TARGETED MONITORING FOR HUMAN PHARMACEUTICALS IN VULNERABLE SOURCE AND FINAL WATERS

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SUMMARY

A range of pharmaceuticals has been detected in soils, surface waters and groundwaters across the world. While the reported concentrations are generally low (i.e. sub µg l^{-1} in surface waters), the substances have been observed throughout the year across a variety of hydrological, climatic and land-use settings. As a result, questions have been raised over the potential for pharmaceuticals in surface waters to enter drinking water supplies and to affect consumers.

In a previous Drinking Water Inspectorate (DWI) funded study, results from a simple exposure model were used alongside information on therapeutic doses of pharmaceuticals to identify pharmaceuticals that are likely to be of most concern in UK drinking water sources. However, this previous study was entirely desk-based and did not involve any experimental measurements of pharmaceutical concentrations. The current study was therefore performed to generate actual measurements on the occurrence of pharmaceuticals in source and treated waters in England.

The study considered a range of pharmaceutical compounds and their metabolites that have either a) high predicted exposure concentrations; b) toxicological concerns; or c) a low predicted exposure to therapeutic dose ratio. An illicit drug and its major metabolite were also investigated. The study compounds (in total 17) covered a range of chemical classes and varied in terms of their physico-chemical properties. The study was done at four sites where concentrations in source water at the drinking water treatment abstraction point were predicted to be some of the greatest in England. The study therefore is likely to provide a 'worst case' assessment of potential human exposure to pharmaceuticals in drinking water in England and Wales.

Ten of the 17 study compounds were detected in untreated source waters at sub-µg/l concentrations. Six of these compounds (namely, benzoylecgonine (a metabolite of cocaine), caffeine, carbamazepine (an antiepileptic medicine), carbamazepine epoxide (a metabolite of carbamazepine), ibuprofen and naproxen (both non-steroidal anti-inflammatory drugs) were also detected in treated drinking water. With the exception of carbamazepine epoxide, concentrations in treated drinking water were generally significantly lower than in source water. Even though England is a densely populated country and in some regions there is limited dilution of wastewater effluents, these observations, made at sites that were predicted to have some of the highest concentrations of pharmaceuticals in England and Wales, are in line with results from similar studies performed in other countries.

Comparison of measured concentrations of the study compounds in drinking waters with information on therapeutic doses demonstrated that levels of these compounds in drinking water in England are many orders of magnitude lower than levels that are given to patients therapeutically. It would therefore appear that the low or non-detectable levels of pharmaceuticals and illicit drugs present in drinking waters in England and Wales do not pose an appreciable risk to human health.

1. INTRODUCTION

Pharmaceuticals play an important role in the treatment and prevention of disease in humans. Whilst the potential side effects on human and animal health arising from direct treatment have been widely documented, only recently have the implications of the occurrence, fate and effects of such medicines in the environment been considered (e.g. Daughton and Ternes, 1999; Boxall *et al*., 2004).

A range of pharmaceuticals, including hormones, antibiotics, NSAIDS, antidepressants and antifungal agents have been detected in soils, surface waters and groundwaters (e.g. Hirsch *et al*., 1999; Kolpin *et al*., 2002). Whilst the reported concentrations are generally low (i.e. sub µg/l in surface waters), the substances have been observed throughout the year across a variety of hydrological, climatic and land-use settings. As a result, questions have been raised over the potential impacts, such as the promotion of the spread of antibiotic resistance, of pharmaceuticals in the environment on human health.

Humans may be exposed to pharmaceuticals in the environment through the consumption of abstracted groundwater and surface waters containing pharmaceuticals or biologically active metabolites. While the health risks arising from this route of exposure in other geographical regions (e.g. USA) has been quantified, limited information is available on the potential exposure of the UK population. In the UK, we live on a densely populated island, with small rivers of limited dilution. Consequently, it might be expected that UK surface waters will have higher exposure to chemicals, including pharmaceuticals, than other developed countries. In common with many other developed countries, in a number of parts of the country discharges of treated sewage effluent occur in catchments that we use for drinking water abstraction.

In a previous DWI funded study, simple modelling approaches were used alongside information on therapeutic doses of pharmaceuticals to identify pharmaceuticals that are likely to be of most concern in UK drinking water sources (Watts *et al*., 2007). However, the previous study was entirely desk-based and did not involve any actual measurements of pharmaceuticals in UK surface waters or use detailed information on toxicological profiles. This project therefore explored the actual levels of occurrence of pharmaceuticals in raw and treated waters in use in England.

1.1. Objectives

The objectives of the project were to:

1. Identify three water treatment works in England or Wales considered to have a relatively high levels of human pharmaceuticals in the source and final waters;

2. Select at least four human pharmaceuticals to monitor, where the selection must include: a compound with a high predicted concentration; a compound of high mammalian toxicity; a compound with a low margin of exposure (the ratio between the therapeutic dose and estimated intake); and an illegal drug;

3. Develop and validate analytical methodologies for the selected determinands with a detection limit of 10-100 ng/l or better;

4. Devise and conduct a monitoring survey over a full calendar year for the selected compounds at the three sites selected under Objective 1 and at scenario B used in the previous DWI-funded study (Watts *et al*., 2007).

5. Interpret the results obtained based on knowledge of the catchment conditions at the time of sampling and compare the results obtained for 'scenario B' with the estimates published in Annex 2 of the previous DWI report.

2. METHODS

2.1. Pharmaceutical selection

There are over 3,000 active pharmaceutical ingredients in use and it impossible to monitor all of these. A number of groups have therefore attempted to prioritise pharmaceuticals in terms of their potential to surface water and drinking waters and potential hazards to ecosystems and human health. Four prioritisation approaches are of relevant to pharmaceuticals in drinking water:

1. Watts *et al*., (2007) – This approach used predicted environmental concentrations and the therapeutic dose of a compound to prioritise pharmaceuticals in use in the UK. Twenty four compounds with the highest exposure to dose ratios were identified.
2. Besse and Garric (2008) – This approach used predicted environmental concentrations alongside data on metabolism, mode of action, ecotoxicity and toxicity to identify substances of potential concern in France. The final priority list included 40 parent compounds and 14 metabolites.
3. A list developed for a nationwide drinking water monitoring study in the USA – In this study, data on predicted concentrations was combined with a review of toxicological data.
4. Global Water Research Coalition (2008) – This study combined 25 prioritization reports to develop a list of priority pharmaceuticals for investigation in further studies.

The prioritisation lists from each of these exercises were therefore obtained and combined (Appendix A). By selecting substances that appeared on three or more of the priority lists, a list of potential determinands (and associated metabolites) was developed (Table 1). These included a number of high exposure compounds as well as substances where toxicological concerns have been raised or compounds which have a low exposure to dose ratio (so they met the requirements of the project specification).

Table 1 Potential determinands for the monitoring project

	Parent compound	**Metabolites**
High exposure	atenolol	
	furosemide	
	ibuprofen	OH-ibuprofen, carboxy-ibuprofen
	ketoprofen	
	paracetamol	
	sulfamethoxazole	acetylsulfamethoxazole
	trimethoprim	
Potential adverse toxicity	carbamazepine	
	diclofenac	
	fluoxetine	norfluoxetine
	naproxen	
Low ratio of exposure to dose	atenolol	
	atorvastatin	
	furosemide	
	ibuprofen	
	simvastatin	hydroxy-acid metabolite of simvastatin
Illegal drug	cocaine and its metabolites	

From this list of potential determinands, a range of substances were selected for further study. The main factor considered in the final compound selection was that the selected compounds could be analysed using one extraction and detection method. Sulfamethoxazole and paracetomol and a number of metabolites were not taken forward for monitoring.

In addition to the compounds identified in previous prioritisation studies, a cytotoxic drug, cyclophosphamide, was selected due to concerns over potential risks to human health (Rowney et al., 2009). The lipid lowering drug, orlistat, was also selected as it had recently become available as an over the counter medicine in the UK so use was expected to increase over the period of monitoring. Caffeine was included as a marker compound to give an indication of human inputs into the study catchments.

The final list of determinands is shown in Table 2 along with information on physico-chemical properties, and excretion by humans and fate in wastewater treatment.

Table 2. Pharmaceuticals, and associated metabolites, selected for study in the monitoring programme. Structures, physico-chemical properties and available data on excretion by humans and removal in wastewater and drinking water treatment are shown.

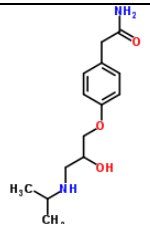
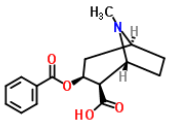
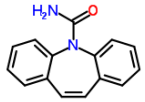
Compound	Structure	Class	Use in England (Kg/yr)[!]	Kow[#]	pKa	Excreted unchanged (%)	STP removal (%)
Atenolol		B-blocker	27780	0.34	9.5	100	<10[+]
benzoylecgonine		cocaine metabolite		2.26	2.25, 11.2	45 of cocaine dose?	-
Caffeine		stimulant	-	0.091	0.6, 14	-	81-99.9[-]
carbamazepine		anti-epileptic	39069	1.90	-	<1	17 (<10-53)[+]

Table 2. Continued

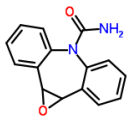
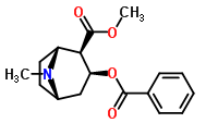
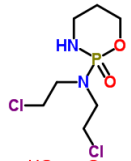
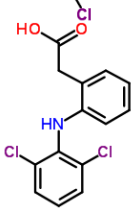
Compound	Structure	Class	Use in England (Kg)	Kow#	pKa	Excreted unchanged (%)	STP removal (%)
carbamazepine epoxide		carbamazepine metabolite		1.26	-	-	0[@]
cocaine		elicit drug	22789	2.28	8.6	10-12	-
cyclophosphamide		chemotherapy agent	11.6	0.23	9.91	25	-
diclofenac		non steroidal anti-inflammatory	151297	4.55	4.0	6-39	31 (<10-80)[+]

Table 2. Continued

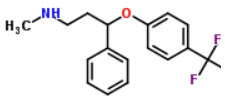
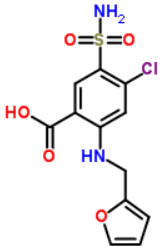
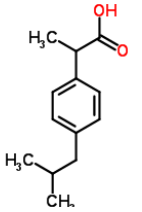
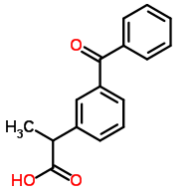
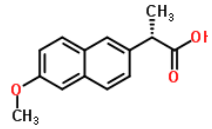
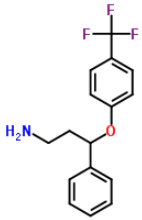
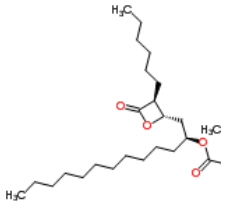
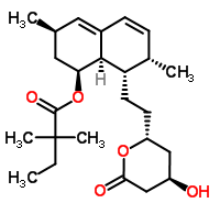
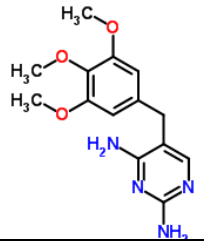
Compound	Structure	Class	Use in England (Kg)	Kow#	pKa	Excreted unchanged (%)	STP removal (%)
fluoxetine		antidepressant	4640	3.93	10.1	≤5	>90%
furosemide		diuretic	15210	3.10	9.83	65	0-75[&]
ibuprofen		non steroidal anti-inflammatory	262553	3.50	4.4	1 - 8	85.7 (52-99)[+]
ketoprofen		non steroidal anti-inflammatory	39959	2.91	5.94	<1	50-60*

Table 2. Continued

Compound	Structure	Class	Use in England (Kg)	Kow#	pKa	Excreted unchanged (%)	STP removal (%)
naproxen		non steroidal anti-inflammatory	53082	2.88	4.15	<1	72 (48-93)[+]
norfluoxetine		metabolite of fluoxetine	-	4.36	-	-	>90
orlistat		anti-obesity	11434	8.95	-	100	-

Compound	Structure	Class	Use in England (Kg)	Kow[#]	pKa	Excreted unchanged (%)	STP removal (%)
simvastatin		hypolipidemic	43661	4.42	4.3	13	22-66^
trimethoprim		antibiotic	8836	0.594	7.3	80	18.3 (<10-40)[+]

[!] – based on NHS prescription data for 2009, # - Chemspider; [+] - Paxeus, 2004; [%] - Zorita *et al*., 2009; ^Lee *et al*., 2009 (data for other statins); [-] - Buerge *et al*., 2003; [@] - Leclerq *et al*., 2009; [&] - Jacobsen *et al*., 2004; * - Kimura *et al*., 2007; [?]- Zuccato *et al*. 2005

2.2. Site selection

The aim of this task was to select three drinking water abstraction sites from rivers which would be expected to be at high risk of abstracting water containing pharmaceutical products. A fourth site, identified in the previous DWI study (Watts *et al*., 2007), was pre-selected. Since the main route of entry for pharmaceutical products is through waste water collection and treatment system, it was expected that these sites would be those below major centres of population.

A previous study had estimated the concentrations of steroid oestrogens in rivers in England and Wales (Williams et al., 2009), including ethinyloestradiol (EE2), which is the active ingredient in the oral contraceptive pill. EE2 is known to pass through sewage treatment works (Johnson and Sumpter, 2001) and to be relatively persistent in river water (Jurgens *et al*., 2002). The concentrations of EE2 should therefore be indicative of concentrations of pharmaceuticals as a whole.

For the initial site selection, we therefore assumed that river reaches with predicted higher concentrations of EE2 would also be expected to contain higher concentrations of other pharmaceutical products. Locations of drinking water abstraction points were therefore obtained from the Environment Agency and overlaid onto the map of EE2 concentrations in river waters in England and Wales. Abstraction points were then ranked in terms of their associated EE2 concentration. The top 30 sites on the ranked list were then taken forward for more detailed characterisation.

Following the initial selection, additional information was sought about each of the sites through telephone conversations with water company staff responsible for the works. In addition to selecting sites which were highly ranked in terms of EE2 concentrations, there were a number of other important selection criteria (both scientific and practical), which would all contribute to making these drinking raw water supplies vulnerable to pharmaceutical contamination which were determined in these interviews, namely:

1. The abstraction identified was still in service.

2. The abstracted water had to either enter the works directly from the river or only be stored for a short time in holding reservoirs prior to entering the works. This was to reduce the possibility of natural degradation of the pharmaceuticals during storage.

3. If the water was stored in a holding reservoir, no water abstracted from other sources should also be stored in this reservoir. If this was not the case then there was the possibility of dilution of high concentration water with low concentration water.

4. The water supply should be reasonably high volume so it could be considered to be an important source.

Following the telephone conversations five sites were visited to further assess their suitability. These included the site identified by Watts *et al*., (2007), which it should be noted would also have been selected by the methods used in this study validating its identification in the previous study as a high risk site. The main issue here was to double check that the information previously provided was as expected and to discuss the practicalities of access and sampling. In addition, information about the

treatment processes used at the works was also gathered. Of the five sites, four were suitable and were selected for monitoring (Table 3).

