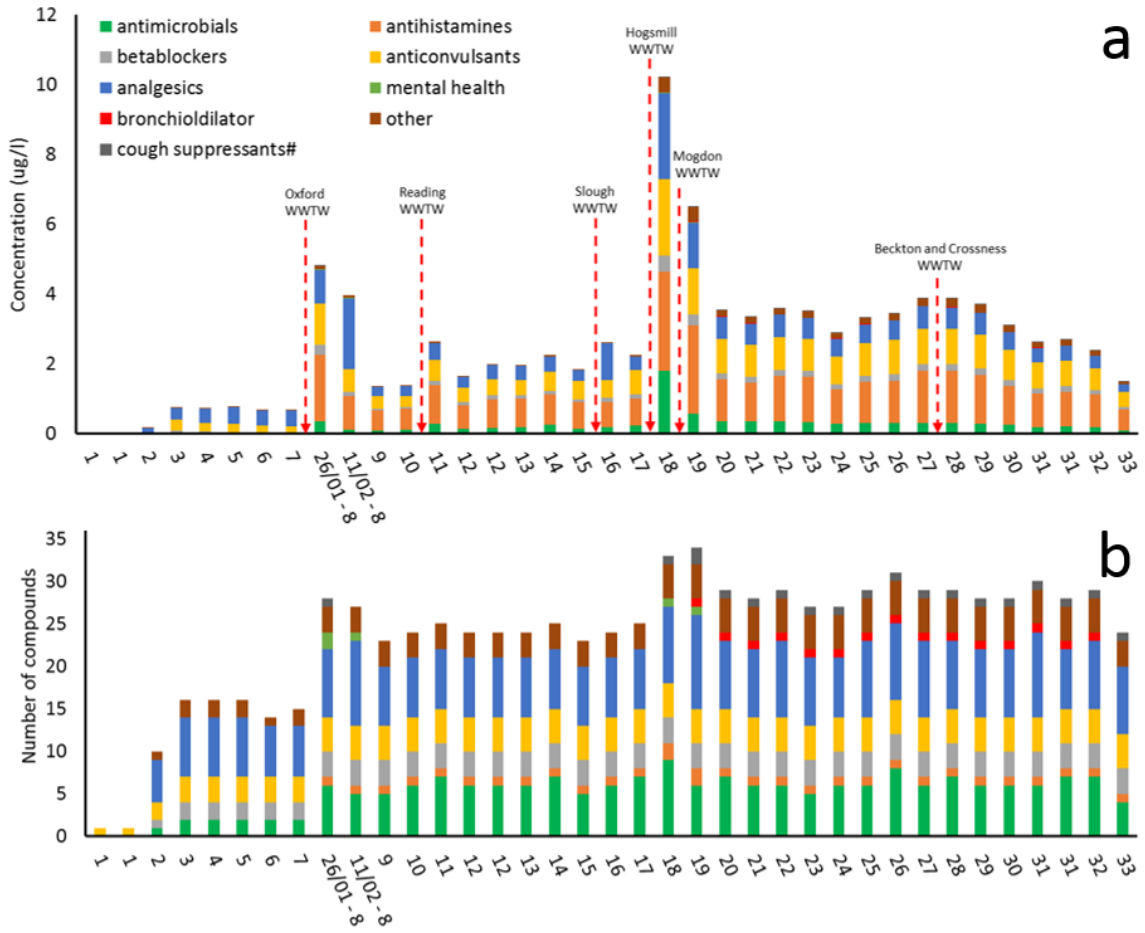

Figure 2. a) Change in concentration and b) number of pharmaceuticals, grouped by type of pharmaceutical along the River Thames sample sites (x axis). Site 8 was sampled on two separate dates as indicated. Note: pharmaceuticals labelled as 'cough suppressants' are also used as recreational drugs. Site 1 is at the source of the Thames, site 33 is the last Thames estuary sample (see Figure 1).

Table 1. List of pharmaceutical and lifestyle compounds detected in the River Thames by LCMS, frequency of detection above the LoD and concentration range.

Pharmaceutical	Type/main use	Frequency %	LoD µg/l	Min µg/l	Max µg/l
Lidocaine[a]	anaesthetic	92	0.001	0.0017	0.12
Clopidol	anticoccidial	89	0.001	0.001	0.0032
Oxfendazole	anthelmintic	3	0.001	0.008	0.008
Azithromycin	antibiotic	3	0.05	0.073	0.073
Clarithromycin	antibiotic	95	0.001	0.0057	0.5
Climbazole	anti-fungal	76	0.001	0.001	0.024
Erythromycin	antibacterial	73	0.005	0.032	0.79
Ketoconazole	anti-fungal	19	0.001	0.0012	0.013
Lincomycin	antibiotic	41	0.001	0.0021	0.0071
Sulfadiazine[b]	antibiotic	11	0.005	0.005	0.0054
Sulfamethoxazole	antibacterial	76	0.005	0.01	0.035
Sulfanilamide	antibiotic	16	0.01	0.02	0.029
Thiabendazole	Anti-fungal	16	0.001	0.001	0.0038

Trimethoprim	antibacterial	92	0.001	0.0034	0.35
Carbamazepine	anticonvulsant	95	0.001	0.0056	0.2
Gabapentin	anticonvulsant	92	0.01	0.16	1.6
Lamotrigine	anticonvulsant	100	0.001	0.0012	0.28
Oxcarbazepine	anticonvulsant	78	0.005	0.01	0.11
Cetirizine	antihistamine	78	0.1	0.58	2.8
Diphenhydramine	antihistamine	5	0.01	0.015	0.05
Paracetamol[c]	anti-inflam*	78	0.005	0.0082	1.2
Codeine	anti-inflam*	95	0.001	0.0078	0.73
Diclofenac[e]	anti-inflam*	92	0.004	0.0059	0.38
Dihydromorphine	analgesic	24	0.005	0.0045	0.013
Hydrocodone	analgesic	78	0.001	0.0063	0.09
Ibuprofen	anti-inflam*	46	0.001	0.03	0.45
Methadone	opioid substitute*	11	0.005	0.0068	0.016
Morphine	opioid*	86	0.001	0.0022	0.082
Naproxen	anti-inflam*	89	0.01	0.027	0.15
Norcodeine	codeine metabolite	35	0.001	0.002	0.0067
Tramadol	anti-inflam*	95	0.001	0.0076	0.67
Dextrorphan[d]	cough suppressant	49	0.001	0.0052	0.035
DXM[e]	cough suppressant	3	0.001	0.0014	0.0014
Amitriptyline	antidepressant*	8	0.005	0.0058	0.02
Oxazepam	muscle relaxant	5	0.001	0.02	0.02
Atenolol	beta-blocker	95	0.001	0.0053	0.13
Sotalol	beta-blocker	92	0.005	0.0065	0.25
Propranolol	beta-blocker	78	0.005	0.0065	0.067
Salbutamol[f]	Bronchodilator	41	0.005	0.0056	0.02
Levamisole	cancer treatment	76	0.001	0.0064	0.31
Furosemide	diuretic	46	0.01	0.038	0.26
Lifestyle substances					
Cocaine	Class A drug	3	0.001	0.0063	0.0063
Sucralose	artificial sweetener	95	0.01	0.17	5.9

*also analgesic, following substances are also called [a]Diocaine, [b] Silvadene, [c] Acetaminophen, [d] Levorphanol, [e] Dextromethorphan, [f]Albuterol, n=37 samples in total for this study. Note: substances in red italics are on, [e]or were recently on, the surface water watch list.

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