Table 3. Characteristics of the selected study sites

Site	Rank[#]	Abstraction and storage	Treatment
1	11	Water abstracted (100ML/day) from the river into a storage reservoir with a residence time of 12 hours	flocculation, clarification, rapid gravity filters (sand and anthracite) GAC and chlorination
2	23	Water abstracted directly from the river (~ 23 ML/day) into treatment	flocculation, clarification, rapid gravity filters (including GAC), ozone and chlorination
3*	15	Water abstracted from the river into a holding reservoir with a residence time of about 1 day	clarification, ozone, rapid gravity filters, ozone again, GAC and chlorination
4	2, 28	Water abstracted from two rivers into a storage reservoir which has a residence time of about 7 days.	clarification, ozone, rapid gravity filters, ozone again, GAC and chlorination.

- based on modelled exposure of source water to EE2; * - Scenario B in previous project (Watts *et al*., 2007)

2.3. Sampling

Site monitoring was undertaken over a period of 12 months to reflect the potential temporal variations in pharmaceutical concentrations in both source and final waters at the four selected sites.

2.3.1. Spot samples

Samples were taken from the raw water that reaches the drinking water treatment plant and from the treated water that enters supply. For both types of water, monthly samples were taken manually in triplicate for all four sites. Samples were placed in methanol-rinsed amber glass bottles (2.5 litre). Following collection, samples were placed in the dark, in cool-boxes containing frozen icepacks (at a temperature <8°C) and transported back to the laboratory for extraction and analysis.

2.3.2. Passive samplers

At two of the sites (Sites 1 and 3), passive samplers were also used. These devices accumulate analytes dissolved in the water into a receiving phase with a high affinity for the compounds of interest. The driving force for movement from the water to the receiving phase is diffusion, and so the rate of uptake by a sampler will depend on the difference between the chemical potentials of an analyte in the bulk water and in the receiving phase, and the structural properties (e.g. sampling area, presence and thickness of a diffusion limiting layer such as a the water boundary layer, and/or a polymeric membrane that separates the receiving phase from the bulk water

compartment). The mass of analyte accumulated over the deployment period can be used to calculate the time weighted average concentration of an analyte in the water. This can be achieved either by use of a theoretical relationship in which the physical and physicochemical parameters have been estimated, or by using laboratory calibration experiments. Passive samplers have been used for monitoring concentrations of pollutants in water since the 1990's. Most of the early work in this areas concentrated on the measurement of non-polar compounds (LogKow >3).

The passive monitoring in this survey utilised the Chemcatcher® passive sampler. Chemcatcher® samplers, comprising a receiving phase (SDB-XC Empore™ disk), and diffusion limiting membrane (polyethersulphone) held in a PTFE housing were used. In order to tailor the exposure of the samplers to the local conditions in the water treatment plants, an over-flow deployment device consisting of a stainless steel tank and water reservoir that is connected to a copper piping distribution system was designed and used. A constant level of water was maintained in the plastic reservoir by a continuous flow of raw and final drinking waters from taps on plant distribution pipes. Water was forced through the copper pipes by the head of pressure maintained in the plastic reservoir, and in this way a turbulent flow was maintained over the sampling surfaces of the Chemcatcher® samplers. The passive samplers were deployed between February 2010 and August 2010 on a monthly basis (at Site 3 it was not possible to monitor for the whole period due to site closures). On sampler retrieval dates, chemcatchers® were removed from the cage and water was added before closing the transport lid.

In order to derive time-weighted average concentrations from the passive sampler measurements of pharmaceutical mass, a calibration study was done at the University of Portsmouth for atenolol, benzoylecgonine, caffeine, carbamazepine, cocaine, diclofenac, furosemide, ibuprofen, ketoprofen, naproxen and trimethoprim. Two compounds (norfluoxetine and fluoxetine) were omitted from the calibration study because of the high costs of analytical standards, and the large quantities needed to maintain the high flow rate of spiked calibration water.

Samplers were attached to the aluminium mesh lid of a calibration tank so that the sampling face was constantly immersed. A flow of water, spiked with the pharmaceuticals of interest, was then maintained through the system. Pharmaceuticals were introduced in a methanolic spiking solution (2 mg l^{-1} of each compound) using an HPLC pump (0.2 mL min^{-1}) into a copper tube carrying a flow (~2 L h-1) of tap water regulated by a needle valve. The overall flow rate was selected on the basis of field measurements in the two water treatment plants. The stock solution of pharmaceuticals was stirred constantly using a magnetic stirrer. Spot samples of water were taken frequently, extracted using Empore disks SDB-XC, and analysed by LC-MS-MS. Temperature, pH and water flow were checked regularly, and 5 Chemcatcher blanks were used to check for laboratory contamination. The mass of each analyte accumulated by the devices at a range of deployment times was then determined.

In the integrative phase there is a straight line relationship between the mass accumulated and elapsed time from deployment (equation 1). The slope of this calibration curve has units of mass per time.

$$C_w = m_t/R_s t \qquad \text{Eqn 1}$$

Where Cw is the concentration in the water, mt is the mass accumulated in the sampler after a deployment time of t, and Rs is the sampling rate under the calibration conditions.

Rs is calculated by dividing the slope of the calibration curve by the concentration of analyte in the water. This can then be used to calculate the time weighted average (TWA) concentration of an analyte under field conditions that match those used in the laboratory by measuring the mass (mt) accumulated over a deployment time t, and substituting the values into equation 1.

2.4. Pharmaceutical analysis

2.4.1. Spot sample extraction, clean-up and concentration

Samples of treated and raw waters (typically 1 litre) were pH adjusted (pH 7.5-8.2) and appropriate internal standards added prior to loading onto a pre-conditioned Waters HLB solid Phase Extraction SPE) (cartridge (200mg/6ml) . The loading rate did not exceed 10 ml/min and the eluate was discarded. The cartridge was washed with water (5 ml) before air drying (under vacuum) for at least 30 minutes. The analytes were then eluted with methanol (8 ml) and then concentrated, under a stream of nitrogen, to a low volume (approximately 50 µl). The extract was reconstituted to a volume of 1 ml using a 90:10 solution of water/methanol prior to analysis by liquid chromatography tandem mass spectrometry (LC-MS/MS).

For some samples it was necessary to use up to three SPE cartridges and to combine the eluates. In cases where it was not possible to load 1000 ml of sample, the remaining volume was measured and the measured concentrations of analytes corrected accordingly.

All sample batches included a blank sample (tap water) and samples over-spiked with analytes of interest at different concentrations to assess analytical recovery for those compounds for which labelled internal standards were not available. All measurements were based on matrix-matched calibration standards.

2.4.2. Passive sampler extraction

After collection, sampler devices were processed as follows: chemcatchers® were rinsed with distilled water and disassembled in a clean area. PES membranes were removed from the top of the disk with clean stainless steel tweezers and the disks were placed on the vacuum manifold and dried for approximately 30 minutes or until dried. Each disk and SDB-XC Empore™ disks were eluted with 18 ml of methanol (HPLC grade). Deuterated compounds were spiked into extracts to correct for recoveries and extracts were reduced to dryness using a gentle nitrogen flow. Samples were then redissolved in 1 ml of 90:10 solution of water/methanol and sent for LC-MS analysis.

2.4.3. LC-MS/MS analysis

LC-MS/MS analyses were performed using a Waters Acquity Ultra-Performance Liquid Chromatography (UPLC) system (Waters, Milford MA, US). Chromatography was performed using a UPLC HSS T3 C18 column (100 x 2.1 mm I.D., 1.8 µm particle size, Waters, Milford MA, US), maintained at 40ºC, with a mobile phase flow rate of 0.5 ml/min. The mobile phase compositions were 5 mM ammonium acetate in water (A) and methanol (B). Gradient elution was employed, starting at 2% B and rising linearly to 50% B over 4 minutes then it was held for 0.3 min at 50% B. Then from 4.3 min to 8 min gradient elution continued from 50%B to 98%B. The composition was held at 98 % B for 3 minutes before returning to the initial conditions, followed by re-equilibration for 2 minutes, giving a total cycle time of 13 minutes. The injection volume of extracts was 20 µl. These UPLC conditions provided the best compromise between speed and chromatographic performance. Separation

between compounds was sufficient for polarity switching to allow all compounds to be acquired in a single run.

The Waters Premier XE LC-MS/MS parameters giving the best overall results were; Capillary Voltage (3000V - positive mode, 2800V – negative mode) Cone Voltage (10-40V), Desolvation Temp (450 °C), Source Temp (120°C), Cone Gas Flow (100 L/hr) and Desolvation gas flow (900 L/hr). Cone voltage and Collision Energy were optimised for each analyte. Further details for individual compounds including MS/MS transitions are provided in Table 4.

Table 4. Summary of UPLC-MS/MS parameters and limits of detection for the analytical method

	tR (min)	MRM transitions	CV (V)	CE (eV)	Internal std	LoD* (ng/l)
atenolol	2.15	267.3-145	32	26	Atenolol d7	2
		267.3-190.1		18		
benzoylecgonine	3.46	290.3-168.1	32	20	Benzoylecgonine	1
		290.3-105		28	d8	
caffeine	3.17	195.2-138	32	20	Caffeine 13C3	2
		195.2-110		24		
carbamazepine	5.48	237.3-194.1	30	20	Carbamazepine	1
		237.3-179.1		34	d10	
carbamazepine	4.7	253.2-180	18	28	-	1
epoxide		253.2-236.1		12		
cocaine	5.1	304.3-182.1	32	20	-	5
		304.3-105		32		
cyclophosphamide	4.65	261-139.9	28	22	-	1
		261-105.9		18		
diclofenac	5.8	294-249.9	22	12	-	10
		294-213.9		18		
fluoxetine	6.2	310.3-44.2	20	12	Fluoxetine d5	5
		310.3-148.1		8		
furosemide	3.88	331.1-81.1	10	10	-	5
Ibuprofen	6	205-160.9	22	6	Ibuprofen d3	2
ketoprofen	4.9	255.3-209.1	28	14	-	1
		255.3-105.1		24		
naproxen	4.85	231.2-185.1	20	14	-	1
		231.2-170		26		
norfluoxetine	6.15	296.3-134.1	12	6	-	10
		296.3-30.5		8		
orlistat	8.7	518.5-182.1	47	22	-	10
		496.5-319.4	26	12		
		496.5-114.1	26	28		

	tR (min)	MRM transitions	CV (V)	CE (eV)	Internal std	LoD* (ng/l)
simvastatin	7.85	441.4-325.3	52	24	-	50
		419.4-285.3	20	10		
		419.4-199.2	20	18		
trimethoprim	3.9	291.3-123.1	36	30	-	5
		291.3-230.2		22		

* - Slight variations in LOD did occur for some compounds during the study

3. RESULTS

Results of the 12-month monitoring study are presented below. Due to temporary site closures, it was not possible to take samples of treated water from Site 3 in January to May and June 2010, source water from Site 3 in March and April and June and of source and treated water from Site 2 in February 2010 (Table 5). Passive sampler data were only generated for the period February to Aug 2010 from Site 1 and for May, July and Aug 2010 for Site 3.

Table 5. Dates of sampling of raw and treated water at the four study sites. A – indicates that a sample was not taken due to site closure. SW = untreated water; TW = treated water.

sampling	Site 1		Site 2		Site 3		Site 4	
	SW	TW	SW	TW	SW	TW	SW	TW
1	20/09/09				22/09/09			
2	20/10/09				21/10/09			
3	17/11/09				19/11/09			
4	15/12/09				16/12/09			
5	12/01/10				15/01/10	-	19/01/10	
6	9/02/10		-		9/02/10	-	9/02/10	
7	9/03/10				-		9/03/10	
8	6/04/10				-		7/04/10	
9	4/05/10				5/05/10			
10	2/06/2010		1/06/10		-		2/06/10	
11	25/06/10		28/06/10		5/07/10			
12	27/07/2010				27/07/10			
13	24/08/2010				24/08/10			

3.1. Spot samples

Mean monthly concentrations at each site are presented in Appendix B and a summary of the concentrations in spot samples is presented in Table 6 (in instances where concentrations in a replicate was lower than the limit of detection, a value of zero was assumed). Cocaine, cyclophosphamide, fluoxetine, norfluoxetine, ketoprofen and orlistat were not detected in any of the spot samples obtained from any of the sites. Atenolol, diclofenac, furosemide and trimethoprim were detected in source water samples from all four sites (Table 6; Figures 1-4) but were not detected in treated drinking water samples.

Benzoylecgonine, caffeine, carbamazepine, carbamazepine epoxide, ibuprofen and naproxen were detected in both untreated source water and treated water (Figures 5a and b -10a and b). With the exception of carbamazepine epoxide at Sites 2 and 4, and carbamazepine at site 2 on one sampling occasion, concentrations in treated water were significantly lower than in the source waters.

Estimated removal efficiencies for the study compounds ranged from 69-100% for benzoylecgonine, 51-100% for caffeine, -6.91-100% for carbamazepine, -131-100% for carbamazepine epoxide, 89-100% for ibuprofen and 89-100% naproxen (Figures 5c -10c).

Table 6. Median concentrations (ng/l) (based on the mean monthly values) for the study compounds in source and treated waters at the study sites. Values are obtained from means for each sampling period. Ranges are provided in parentheses.

	site 1		site 2		site 3		site 4	
	source	treated	source	treated	source	treated	source	treated
atenolol	38.8 (18.1 – 66.3)	<2	53.0 (31.2 – 91.2)	<2	18.4 (8.2 – 67.6)	<2	25.3 (19.6 – 114)	<2
benzoylecgonine	1.2 (<1 – 2.06)	<1	3.12 (<1 – 5.77)	<1	2.85 (1.25 – 4.80)	<1	9.80 (1.99 – 16.3)	1.98 (<1 – 3.51)
caffeine	176 (86.7 – 441)	15.7 (7.56 – 79.3)	93.8 (63.7 – 224)	8.75 (3.05 – 46.3)	102 (54.7 – 199)	4.05 (<2 – 8.83)	227 (82.2 – 329)	13.5 (<2 – 29.2)
carbamazepine	86.3 (49.4 – 199)	11.8 (8.37 – 17.3)	139 (45.0 – 277)	2.88 (1.22 – 148)	255 (34.3 – 555)	<1 (<1 – 1.25)	185 (16.4 – 480)	1.03 (<1 – 3.96)
carbamazepine epoxide	6.53 (2.83 – 11.3)	3.89 (2.27 – 6.10)	7.50 (2.47 – 19.7)	4.92 (2.88 – 16.6)	13.2 (<1 – 24.7)	4.45 (<1 – 6.01)	7.62 (1.12 – 16.7)	6.24 (1.93 – 10.7)
cocaine	<5	<5	<5	<5	<5	<5	<5	<5
cyclophosphamide	<1	<1	<1	<1	<1	<1	<1	<1
diclofenac	<10 (<10 – 24.3)	<10	12.3 (<10 – 39.0)	<10	12.6 (<10 – 76.3)	<10	11.9 (<10 – 47.1)	<10
fluoxetine	<5	<5	<5	<5	<5	<5	<5	<5
furosemide	6.44 (<5 – 28.9)	<5	17.0 (<5 – 43.1)	<5	<5 (<5 – 36.0)	<5	13.3 (<5 – 63.5)	<5
ibuprofen	19.4 (6.33 – 30.8)	<2 (<2 - 3.07)	10.2 (<2 – 38.4)	<2	6.77 (<2 – 21.5)	<2	17.1 (<2 – 38.2)	<2
ketoprofen	<1	<1	<1	<1	<1	<1	<1	<1
naproxen	17.3 (10.2 – 26.4)	<1	17.7 (6.93 – 42.2)	<1	12.4 (4.85 – 28.9)	<1	21.7 (11.1 – 44.4)	<1 (<1- 2.72)
norfluoxetine	<10	<10	<10	<10	<10	<10	<10	<10
orlistat	<10	<10	<10	<10	<10	<10	<10	<10
simvastatin	<50	<50	<50	<50	<50	<50	<50	<50
trimethoprim	11.0 (<5 – 13.8)	<5	10.4 (<5 – 13.8)	<5	<5 (<5 – 8.27)	<5	6.1 (<5 – 26.4)	<5

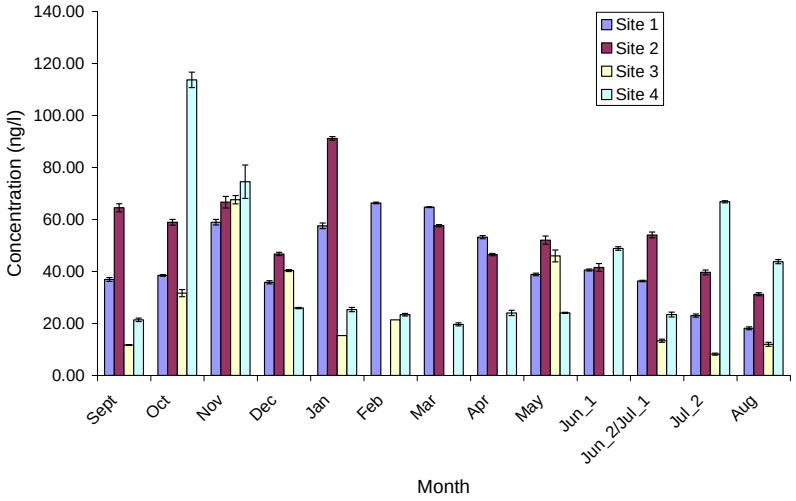


Figure 1. Mean concentrations (±S.D) of atenolol in untreated source waters at the four study sites.

A)

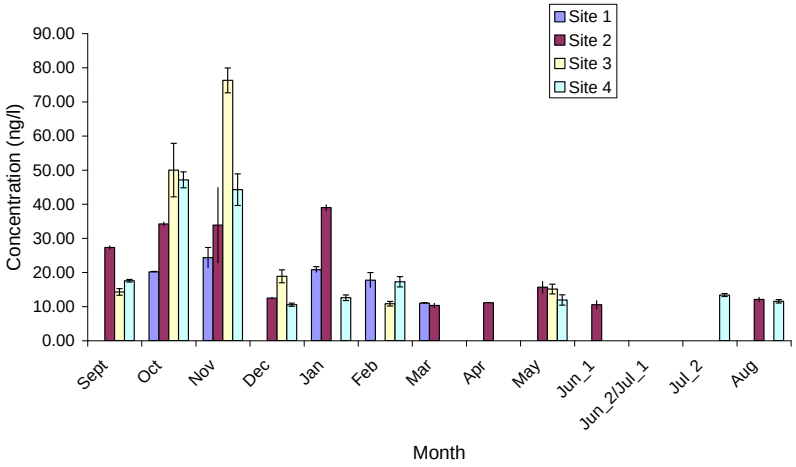


Figure 2. Mean concentrations (±S.D) of diclofenac in untreated source waters at the four study sites.

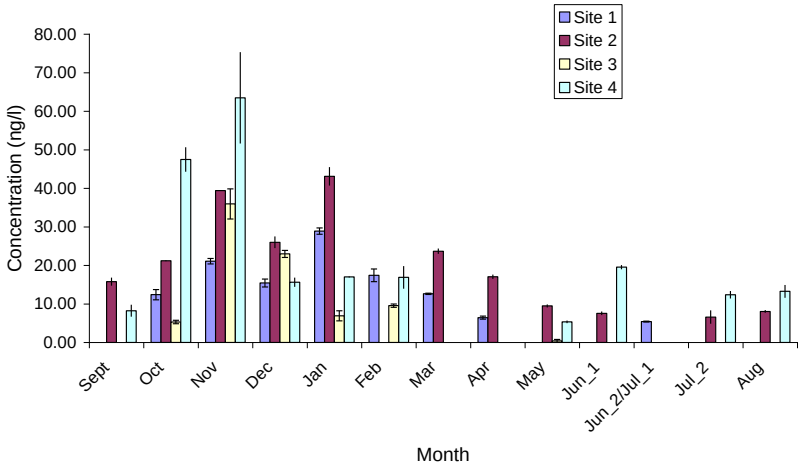


Figure 3. Mean concentrations (±S.D) of furosemide in untreated source waters at the four study sites.

A)

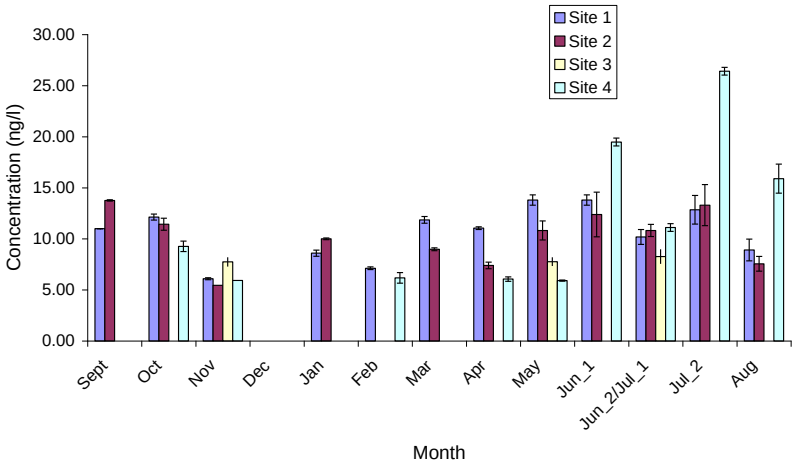
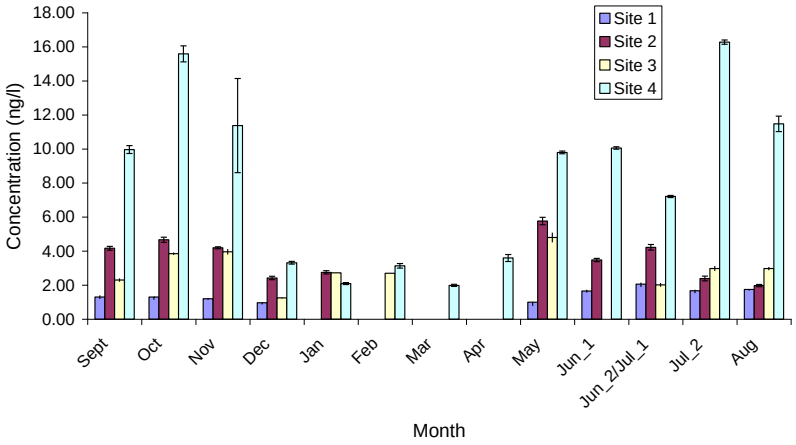
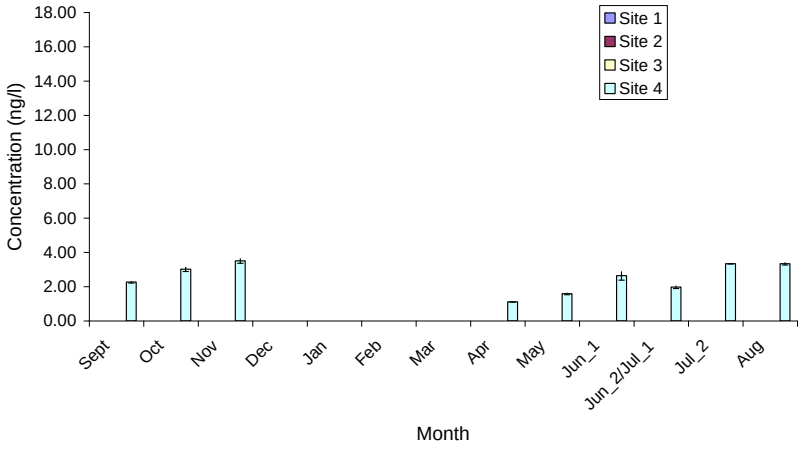


Figure 4 Mean concentrations (±S.D) of trimethoprim in untreated source waters at the four study sites.

A)



B)



C)

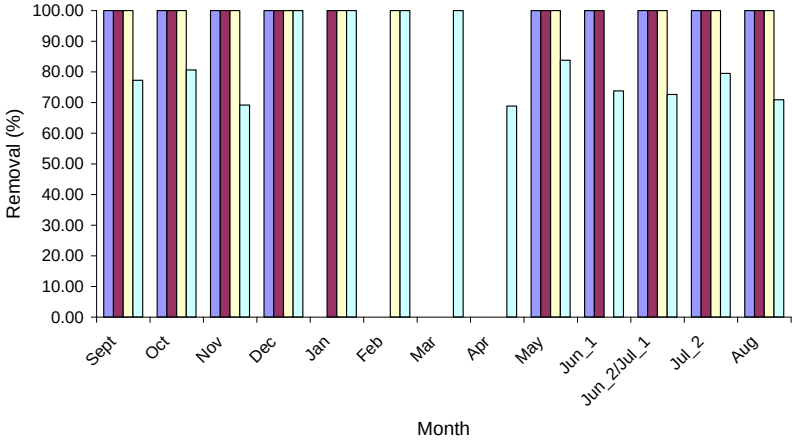
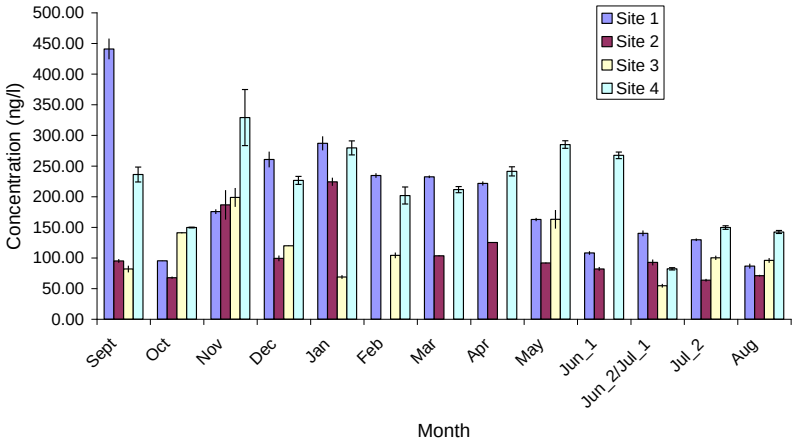
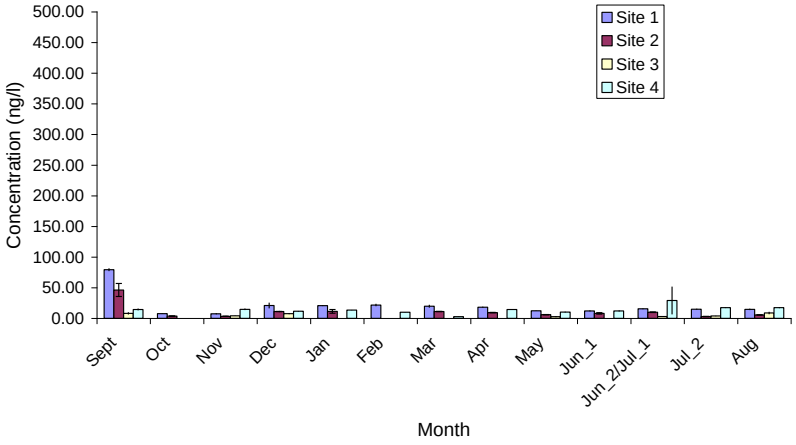


Figure 5. Mean concentrations (±S.D) of benzoylecgonine in A) untreated source waters and B) treated drinking water at the four study sites. Graph C indicates the treatment efficiency for removal of the compound at the four sites.

A)



B)



C)

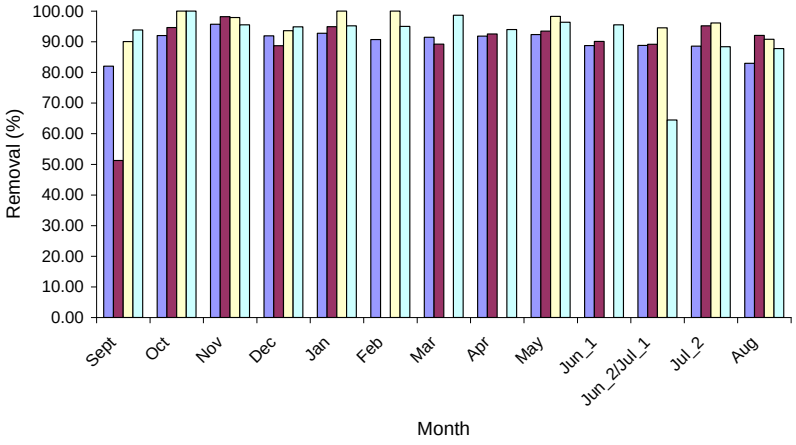


Figure 6. Mean concentrations (±S.D) of caffeine in A) untreated source waters and B) treated drinking water at the four study sites. Graph C indicates the treatment efficiency for removal of the compound at the four sites.

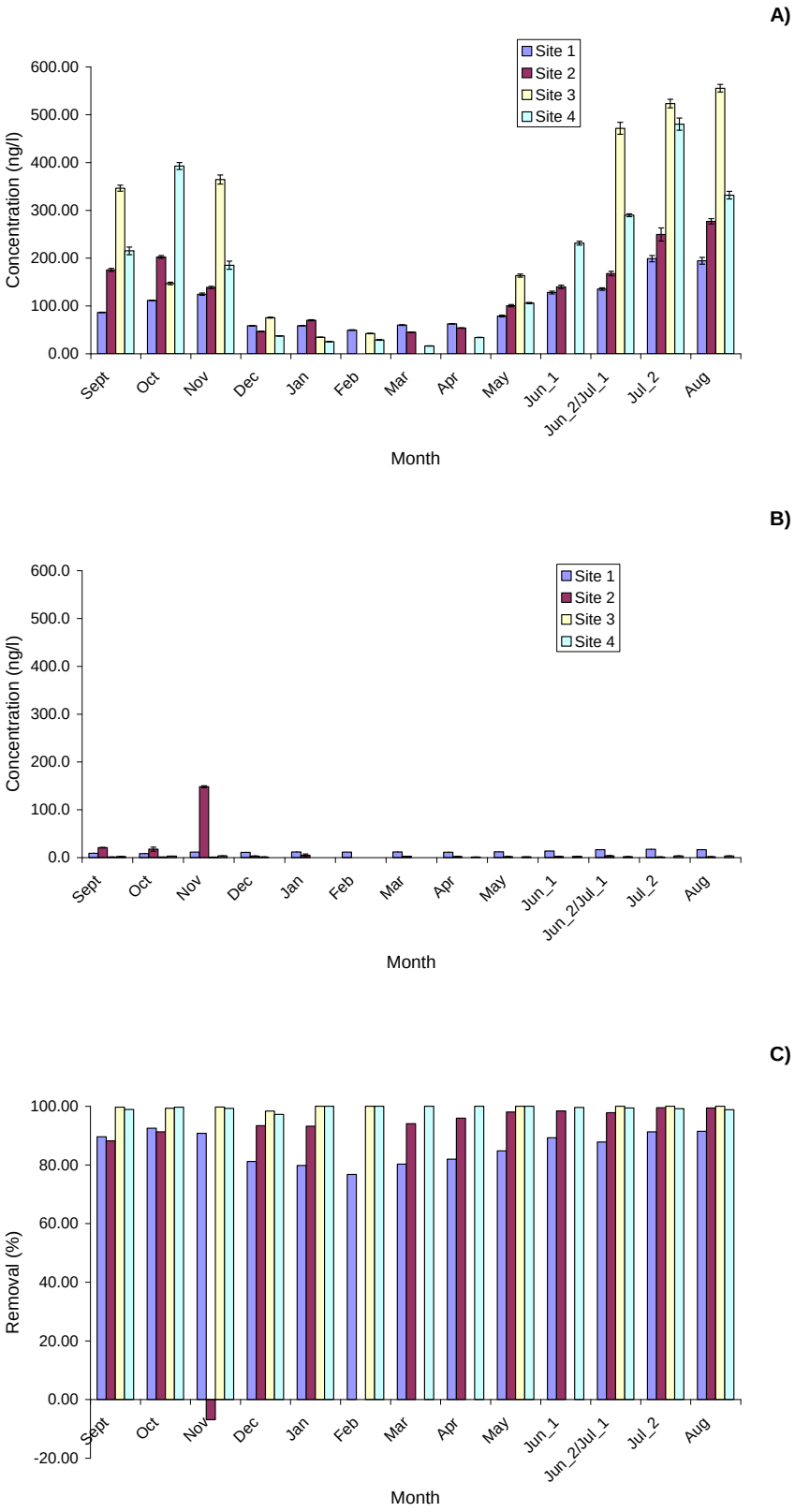


Figure 7. Mean concentrations (±S.D) of carbamazepine in A) untreated source waters and B) treated drinking water at the four study sites. Graph C indicates the treatment efficiency for removal of the compound at the four sites.

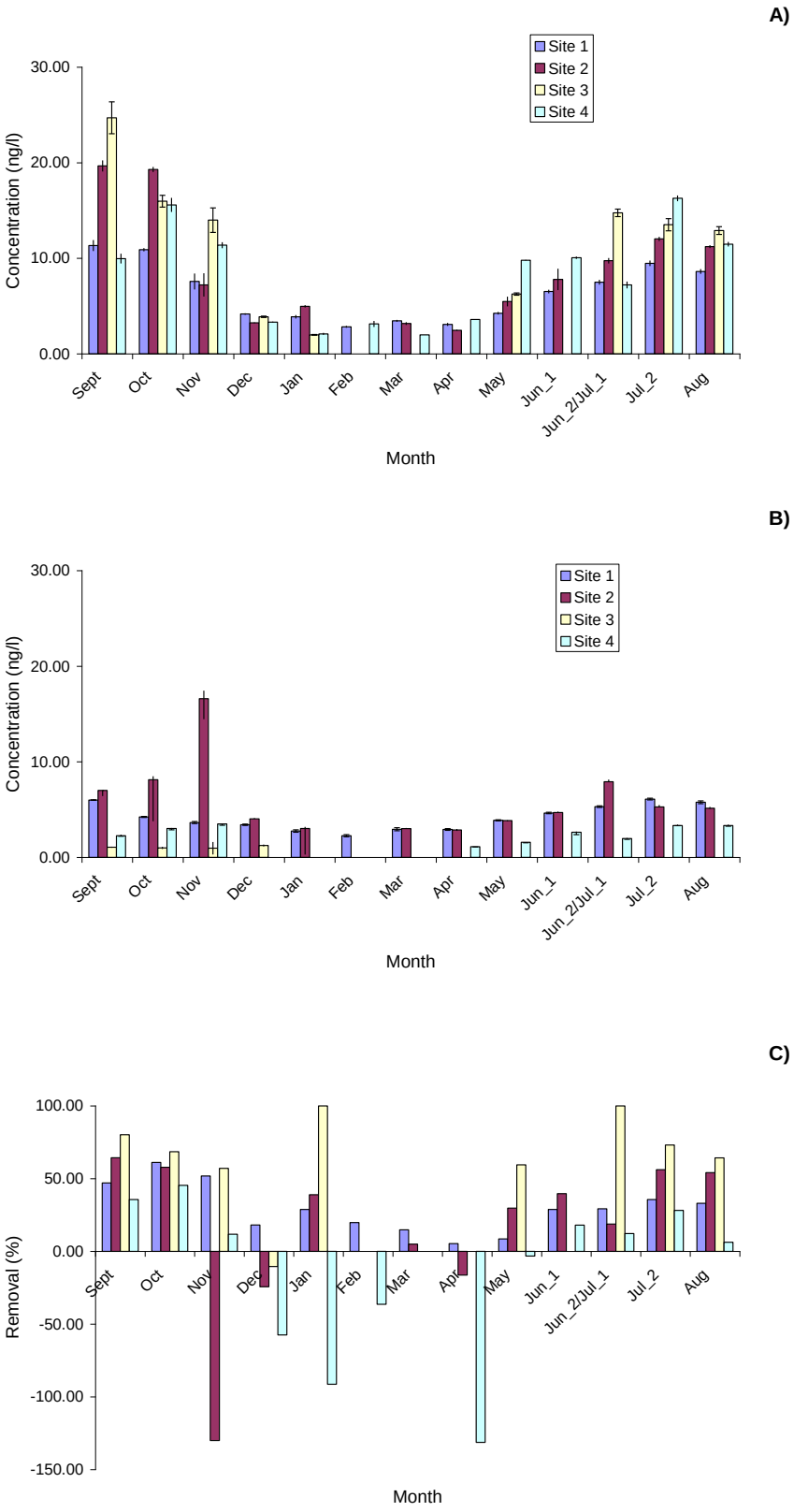


Figure 8. Mean concentrations (±S.D) of carbamazepine epoxide in A) untreated source waters and B) treated drinking water at the four study sites. Graph C indicates the treatment efficiency for removal of the compound at the four sites.

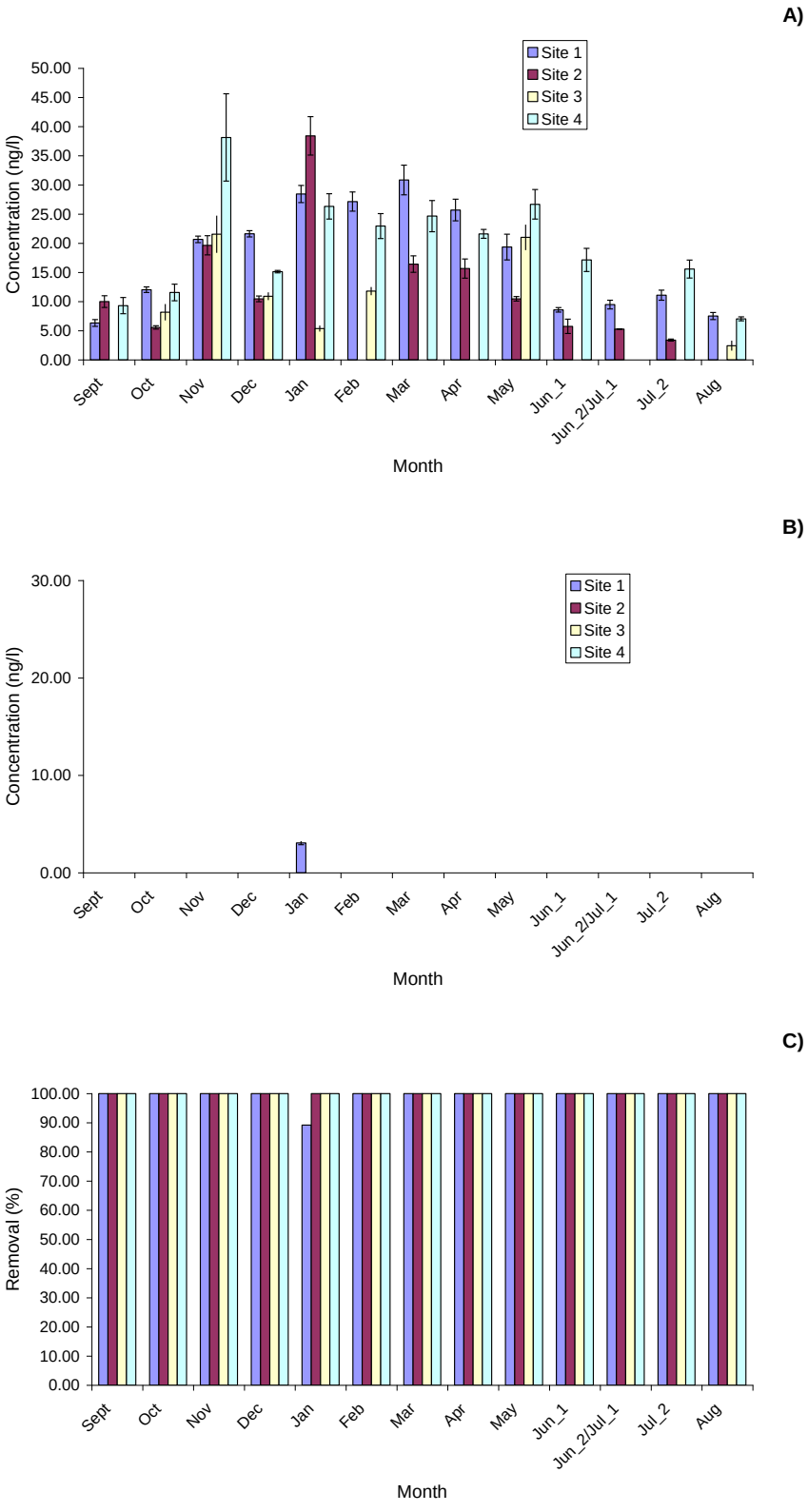


Figure 9. Mean concentrations (±S.D) of ibuprofen in A) untreated source waters and B) treated drinking water at the four study sites. Graph C indicates the treatment efficiency for removal of the compound at the four sites.

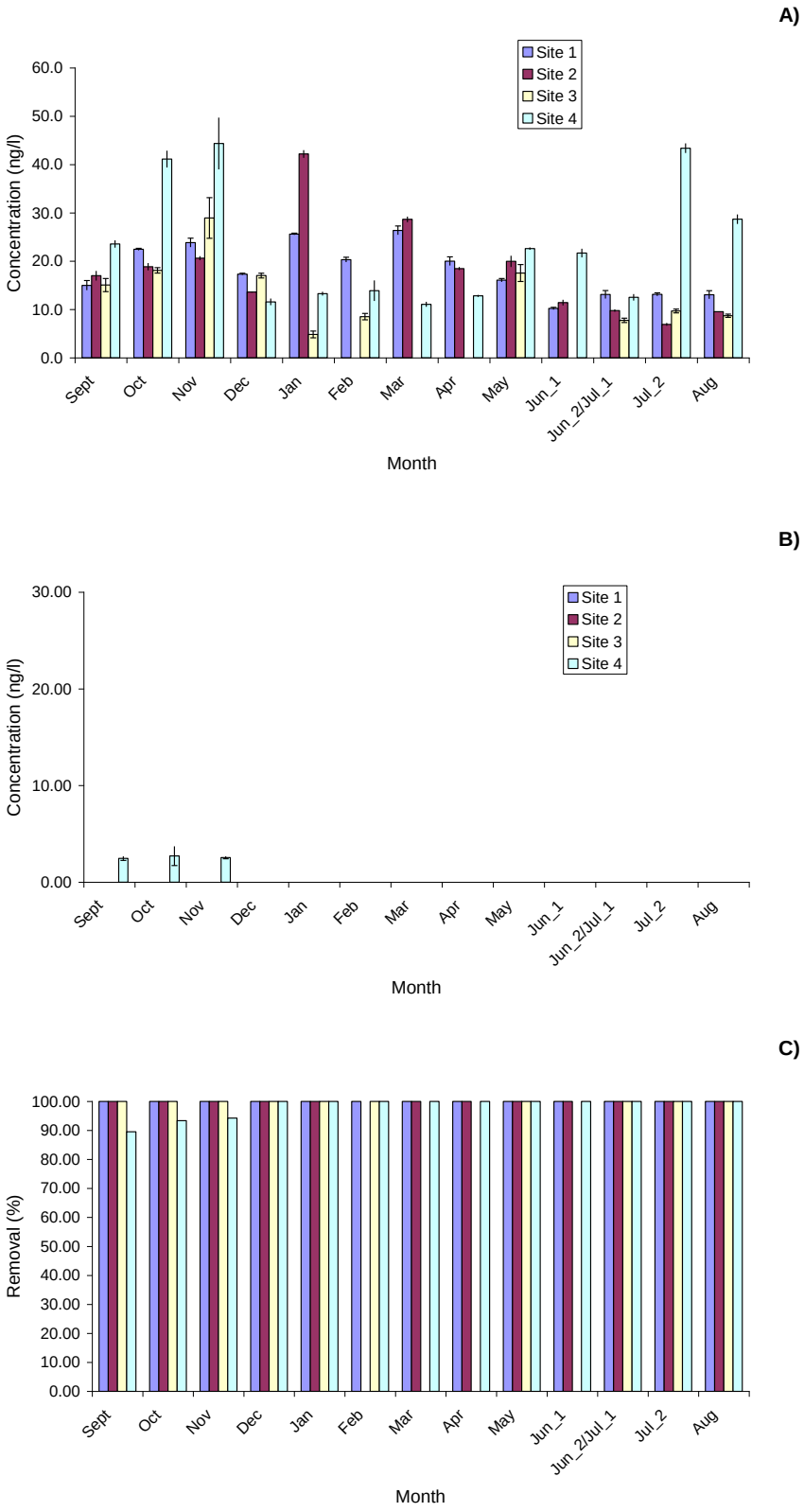


Figure 10. Mean concentrations (±S.D) of naproxen in A) untreated source waters and B) treated drinking water at the four study sites. Graph C indicates the treatment efficiency for removal of the compound at the four sites.

3.2. Passive samplers

The masses of individual pharmaceuticals recovered in the receiving phase of the Chemcatchers are given in Appendix C and estimated water concentrations are given in Appendix D.

Field blank passive samplers were used to check for laboratory contamination during preparation. One blank per field visit was used at Site 1, and two at Site 3. Atenolol, benzoylecgonine, diclofenac, furosemide, ibuprofen and ketoprofen were not detected in any of the blanks. Carbamazepine, cocaine and diclofenac were each detected in one out of the ten blank samples at amounts close to the analytical limit of detection. Trimethoprim was detected in three of the ten blanks at amounts close to the LOD. Caffeine was detected in seven out of ten blanks, in six of these the levels were close to the LOD. Concentrations of fluoxetine and for norfluoxetine in the blanks were high compared to samples of raw and treated waters. Based on these findings it was concluded that the results for fluoxetine and norfluoxetine were unreliable so these data are not discussed further. For other substances that had been regularly been seen in the blank samples, the results were blank corrected by deducting the masses seen on the blank samplers from the masses seen on the raw and treated water samplers.

The results for the passive samplers deployed in source water and treated water are summarised in Table 7. Benzoylecgonine, cocaine and ketoprofen were not detected in any sample. Caffeine, ibuprofen, naproxen, carbamazepine, atenolol, and diclofenac were detected in one or more of the passive samplers and it was possible to estimate corresponding time-weighted average (TWA) concentrations in water for these substances (Table 7). While trimethoprim and furosemide were detected in some of the passive samplers, due to problems with the calibration experiments (i.e. neither compound was detectable in the calibration tank water or the calibration samplers), it was not possible to estimate TWA concentrations for these substances. Data for these two compounds are therefore only presented as either ‘detected’ or ‘non-detected’.

Results obtained from the passive sampling at the two study sites are compared to the results of the spot sampling in Figures 11 and 12. There was fair agreement between the concentration estimates obtained from passive sampling with measured concentrations in spot samples for atenolol and caffeine (Figures 11 and 12). For ibuprofen and naproxen there was a poorer agreement in numerical terms, but reasonable agreement in terms of presence or absence in individual sampling periods. For carbamazepine the estimated concentrations at Site 1 from passive sampling were considerably higher than measurements from spot sampling (Figure 11). In contrast, at Site 3, estimated concentrations from the passive samplers were lower than concentrations detected in the spot samples (Figure 12). Diclofenac was only rarely detected in either passive samplers or spot samples and there was limited agreement between the two approaches in terms of presence or absence of the compound.

The mismatch between the passive sampler results and spot sample data may be due to the large uncertainties in the indicative sampling rates. Low sampling rates (less than 10 ml d^{-1}) were seen for the passive samplers in the calibration experiments. The regression line calibration fits were also poor for many of the study compounds (Appendix E; e.g. for carbamazepine, an r^2 value of only 0.24 was obtained). These uncertainties are probably a function of the low temperature, and poor turbulence in the calibration experiments (as these were set up to mimic the field sampling conditions, similar low rates would be expected in the field). Much

higher sampling rates (in the range of 10's – 100's ml d^{-1}) are usually seen under conditions of higher turbulence that are more typical of situations where passive samplers have been successfully used in field monitoring investigations in the past. The uptake of pharmaceuticals may also have been affected in both laboratory and field by the accumulation of lime scale from the tap water, and aluminium hydroxide produced by the effects of the water on the aluminium deployment mesh, and in a few cases bacterial growth on the diffusion limiting membranes. The differences in relationships between passive and spot sample data at the two study sites, particularly for carbamazepine, also indicates that the samplers may have performed differently at the two study sites.

Table 7. Time weighted average concentration ranges (ng/l) from the seven passive sampling periods at Sites 1 and the three passive sampling periods at Site 3.

	site 1		site 3	
	source	**treated**	**source**	**treated**
atenolol	23 - 118	ND	ND	ND
benzoylecgonine	ND	ND	ND	ND
caffeine	53 - 234	ND - 55	27- 69	ND – 17
carbamazepine	80 - 2013	37 - 373	13 - 183	ND – 154
cocaine	ND	ND	ND	ND
diclofenac	ND - 96	ND	ND	ND
furosemide	Detected	ND	ND	ND
ibuprofen	14 - 90	ND	ND	ND
ketoprofen	ND	ND	ND	ND
naproxen	16 - 97	ND	ND	ND
trimethoprim	Detected	ND	Detected	ND

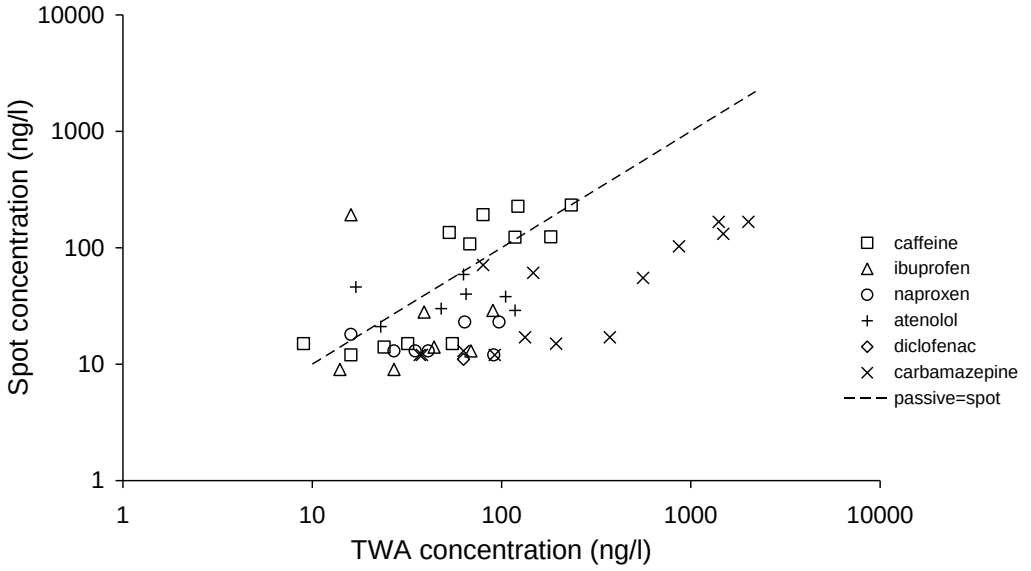


Figure 11. Comparison of time weighted average concentrations, obtained using passive samplers, in source waters and treated waters at Site 1 with concentrations from spot samples

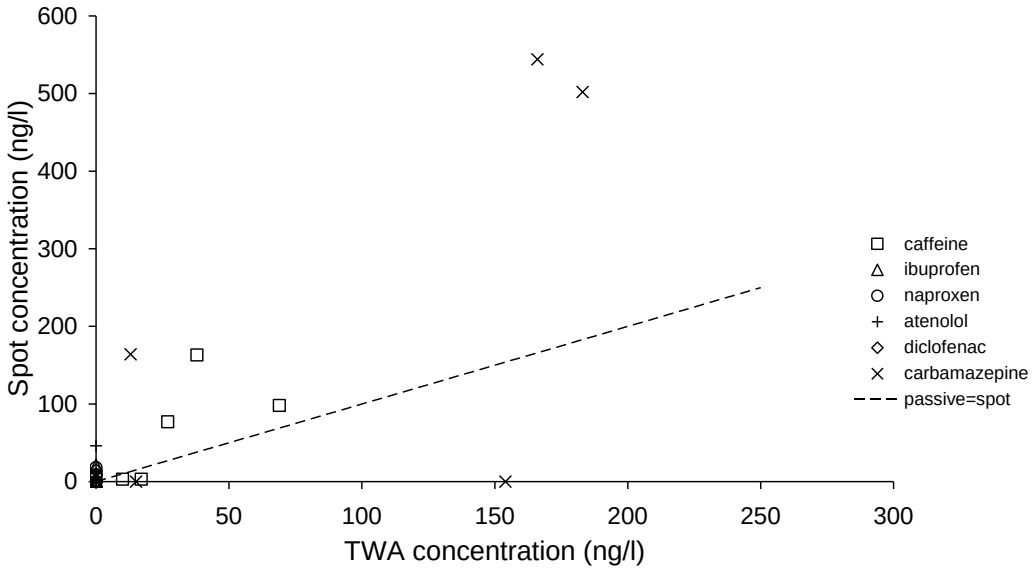


Figure 12. Comparison of time weighted average concentrations, obtained using passive samplers, in source water and treated waters at Site 3 with concentrations from spot samples

4. DISCUSSION

In the previous DWI funded study, simple modelling approaches were used alongside information on therapeutic doses of pharmaceuticals to identify substances that are likely to be of most concern in UK drinking waters. This previous study was entirely desk-based and did not make any measurements of pharmaceutical concentrations in water in England and Wales. A major recommendation from the previous study was that a targeted monitoring programme be performed to assess actual levels of exposure of pharmaceuticals in source waters and treated waters in England and Wales. The current project therefore addressed this knowledge gap by exploring the occurrence of pharmaceuticals in raw and treated waters in England.

The study considered a range of pharmaceutical compounds that have either a) high predicted exposure concentrations; b) toxicological concerns; or c) a low predicted exposure to therapeutic dose ratio. An illicit drug and its major metabolite were also investigated. The study compounds covered a range of chemical classes and varied in terms of their physico-chemical properties. The study was done at four sites where concentrations in source water at the drinking water treatment abstraction point were predicted to be some of the greatest in England.

4.1. Comparison of measurements for source waters with previous UK monitoring studies and predictions from previous DWI study

Ten of the 17 study compounds were detected in untreated source waters at sub-µg/l concentrations (based on spot sample data). A number of the study compounds have been studied in previous monitoring studies in the UK (Ashton *et al*., 2004; Thomas and Hilton, 2004; Roberts and Thomas, 2006; Boucard *et al*., 2006; Kasprzyk-Hordern *et al*., 2009). Concentration ranges seen in the current study were within the ranges reported in these previous studies (Table 8).

In the previous DWI-funded study, pharmaceuticals were prioritised based on their predicted exposure concentrations in drinking waters. Site 3 was used as a basis for this previous modelling work. A previous modelling study has also predicted the potential exposure concentrations of cytotoxic drugs in a UK catchment (Rowney et al., 2009). Comparison of the exposure predictions from these previous studies with measurements made in the current study at Site 3 showed that, with the exception of carbamazepine, measured concentrations in source waters were at least an order of magnitude lower than concentrations predicted for drinking water (Table 8).This is not surprising because of the worst case assumptions made in the Watts *et al* study. The rank order of exposure concentrations for the compounds was also different between the previous DWI-funded study and the current study.

The differences between the predicted and measured concentrations are probably explained by the fact that, due to lack of data on the fate and behaviour of pharmaceuticals in the environment, a simplistic modelling approach was used in the previous DWI project for determining exposure. This simple model did not consider either metabolism in the treated patient, or the potential for dissipation of a pharmaceutical between the wastewater effluent discharge and the drinking water abstraction point. Removal of pharmaceuticals during wastewater treatment was only considered if experimental data were available. The pharmaceutical usage data employed in the previous study was taken from 2004 so it is also possible that pharmaceutical usage has changed – this might explain the observations for carbamazepine where measured concentrations are higher than predicted

concentrations in source waters. The previous study did make it quite clear that the predicted values will be worst case estimates.

Table 8 Comparison of measured concentrations from this study with previously measured values or previously predicted concentrations. Data median values (ranges in parentheses.

	Previously predicted concentration for site 3 (ng/l)[>]	Median measured source water concentration for site 3	Median measured treated water concentrations for site 3	Results from previous monitoring in the UK (ng/l)
atenolol	8360	18.4 (8.2 – 67.6)	<2	<1 – 560[+]
benzoylecgonine	-	2.85 (1.25 – 4.80)	<1	-
caffeine	-	102 (54.7 – 199)	4.05 (<2 – 8.83)	-
carbamazepine	23	255 (34.3 – 555)	<1 (<1 – 1.25)	1 – 647[+]
carbamazepine epoxide	-	13.2 (<1 – 24.7)	4.45 (<1 – 6.01)	-
cocaine	2530	<5	<5	-
cyclophosphamide	70.2	<1	<1	-
diclofenac	5000	12.6 (<10 – 76.3)	<10	<LOQ (568)[$] <LOQ[&] <0.5 – 261[+]
fluoxetine	88.2	<5	<5	2 – 43.78*
ibuprofen	18920	<5 (<5 – 36.0)	<5	826 (5044)[$] 297 (2370)[#] 48 (930)[&] <0.3 – 74[+]
furosemide	5270	6.77 (<2 – 21.5)	<2	<6 – 636[+]
ketoprofen	230	<1	<1	<0.5 – 12[+]
naproxen	6330	12.4 (4.85 – 28.9)	<1	<0.3 – 146[+]
norfluoxetine	-	<10	<10	4.5 – 83*
orlistat	1540	<10	<10	-
simvastatin	3240	<50	<50	<50[+]
trimethoprim	1270	<5 (<5 – 8.27)	<5	<LOQ (42)[$] 9 (19)[#] 7 (569)[&] <0.5 – 120[+]

[>] - predicted values taken from Watts *et al*., 2007 except cyclophosphamide which was obtained from Rowney *et al*., 2009; [$] - Ashton *et al*., 2004; [&] - Thomas and Hilton, 2004; *- Boucard *et al*., 2006; [#] - Thomas and Hilton, 2004; [+] - Kasprzyk-Hordern *et al*., 2009. [?] – concentration range from passive samplers

In order to establish whether metabolism, removal in treatment or discrepancies in usage data do account for the differences between measurements and predictions from the previous project, exposure estimates were revised using more recent usage data, metabolism information and removal in treatment and Equation 2.

$$PEC = \frac{A \times F_{exc} \times (1 - F_{rem})}{V \times D} \qquad \text{Equation 2}$$

Where: PEC = predicted environmental concentration (mg/l); A = dose of pharmaceuticals (mg/capita/d; obtained from prescription data for England for 2009); Fexc = Fraction excreted by patient; Frem = Fraction removed in wastewater treatment works; V = Volume of wastewater per capita per day (default 147 l); D = Dilution factor for wastewater in receiving water (default 10). A population value of 51.4 Million was used in the calculations.

Revised exposure estimates were significantly lower than obtained in the previous DWI study. Estimates for furosemide and naproxen were within an order of magnitude of the measured values in source waters (Table 9). However there were still large discrepancies between predictions and measurement for diclofenac, ibuprofen and carbamazepine (Table 9). The application of a more complex model

that also considers fate in surface waters might improve the estimates for some of these substances.

4.2. Temporal and spatial variations in concentrations in source waters

Concentrations of the study compounds varied across the four study sites. There was however no clear pattern and there was no one site that had consistently higher concentrations than the other sites for all pharmaceuticals. Possible explanations for this could be differences in pharmaceutical prescribing patterns in the regions studied, differences in the design and performance of wastewater treatment works in the study catchments or differences in the dissipation behaviour of the study compounds between the emission to surface water and the drinking water abstraction points at the individual study sites.

Concentrations of the study compounds at each of the study sites also varied across the year. Differences in concentration between sampling occasions at a study site might be explained by variations in: a) prescribing patterns; b) river flows; and c) differences in dissipation rates in wastewater treatment processes and surface water bodies in a catchment over the year. These factors are discussed in more detail below.

Data are available from the National Health Service Information Centre on the number of prescriptions (by drug class) made by Primary Care Trusts in the UK on a quarterly basis. Data were therefore obtained on prescriptions of the different drug classes investigated in the study (Figure 13).

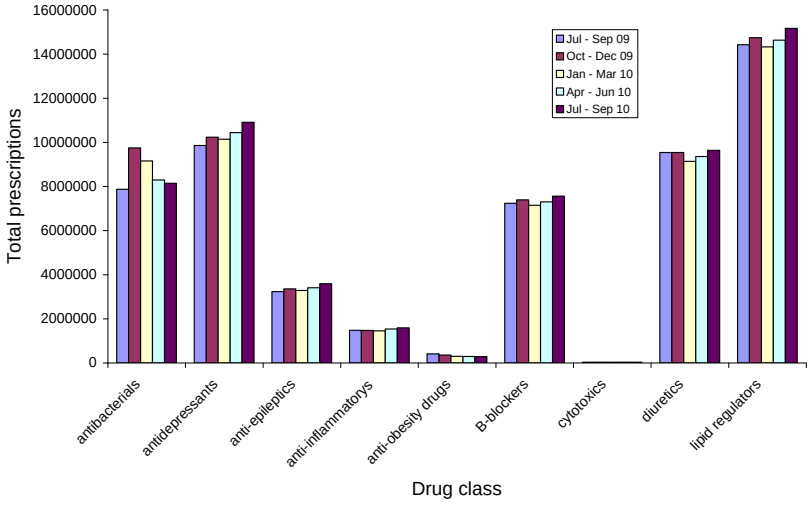


Figure 13. Total prescriptions for the study pharmaceutical compound classes for England. Derived from Primary Care Trust prescription data from the NHS Information Centre.

Table 9 Comparison of measured concentrations of the study compounds with concentrations predicted using a simple model

Compound	Use in England (kg/yr)	Excreted unchanged (%)	STP removal (%)	Median measured concentration (ng/l)	PEC (ng/l)	MEC:PEC
atenolol	27780	100	10	40 (8.2 – 114)	907	0.04
carbamazepine	39069	1	17	132 (16.4 – 555)	11.8	11.2
cyclophosphamide	11.6	25	0	<5	0.1	NA
diclofenac	151297	22.5	31	10.6 (<10 – 76.3)	852	0.01
fluoxetine	4640	5	90	<5	0.8	NA
furosemide	15210	65	37.5	9.6 (<5 - 63.5)	224	0.04
ibuprofen	262553	4.5	85.7	11.7 (<2 - 38.4)	61.3	0.19
ketoprofen	39959	1	55	<1	6.5	NA
naproxen	53082	1	72	17.0 (4.9 - 44.4)	5.4	3.1
orlistat	11434	100	0	<10	415	NA
simvastatin	43661	13	44	<50	115	NA
trimethoprim	8836	80	18.3	8.0 (<5 - 26.4)	209	0.04

With the exception of the antibacterial class, where use from October to December was around 17-20% greater than use from April to September, there was little variation in the usage of the different classes of pharmaceutical studied (Figure 17). The data therefore suggest that, with the exception of trimethoprim, variations in concentration over time are not caused by variations in use of a particular compound.

Data on river flows in England and Wales are collected by the Environment Agency. Flow data for the nearest gauging station to each site for the full study period are shown graphically in Appendix F. In order to explore whether differences in concentrations over time could partly be explained by differences in river flows, relationships between flow data and concentrations of carbamazepine were explored. Carbamazepine is recalcitrant in the environment so is a good compound for this type of analysis. For all sites, there was a trend towards lower carbamazepine concentrations at higher flow rates (Figure 14) although this did not explain all the variability in measured concentrations. The results therefore indicate that river flow is an important factor in determining pharmaceutical concentrations but, even for a compound like carbamazepine, river flow alone does not explain all the variation in observed concentrations.

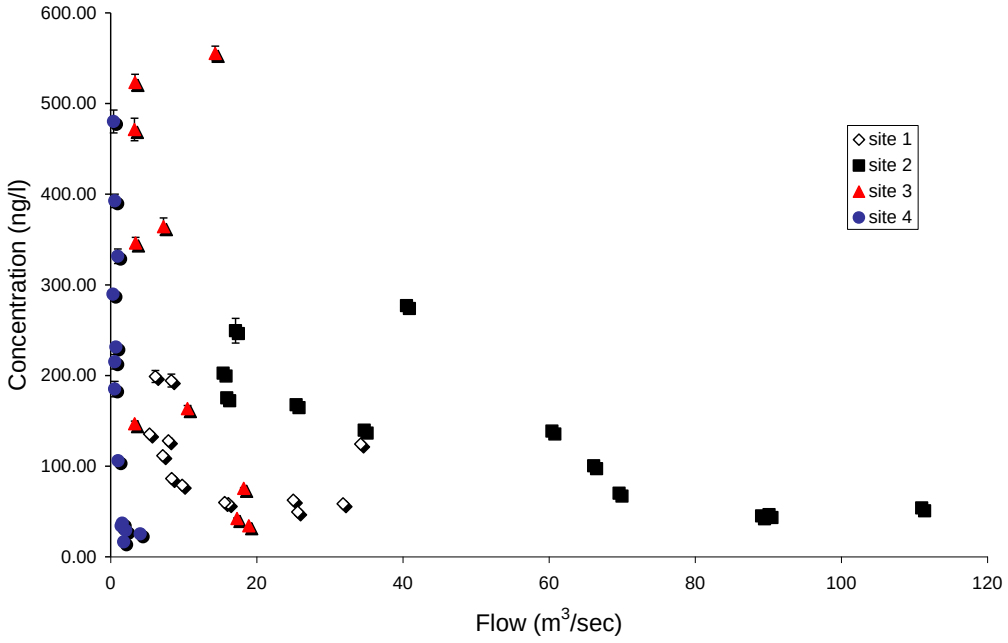


Figure 14. Relationship between measured concentrations of carbamazepine in source water and river flow rate at the four study sites over the study period.

4.3. Concentrations in drinking waters

Six of the 17 study compounds were detected in treated drinking water at the study sites, namely benzoylecgonine, caffeine, carbamazepine, carbamazepine epoxide, ibuprofen and naproxen. With the exception of carbamazepine epoxide, concentrations in the treated drinking water were significantly lower than in the source waters. The measured concentrations of the study compounds in drinking water samples were in good agreement with concentrations measured previously in similar studies that have monitored the study pharmaceuticals in drinking water in the USA, Canada, Spain and Sweden (Table 10).

By comparing monthly concentrations in both source water and treated drinking water, it is possible to develop a rough estimate of the removal efficiencies for the

study compounds in the treatment works that were investigated. Removal efficiencies for atenolol, diclofenac, furosemide and trimethoprim were 100% at all study sites on all sampling occasions. Estimated removal efficiencies for the other study compounds ranged from 69-100% for benzoylecgonine, 51-100% for caffeine, 77 - 100% for carbamazepine (on one occasion removal was -6.91% at one site), -131-100% for carbamazepine epoxide, 89-100% for ibuprofen and 89-100% naproxen (Table 11). With the exception of carbamazepine epoxide, these removal efficiencies are in good agreement with removal efficiencies seen in similar studies elsewhere (Table 11).

Table 10 Comparison of measured concentrations in drinking water from this study with measured concentrations from previous studies. Results from previous studies are either presented at mean or media concentrations with maximum concentrations in parentheses or as maximum concentrations

	Results from previous monitoring (ng/l)	Concentration in drinking water (ng/l)
atenolol	1.2 (18)[+]	<2
	12 (23)[$]	
	<0.1 – 1.3[@]	
caffeine	119*	11.2 (<2 – 79.3)
	ND[&]	ND – 69[?]
carbamazepine	6.0 (18)[+]	2.3 (<1 – 148)
	ND[$]	ND – 373[?]
	0.21 (601)[#]	
	258*	
carbamazepine epoxide	2 (1)[$]	14.5 (<1 – 16.6)
diclofenac	ND[+]	<10
	<0.1 – 0.7[@]	
fluoxetine	0.7 (0.82)[+]	<5
	ND[^]	
	ND*	
ibuprofen	ND[^]	<2 (<2 – 3.07)
	0.33 (25)[#]	
	ND*	
	<0.1 – 1.3[@]	
furosemide	ND[$]	<5
	ND*	
	<0.7 – 1.5[@]	
naproxen	ND[+]	<1 (<1 – 2.72)
	ND[^]	
	<1 – 1.3[@]	
norfluoxetine	ND[+]	<10
trimethoprim	ND[+]	<5
	ND*	
	<0.3 – 0.5[@]	

[+] - Benotti *et al*., 2009; [^] - Boyd *et al*., 2003; [$] - Huerta-Fontela *et al*., 2011; [#] - Kleywegt *et al*., 2011; * - Stackelberg *et al*., 2004; [&] -Stackelberg *et al*., 2007; [@] - Wahlberg *et al*., 2011; ? – passive sampling data

Concentrations of carbamazepine epoxide were higher in a number of drinking water samples obtained Sites 2 and 4 than the corresponding source water concentrations. One possible explanation for the some of the observed increases in concentration for this compound is that the treatment processes at these two plants convert the parent carbamazepine that occurs in source waters to the epoxide. Work by Kotcharaksa (2008) into the degradation mechanisms of carbamazepine during chlorination supports this hypothesis. In this study, carbamazepine epoxide was observed to be

one of the reaction intermediates formed during the chlorination of carbamazepine (Figure 15). This highlights the importance of considering the potential risks of transformation products of pharmaceuticals in drinking waters.

Table 11 Comparison of removal efficiencies for the study drinking water treatment plants with previously reported removal efficiencies for conventional treatment plants.

	Removal in drinking water treatment (%)		Reference
	Current study	Previous studies	
atenolol	100	97	Huerta-Fontela *et al*., 2011
benzoylecgonine	69 - 100	82	Huerta-Fontela *et al*., 2008
caffeine	51 - 100	88	Stackelberg *et al*., 2007
carbamazepine	77* - 100	85 - >99	Stackelberg *et al*., 2007; Huerta-Fontela *et al*., 2011
carbamazepine epoxide	-131 - 100	99	Huerta-Fontela *et al*., 2011
furosemide	100	>99	Huerta-Fontela *et al*., 2011
naproxen	90 - 100	100	Boyd *et al*., 2003

*- one outlier value (-6.9%) omitted

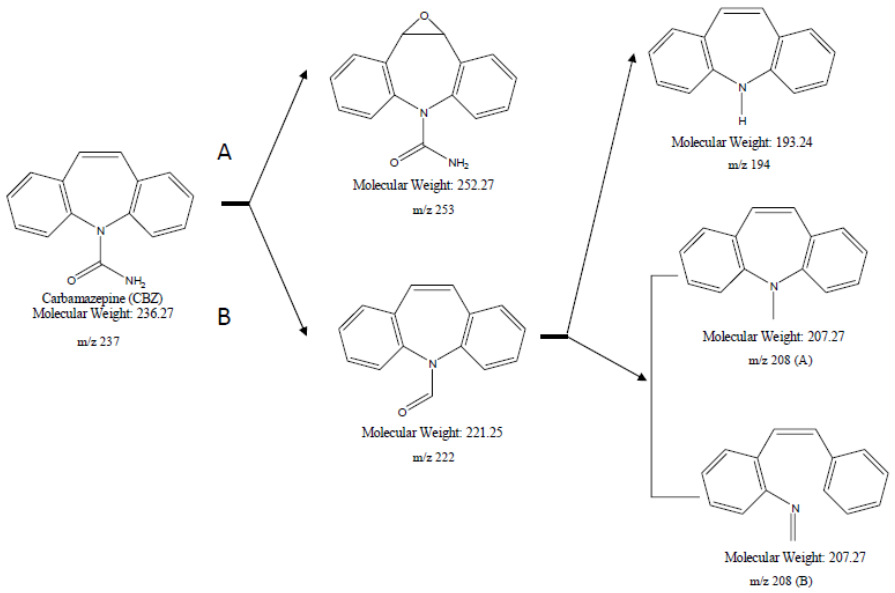


Figure 15. Possible reaction intermediates formed by reaction of carbamazepine with chlorine (Taken from Kotcharaksa, 2008)

4.4. Passive samplers

Passive sampling can provide TWA concentrations of compounds over deployment periods of several weeks, but measure only the freely dissolved material, and not that bound to organic and inorganic suspended matter and dissolved organic carbon. Where there is limited binding, then the concentrations measured by passive sampling should be in agreement with those measured in frequent spot samples of water. Where spot samples are taken infrequently, then there may be a difference between the estimates of concentration provided by the two methods when the concentration in the water fluctuates in time. Where sampling rates of the passive samplers are high (up to tens of litres per day, as found in some samplers for non-polar organic compounds) then this technology can provide estimates of concentrations that fall below the limit of detection of routine small volume (less than 5 L) spot sampling methods.

In this study, the low sampling rates achieved by the passive samplers reduced the utility of the estimates of concentrations of some of the pharmaceuticals, and resulted in an inability to detect concentrations below the limit of detection of spot sampling. For some determinands, apparent contamination of field blanks was an issue meaning that these data could not be used. However, for a number of compounds where blanks were deemed acceptable and where it was possible to derive calibration data for the samplers, it was possible to estimate TWA concentrations at the sites. There was however significant disagreement between the spot sampling data and the TWA results which is most likely due to large uncertainties around the calibration results. Where the two methods are in agreement it gives some reassurance that the spot samples are providing representative information of exposures over time.

Overall, the passive sampling data indicate that much more development work is required on these types of systems before they can be used routinely in monitoring of drinking water. Any future work should probably focus on the development of systems that can be installed into treatment plants and which achieve high rates of sampling, thus overcoming the calibration uncertainties that were observed in this study.

4.5. Implications for human health

In the previous DWI-funded project, predictions of exposure were compared to therapeutic dose values in order to identify pharmaceuticals that may pose a risk to human health. Only ten compounds or classes of compounds had therapeutic dose concentrations within three orders of magnitude of the exposure predictions (the margin of exposure considered by Watts *et al*., 2007 to be of potential concern), these included the non steroidal anti-inflammatory drugs and cocaine.

When the measured concentrations obtained in the current study are used to refine the margins of exposure obtained in the previous project, margins of exposure are significantly increased compared to the previous study (Table 12). These results are re-assuring and indicate that the study pharmaceuticals (and probably pharmaceuticals in general) present in drinking water in England pose no appreciable risk to human health.

Table 12 Comparison of margins of exposure obtained in this study (from maximum concentrations in spot samples) with margins of exposure calculated in the previous DWI-funded prioritisation study (Watts *et al*., 2007)

	Watts *et al*., 2007 (ng/l)	MoE	Maximum concentration in treated water (ng/l)	Treated water MoE (based on maximum concentration)
atenolol	8360	5.98×10^3	<2	$>2.50 \times 10^7$
benzoylecgonine	-	-	3.51	-
caffeine	-	-	79.3	-
carbamazepine	23	1.7×10^7	148	2.64×10^6
carbamazepine epoxide	-	-	16.6	-
cocaine	2530	395	<5	$>2.00 \times 10^5$
cyclophosphamide	-	-	<1	-
diclofenac	5000	1.50×10^4	<10	$>7.50 \times 10^6$
fluoxetine	88.2	2.27×10^5	<5	$>4.00 \times 10^6$
ibuprofen	18920	1.06×10^4	3.07	6.5×10^7
furosemide	5270	3.79×10^3	<5	$>4.00 \times 10^6$
ketoprofen	230	4.45×10^5	<1	$>1.02 \times 10^8$
naproxen	6330	7.89×10^4	2.72	1.83×10^8
norfluoxetine	-	-	<10	-
orlistat	1540	7.80×10^4	<10	$>1.20 \times 10^7$
simvastatin	3240	1.54×10^3	<50	$>1.00 \times 10^5$
trimethoprim	1270	7.90×10^4	<5	$>2.01 \times 10^7$

4.6. Conclusions

This study was performed to determine the potential level of exposure of pharmaceuticals in source waters and treated drinking waters in England. The study measured a range of pharmaceuticals and illicit drugs at four sites over a 12 month period. Generally results agreed with similar studies that have been done elsewhere and showed that concentrations of pharmaceuticals and illicit drugs in English surface waters are at levels in the below 1 µg/l. Concentrations of pharmaceuticals and drugs in drinking waters are generally significantly lower than seen in surface waters indicating that the treatment systems in use in England and Wales are effective at removing these contaminants. Comparison of measured concentrations of the study compounds in drinking waters with information on therapeutic doses demonstrated that levels of these compounds in drinking water in England are many orders of magnitude lower than levels that are given to patients therapeutically. It would therefore appear that the presence of low levels of pharmaceuticals and illicit drugs in drinking waters in England and Wales do not pose an appreciable risk to human health.

4.7. Recommendations

During the study, a number of areas have been identified that are worthy of further study, namely:

- The application of more complex modelling approaches for estimating the concentrations of pharmaceuticals in surface waters – It is clear from this study that the simple models used in risk assessment do not always provide good estimates of exposure. By applying more complex models that consider

fluctuations in pharmaceutical use in a catchment, catchment hydrology and the potential for a compound to dissipate in different environmental compartments, it may be possible to better identify those pharmaceuticals that pose the greatest risk to the environment and to human health.

- More detailed evaluation of the toxicological risks of pharmaceuticals in drinking water – In this study and the previous study, a very simple approach was used to establish whether levels of pharmaceuticals in the environment are of concern to human health or not. While the assessment are re-assuring and indicate that levels are much lower than levels where toxicological effects would be seen, it would be worthwhile to perform a much more thorough evaluation of the available data on the effects of pharmaceuticals on human health. Such a study should recognise that the exposure will be long-term and that consumers will be exposed to a mixture of substances in their drinking water.

- Assessment of the potential for transformation products to be formed in drinking water treatment – The data for carbamazepine epoxide indicate that in some instances, drinking water treatment processes can convert one substance to another substance which may be of concern. It would be worthwhile to develop a better understanding of the mechanisms of removal of pharmaceuticals in different drinking water treatment processes and of the potential for compounds to be formed which may be of toxicological concern.

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APPENDIX A: CONSOLIDATED LIST OF PHARMACEUTICALS (AND METABOLITES) IDENTIFIED IN DIFFERENT PRIORITISATION EXERCISES OF RELEVANCE TO DRINKING WATER

Molecule	Class	PEC	Reason	Monitored/ Detected	Metabolite	Prioritisation
acamprosate	alcoholism treatment	648	low exposure:dose			1
allopurinol	antigout	150	High PEC		oxypurinol	2
aminophylline	muscle relaxant	2310	low exposure:dose			1
amiodarone	amiodarone	555	high Kow, adverse effects linked to iode CYP-450 and P-gp inhibitor		N-desethyl amiodarone	2
amoxicillin	antibiotic	6847	High PEC	Y		2,4
amphetamine	illegal drug	5270	low exposure:dose			2
amphotocerin B	antifungal	415	High PEC, kidney toxicity			2
atorvastatin	lipid lowering agent	-	-	Y		1,3
atenolol	β-blocker	419	High PEC	Y		2,3,4
beclometasone	anti-asthmatic	728	low exposure:dose			1
bendroflumethiazide	dicuretic	224	low exposure:dose			1
bezafibrate	lipid lowering agent	476	High PEC, muscular disease, PPAR agonist	Y		2,4
buflomedil	anti-eschemic	291	High PEC			2
carbamazepine	anticonvulsant	765	High PEC, P450 inducer	Y	10,11-epoxycarbamazepine	2,3,4
ceftriaxone	antibiotic	315	High PEC			2
ciclosporin	immunosupression	550	low exposure:dose			1
ciprofloxacin	antibiotic	139	High PEC	Y		2,4
clarithromycin	antibiotic	62	CYP-450 and P-gp inhibitor	Y		2
codeine	analgesic	3240	low exposure:dose	Y		1,4

Molecule	Class	PEC	Reason	Monitored/ Detected	Metabolite	Prioritisation
cyamemazine	antipsychotic	124	endocrine and metabolic disorders			2
diamorphine	illegal drug	130	low exposure:dose			2
diazepam	tranquilizer	-	-	Y		3,4
diclofenac	NSAID	35	adverse effects on kidney	Y		1,2,3,4
diosmin	vitaminic P	8528	potent estrogen		deglycosylated diosmin	2
doxazosin	β-blocker	88	low exposure:dose			1
doxycycline	antibiotic	103	High PEC	Y		2,4
enalapril	ACE inhibitor	-	-	Y		3,4
ecstasy	illegal drug	1075	low exposure:dose			1
ethinylestradiol	contraceptive	-	-	Y		3
fluoxetine	SSRI	9	serotonin receptor agonist, P-gp inhibitor	Y	norfluoxetine	2,3,4
fosfomycin	antibiotic	155	High PEC			2
furosemide	diuretic	486	High PEC, low exposure:dose	Y		1,2,4
gemfibrozil	antilipidemic	-	-	Y		3,4
ibuprofen	NSAID	1370	Potential renal toxicity	Y	2-OH-ibuprofen, carboxy-ibuprofen	1,2,4
ketoprofen	NSAID	421	Potential renal toxicity	Y		1,2
losartan	ATH sartan	334	Decrease in aldosterone secretion		5-carboxylic acid metabolite	2
lisinopril	agiotensin converting enzyme inhibitor	2240	low exposure:dose			1
LSD	illegal drug	3350	low exposure:dose			1
meprobamate	anti-anxiety agent	-	-	Y		3
metformin	antidiabetic	15367	High PEC	Y		2,4

Molecule	Class	PEC	Reason	Monitored/ Detected	Metabolite	Prioritisation
methadone	opioid agonist	94.4	low exposure:dose			1
methylbenzoylecgonine	illegal drug	2530	low exposure:dose	Y		1
metronidazole	antiprotozoal	150	High PEC		OH-metronidazole	2
naftidrofuryl	anti-eschemic	1039	serotoninergic 5-HT2 receptor agonist			2
naproxen	NSAID	597	Potential renal toxicity	Y		1,2,3,4
nitroglycerin	vasodilator	1040	low exposure:dose			1
ofloxacin	antibiotic	94	High PEC	Y		2
norethisterone	progesterone derivative	251	low exposure:dose			1
oxazepam	benzodiazepine	207	High PEC	Y		2,4
paracetamol	antipyretic/analgesic	64101	High PEC	Y		2,4
piperacillin	piperacillin	102	High PEC			2
pravastatin	lipid lowering agent	125	Adverse effects on muscles, carcinogenic effects in rodents			2
prednisolone	corticoid	85	immunomodulating effects	Y		2
pristinamycin	antibiotic	910	High PEC			2
propranolol	β-blocker	68	Adverse effects on thyroid	Y	4-OH-propanolol	2
ramipril	diuretic	9370	low exposure:dose			1
ranitidine	antacid	133	High PEC	Y		2,4
sertraline	SSRI	20	Serotoninergic activity, P450 inhibitor	Y		2
simvastatin	lipid lowering agent	75.4	low exposure:dose	N		1,2,4*
sulfamethoxazole	antibiotic	153	High PEC	Y	acetylsulfamethoxazole	2,3,4
tetrahydrocannabinol	illegal drug	9740	low exposure:dose			1

Molecule	Class	PEC	Reason	Monitored/ Detected	Metabolite	Prioritisation
tramadol	analgesic	177	High PEC	Y	demethyltramadol	2
trimethoprim	antibiotic	38	High PEC	Y		2,3,4
valproic acid	anticonvulsant	1357	P450 inhibitor			2,4
vancomycin	antibiotic	21				2
zidovudine	anti-viral	648	low exposure:dose			1

Metabolite	Parent compound	Reason	PEC	Monitored	Prioritisation
salicylic acid	aspirin	active metabolite	-	Y	2
fenofibric acid	fenofibrate	active metabolite	1148	Y	2
perindoprilat	pendopril	active metabolite	192		2
ramiprilat	ramipril	active metabolite	125		2
demethyltramadol	tramadol	active, high excretion rate	355		2
hydroxy-ibuprofen	ibuprofen	high excretion rate	1370	Y	2
carboxy-ibuprofen	carboxy-ibuprofen	high excretion rate	2027	Y	2
acetyl-sulfamethoxazole	sulfamethoxazole	high excretion rate	229	Y	2
14-OH-clarithromycin	clarithromycin	active metabolite	52		2
norfluoxetine	fluoxetine	active, high excretion rate	24	N	2,3,4
OH-metronidazole	metronidazole	active, high excretion rate	234		2
β-hydroxy-acid-metabolite	simvastatin	active metabolite	87	N	2,3,4
2-OH-atorvastatin	atorvastatin	active metabolite	-	N	2,3
4-OH-atorvastatin	atorvastatin	active metabolite	-	N	2,3

1- Watts and Crane (2007); 2 - Besse and Garric (2008); 3 – US Monitoring list; 4 – Global Water Research Coalition (2008); *- metabolite

APPENDIX B – SPOT SAMPLING DATA (VALUES ARE EXPRESSED IN NG/L AND ARE MEANS OF THREE REPLICATE SAMPLES)

Table B1. Concentration of atenolol in spot samples obtained during the study

	Site 1			Site 2			Site 3			Site 4		
	RW		TW	RW		TW	RW		TW	RW		TW
	Mean	SD		Mean	SD		Mean	SD		Mean	SD	Mean
Sept	36.90	0.75	<LOD	64.50	1.56	<LOD	11.70	0.17	<LOD	21.37	0.65	<LOD
Oct	38.47	0.32	<LOD	58.90	1.10	<LOD	31.65	1.35	<LOD	113.68	2.96	<LOD
Nov	58.93	1.05	<LOD	66.64	2.22	<LOD	67.56	1.59	<LOD	74.52	6.43	<LOD
Dec	35.84	0.62	<LOD	46.72	0.62	<LOD	40.33	0.37	<LOD	25.93	0.24	<LOD
Jan	57.55	1.08	<LOD	91.17	0.68	<LOD	15.32	<LOD	NS	25.32	0.84	<LOD
Feb	66.34	0.31	<LOD	NS	-	NS	21.37	<LOD	NS	23.35	0.51	<LOD
Mar	64.73	0.18	<LOD	57.60	0.44	<LOD	NS	<LOD	NS	19.62	0.58	<LOD
Apr	53.19	0.59	<LOD	46.49	0.43	<LOD	NS	<LOD	NS	24.02	1.01	<LOD
May	38.84	0.51	<LOD	52.04	1.57	<LOD	45.97	2.28	<LOD	24.06	0.23	<LOD
Jun_1	40.54	0.38	<LOD	41.51	1.52	<LOD	NS	<LOD	NS	48.83	0.70	<LOD
Jun_2/Jul_1	36.31	0.26	<LOD	54.04	1.11	<LOD	13.34	0.62	<LOD	23.42	0.93	<LOD
Jul_2	23.04	0.61	<LOD	39.64	0.92	<LOD	8.18	0.37	<LOD	66.80	0.41	<LOD
Aug	18.13	0.57	<LOD	31.2	0.6	<LOD	12.0	0.8	<LOD	43.74	0.79	<LOD

Table B2. Concentration of benzoylecgonine in spot samples obtained during the study

	Site 1			Site 2			Site 3			Site 4			
	RW		TW	RW		TW	RW		TW	RW		TW	
	Mean	SD		Mean	SD		Mean	SD		Mean	SD	Mean	SD
Sept	1.30	0.10	<LOD	4.17	0.12	<LOD	2.30	0.10	<LOD	9.97	0.23	2.27	0.06
Oct	1.30	0.00	<LOD	4.67	0.15	<LOD	3.85	0.07	<LOD	15.59	0.47	3.02	0.13
Nov	1.20	0.04	<LOD	4.19	0.06	<LOD	3.96	0.16	<LOD	11.37	2.77	3.51	0.14
Dec	0.97	0.03	<LOD	2.42	0.10	<LOD	1.25	0.03	<LOD	3.32	0.08	<LOD	<LOD
Jan	<LOD	-	<LOD	2.75	0.10	<LOD	2.72		NS	2.09	0.06	<LOD	<LOD
Feb	<LOD	-	<LOD	NS	-	NS	2.70		NS	3.13	0.13	<LOD	<LOD
Mar	<LOD	-	<LOD		0.01	<LOD	NS	0.10	NS	1.99	0.06	<LOD	<LOD
Apr	<LOD	-	<LOD		0.33	<LOD	NS	0.18	NS	3.60	0.21	1.12	0.03
May	1.00	0.02	<LOD	5.77	0.22	<LOD	4.80	0.29	<LOD	9.80	0.08	1.59	0.06
Jun_1	1.66	0.07	<LOD	3.48	0.10	<LOD	NS	-	NS	10.06	0.07	2.64	0.26
Jun_2/Jul_1	2.06	0.10	<LOD	4.22	0.16	<LOD	2.02	0.11	<LOD	7.21	0.07	1.98	0.09
Jul_2	1.67	0.06	<LOD	2.39	0.14	<LOD	2.98	0.15	<LOD	16.28	0.13	3.34	0.02
Aug	1.75	0.03	<LOD	1.98	0.06	<LOD	2.97	0.10	<LOD	11.48	0.46	3.34	0.08

Table B3. Concentration of caffeine in spot samples obtained during the study

	Site 1				Site 2				Site 3				Site 4			
	RW		TW		RW		TW		RW		TW		RW		TW	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Sept	441.00	17.00	79.33	2.31	95.00	3.00	46.33	10.69	81.90	5.42	8.16	1.84	236.09	12.11	14.57	1.45
Oct	95.17	0.32	7.60	0.40	67.77	1.79	3.63	0.68	141.08	0.87	<LOD	-	149.59	0.65	<LOD	-
Nov	175.53	3.85	7.56	0.15	186.56	23.98	3.38	0.14	198.76	15.44	4.22	0.14	329.06	45.78	14.78	1.27
Dec	260.58	12.79	21.07	4.69	99.25	4.62	11.22	0.07	119.77	0.49	7.66	0.11	226.58	6.52	11.60	0.58
Jan	287.06	11.47	20.76	0.73	224.25	6.61	11.42	2.95	68.82	3.04	NS	-	279.49	11.51	13.47	0.23
Feb	234.51	3.81	21.79	1.92	NS	-	NS	-	104.08	4.66	NS	-	201.85	13.87	10.10	0.18
Mar	232.35	2.12	19.87	2.43	103.56	1.14	11.17	0.27	NS	-	NS	-	211.55	5.00	2.88	0.26
Apr	221.60	3.36	18.13	0.96	125.21	0.74	9.36	0.34	NS	-	NS	-	241.25	7.56	14.55	0.21
May	162.69	2.74	12.44	0.27	91.66	0.77	5.98	0.25	163.05	15.13	2.82	0.13	284.98	6.20	10.35	0.67
Jun_1	108.02	3.00	12.18	0.09	82.08	3.17	8.14	1.17	NS	-	NS	-	267.35	5.40	12.03	0.22
Jun_2/Jul_1	140.09	4.75	15.68	0.70	92.63	4.78	10.03	0.37	54.74	3.06	3.00	0.46	82.22	1.77	29.22	22.62
Jul_2	129.71	2.11	14.87	0.11	63.70	2.17	3.05	0.20	100.22	3.58	3.88	0.32	149.59	2.84	17.40	0.69
Aug	86.65	3.99	14.77	1.14	70.94	1.40	5.65	0.21	95.88	3.85	8.83	2.03	142.25	2.45	17.40	0.07

Table B4. Concentration of carbamazepine in spot samples obtained during the study

	Site 1				Site 2				Site 3				Site 4			
	RW		TW		RW		TW		RW		TW		RW		TW	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Sept	86.33	0.58	9.0	0.0	175.3	3.2	20.7	0.6	346.13	6.31	1.07	0.06	215.17	7.97	2.37	0.12
Oct	111.53	0.67	8.4	0.2	202.5	2.9	17.6	4.3	146.93	2.66	1.00	0.05	392.67	7.36	1.31	0.06
Nov	124.50	2.35	11.5	0.3	138.6	2.5	148.2	2.1	364.29	9.50	0.96	0.06	185.07	8.51	1.37	0.03
Dec	58.50	0.47	11.0	0.3	46.6	0.2	3.1	0.0	75.52	0.86	1.25	0.02	37.14	0.17	1.03	0.07
Jan	58.64	0.07	11.9	0.2	70.0	1.1	4.8	2.7	34.34	0.01	NS	-	25.24	0.58	<LOD	-
Feb	49.40	0.64	11.5	0.2	NS	-	NS		42.34	0.56	NS	-	29.00	0.92	<LOD	-
Mar	59.91	0.80	11.8	0.1	45.0	0.1	2.7	0.0	NS	-	NS	-	16.39	0.28	<LOD	-
Apr	62.47	0.27	11.3	0.1	53.9	0.6	2.2	0.1	NS	-	NS	-	34.03	0.19	<LOD	-
May	78.9	1.76	12.0	0.3	100.4	2.3	2.0	0.1	163.47	3.41	<LOD	-	106.00	1.43	<LOD	-
Jun_1	128.0	2.89	13.8	0.3	139.7	3.6	2.2	0.0	NS	-	NS	-	231.36	4.00	0.97	0.06
Jun_2/Jul_1	135.33	2.65	16.5	0.4	167.7	4.7	3.7	0.05	471.45	12.40	<LOD	-	289.66	3.05	1.73	0.06
Jul_2	198.9	6.6	17.3	0.1	249.40	13.67	1.22	0.05	523.22	9.01	<LOD	-	480.19	12.64	3.96	0.09
Aug	194.40	7.16	16.6	0.2	277.00	5.39	1.59	0.08	555.29	8.00	<LOD	-	331.62	8.03	3.96	0.09

Table B5. Concentration of carbamazepine epoxide in spot samples obtained during the study

	Site 1				Site 2				Site 3				Site 4			
	RW		TW		RW		TW		RW		TW		RW		TW	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Sept	11.33	0.58	6.00	0.00	19.67	0.58	7.00	0.00	24.70	1.66	4.90	0.10	16.67	0.51	10.73	0.06
Oct	10.90	0.17	4.23	0.06	19.30	0.26	8.13	0.35	15.97	0.62	5.03	0.22	14.95	0.74	8.16	0.11
Nov	7.58	0.83	3.65	0.10	7.22	1.22	16.60	0.85	13.99	1.29	6.01	0.15	9.91	0.32	8.74	0.65
Dec	4.17	0.08	3.41	0.07	3.25	0.04	4.04	0.09	3.88	0.07	4.29	0.19	1.93	0.06	3.04	0.10
Jan	3.88	0.19	2.76	0.12	4.97	0.13	3.03	0.17	1.99	0.04	NS	-	1.12	0.10	2.15	0.02
Feb	2.83	0.10	2.27	0.12	NS	-	NS	-	0.50		NS	-	1.41	0.32	1.93	0.13
Mar	3.46	0.09	2.95	0.16	3.18	0.15	3.02	0.07	NS	-	NS	-	0.50		0.50	
Apr	3.09	0.15	2.92	0.09	2.47	0.04	2.88	0.09	NS	-	NS	-	1.33	0.01	3.08	0.03
May	4.25	0.13	3.89	0.06	5.48	0.51	3.85	0.03	6.26	0.13	2.53	0.04	4.32	0.05	4.46	0.02
Jun_1	6.53	0.19	4.64	0.08	7.79	1.12	4.70	0.10	NS	-	NS	-	7.62	0.13	6.24	0.12
Jun_2/Jul_1	7.50	0.25	5.31	0.08	9.75	0.29	7.92	0.22	14.75	0.39	0.50		10.59	0.36	9.30	0.03
Jul_2	9.48	0.29	6.10	0.09	12.03	0.22	5.28	0.20	13.52	0.64	3.63	0.11	13.84	0.30	9.94	0.15
Aug	8.62	0.25	5.77	0.15	11.22	0.16	5.15	0.14	12.90	0.40	4.61	0.12	10.60	0.24	9.94	0.18

Table B6. Concentration of diclofenac in spot samples obtained during the study

	Site 1			Site 2			Site 3			Site 4		
	RW		TW	RW		TW	RW		TW	RW		TW
	Mean	SD	Mean	Mean	SD	Mean	Mean	SD	Mean	Mean	SD	Mean
Sept	<LOD	-	<LOD	27.33	0.58	<LOD	14.30	0.95	<LOD	17.57	0.38	<LOD
Oct	20.17	0.15	<LOD	34.23	0.65	<LOD	50.00	7.85	<LOD	47.14	2.32	<LOD
Nov	24.33	3.00	<LOD	33.86	11.11	<LOD	76.29	3.64	<LOD	44.26	4.64	<LOD
Dec	<LOD	-	<LOD	12.48	0.32	<LOD	18.86	1.89	<LOD	10.56	0.46	<LOD
Jan	20.82	0.86	<LOD	38.99	0.95	<LOD	<LOD	n/a	NS	12.60	0.83	<LOD
Feb	17.76	2.21	<LOD	NS	-	NS	10.84	0.68	NS	17.28	1.52	<LOD
Mar	11.00	0.20	<LOD	10.35	0.71	<LOD	NS	-	NS	<LOD	-	<LOD
Apr	<LOD	-	<LOD	11.15	0.13	<LOD	NS	-	NS	<LOD	-	<LOD
May	<LOD	-	<LOD	15.69	1.79	<LOD	15.13	1.44	<LOD	11.93	1.50	<LOD
Jun_1	<LOD	-	<LOD	10.54	1.29	<LOD	NS	-	NS	<LOD	-	<LOD
Jun_2/Jul_1	<LOD	-	<LOD	<LOD	-	<LOD	<LOD	n/a	<LOD	<LOD	-	<LOD
Jul_2	<LOD	-	<LOD	<LOD	-	<LOD	<LOD	n/a	<LOD	13.39	0.43	<LOD
Aug	<LOD	-	<LOD	12.10	0.74	<LOD	<LOD	n/a	<LOD	11.56	0.50	<LOD

Table B7. Concentration of furosemide in spot samples obtained during the study

	Site 1			Site 2			Site 3			Site 4		
	RW		TW	RW		TW	RW		TW	RW		TW
	Mean	SD	Mean	Mean	SD	Mean	Mean	SD	Mean	Mean	SD	Mean
Sept	<LOD	-	<LOD	15.77	1.05	<LOD	<LOD	<LOD	<LOD	8.23	1.55	<LOD
Oct	12.40	1.32	<LOD	21.20	0.12	<LOD	5.30	0.45	<LOD	47.48	3.17	<LOD
Nov	21.09	0.70	<LOD	39.42	0.07	<LOD	35.95	3.90	<LOD	63.48	11.86	<LOD
Dec	15.42	1.04	<LOD	26.00	1.52	<LOD	22.98	0.93	<LOD	15.62	1.20	<LOD
Jan	28.90	0.82	<LOD	43.10	2.38	<LOD	6.92	1.31	NS	16.99	0.13	<LOD
Feb	17.42	1.66	<LOD	NS	-	NS	9.55	0.44	NS	16.89	2.92	<LOD
Mar	12.62	0.17	<LOD	23.68	0.69	<LOD	NS	-	NS	<LOD	-	<LOD
Apr	6.44	0.39	<LOD	17.04	0.57	<LOD	NS	-	NS	<LOD	-	<LOD
May	<LOD	-	<LOD	9.48	0.39	<LOD	0.40	0.40	<LOD	5.34	0.34	<LOD
Jun_1	<LOD	-	<LOD	7.56	0.47	<LOD	NS	NS	NS	19.54	0.55	<LOD
Jun_2/Jul_1	5.42	0.11	<LOD	<LOD	-	<LOD	<LOD	-	<LOD	<LOD	-	<LOD
Jul_2	<LOD	-	<LOD	6.59	1.73	<LOD	<LOD	-	<LOD	12.38	0.97	<LOD
Aug	<LOD	-	<LOD	8.05	0.35	<LOD	<LOD	-	<LOD	13.25	1.67	<LOD

Table B8. Concentration of ibuprofen in spot samples obtained during the study

	Site 1				Site 2			Site 3			Site 4		
	RW		TW		RW		TW	RW		TW	RW		TW
	Mean	SD	Mean	SD	Mean	SD	Mean	Mean	SD	Mean	Mean	SD	Mean
Sept	6.33	0.58	<LOD	-	10.00	1.00	<LOD	<LOD	<LOD	<LOD	9.30	1.39	<LOD
Oct	12.03	0.47	<LOD	-	5.57	0.29	<LOD	8.17	1.41	<LOD	11.56	1.43	<LOD
Nov	20.67	0.56	<LOD	-	19.65	1.65	<LOD	21.54	3.19	<LOD	38.15	7.49	<LOD
Dec	21.63	0.53	<LOD	-	10.46	0.50	<LOD	10.91	0.66	<LOD	15.14	0.21	<LOD
Jan	28.45	1.47	3.07	0.19	38.41	3.30	<LOD	5.37	0.51	NS	26.32	2.17	<LOD
Feb	27.14	1.64	<LOD	-	NS	-	NS	11.79	0.70	NS	22.95	2.14	<LOD
Mar	30.84	2.54	<LOD	-	16.42	1.41	<LOD	NS	-	NS	24.65	2.67	<LOD
Apr	25.70	1.86	<LOD	-	15.66	1.65	<LOD	NS	-	NS	21.61	0.76	<LOD
May	19.36	2.21	<LOD	-	10.47	0.37	<LOD	21.01	2.18	<LOD	26.68	2.54	<LOD
Jun_1	8.58	0.39	<LOD	-	5.75	1.22	<LOD	NS	-	NS	17.14	1.98	<LOD
Jun_2/Jul_1	9.49	0.74	<LOD	-	5.27	0.05	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD	<LOD
Jul_2	11.09	0.87	<LOD	-	3.40	0.17	<LOD	<LOD	<LOD	<LOD	15.59	1.54	<LOD
Aug	7.52	0.60	<LOD	-	<LOD	-	<LOD	2.44	0.85	1.00	7.03	0.34	<LOD

Table B9. Concentration of naproxen in spot samples obtained during the study

	Site 1			Site 2			Site 3			Site 4			
	RW		TW	RW		TW	RW		TW	RW		TW	
	Mean	SD		Mean	SD		Mean	SD		Mean	SD	Mean	SD
Sept	15.0	1.00	<LOD	17.0	1.00	<LOD	15.07	1.36	<LOD	23.57	0.76	2.47	0.21
Oct	22.5	0.21	<LOD	18.9	0.76	<LOD	18.11	0.57	<LOD	41.13	1.73	2.72	0.99
Nov	23.9	0.92	<LOD	20.6	0.42	<LOD	28.94	4.21	<LOD	44.35	5.35	2.55	0.13
Dec	17.3	0.19	<LOD	13.6	0.09	<LOD	17.03	0.50	<LOD	11.59	0.70	<LOD	-
Jan	25.6	0.18	<LOD	42.2	0.81	<LOD	4.85	0.69	NS	13.28	0.39	<LOD	-
Feb	20.3	0.51	<LOD	NS		NS	8.53	0.65	NS	13.90	2.14	<LOD	-
Mar	26.4	0.92	<LOD	28.7	0.58	<LOD	NS	NS	NS	11.08	0.51	<LOD	-
Apr	20.0	0.90	<LOD	18.5	0.32	<LOD	NS	NS	NS	12.83	0.21	<LOD	-
May	16.1	0.35	<LOD	20.0	1.16	<LOD	17.55	1.76	<LOD	22.61	0.25	<LOD	-
Jun_1	10.2	0.25	<LOD	11.4	0.59	<LOD	NS	NS	NS	21.70	0.90	<LOD	-
Jun_2/Jul_1	13.1	0.83	<LOD	9.8	0.26	<LOD	7.77	0.45	<LOD	12.53	0.68	<LOD	-
Jul_2	13.1	0.32	<LOD	6.9	0.29	<LOD	9.70	0.39	<LOD	43.40	1.00	<LOD	-
Aug	13.1	0.84	<LOD	9.5	0.05	<LOD	8.72	0.33	<LOD	28.69	0.98	<LOD	-

Table B10. Concentration of trimethoprim in spot samples obtained during the study

	Site 1			Site 2			Site 3			Site 4		
	RW		TW	RW		TW	RW		TW	RW		TW
	Mean	SD	Mean	Mean	SD	Mean	Mean	SD	Mean	Mean	SD	Mean
Sept	11.00	0.00	<LOD	13.77	0.06	<LOD	<LOD	-	<LOD	<LOD	-	<LOD
Oct	12.13	0.29	<LOD	11.43	0.59	<LOD	<LOD	-	<LOD	9.27	0.51	<LOD
Nov	6.10	0.10	<LOD	5.45		<LOD	7.74	0.46	<LOD	5.93	-	<LOD
Dec	<LOD	-	<LOD	<LOD	-	<LOD	<LOD	-	<LOD	<LOD	-	<LOD
Jan	8.60	0.30	<LOD	10.00	0.08	<LOD	<LOD	-	NS	<LOD	-	<LOD
Feb	7.12	0.14	<LOD	NS	-	NS	<LOD	-	NS	6.18	0.52	<LOD
Mar	11.86	0.32	<LOD	8.98	0.14	<LOD	NS	-	NS	<LOD	-	<LOD
Apr	11.05	0.13	<LOD	7.40	0.32	<LOD	NS	-	NS	6.06	0.21	<LOD
May	13.80	0.50	<LOD	10.82	0.93	<LOD	7.77	0.43	<LOD	5.92	0.05	<LOD
Jun_1	13.80	0.50	<LOD	12.38	2.18	<LOD	NS	-	NS	19.48	0.38	<LOD
Jun_2/Jul_1	10.19	0.72	<LOD	10.82	0.60	<LOD	8.27	0.72	<LOD	11.11	0.38	<LOD
Jul_2	12.85	1.40	<LOD	13.30	2.01	<LOD	<LOD	-	<LOD	26.42	0.38	<LOD
Aug	8.91	1.07	<LOD	7.56	0.72	<LOD	<LOD	-	<LOD	15.89	1.42	<LOD

APPENDIX C. PASSIVE SAMPLER MASS DATA

Table C1. Mass (ng) of pharmaceuticals recovered in the receiving phase of the deployed Chemcatcher samplers for Site 1. Values for raw water (RW) and treated water (TW) are means of three replicates. Only one sample blank was used. Underlined values are indicative values only.

	Feb /Mar blank	RW	TW	Mar /Apr blank	RW	TW	Apr /May blank	RW	TW	May /Jun blank	RW	TW	Jun blank	RW	TW	Jun /Jul blank	RW	TW	Jul /Aug blank	RW	TW
atenolol	<1	23.1	<1	<1	4.5	<1	<1	3.3	<1	<1	13.2	<1	<2	11.5	<2	<1	10.7	<1	<1	4.6	<1
benzoylecgonine	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
caffeine	15.6	61.5	8.97	21.3	34.4	13.1	1.4	15.7	6.2	0.8	24.0	3.2	1.2	29.2	3.9	4.2	16.0	6.1	3.9	13.3	10.8
carbamazepine	<1	47.0	3.2	<1	8.3	3.1	<1	6.7	7.7	<1	75.2	5.5	<1	103	9.0	2.0	195	14.8	<1	118	21.2
cocaine	<2	<2	<2	<1	<1	<1	<1	<1	<1	<1	<1	<1	<2	<2	<2	<1	<1	<1	1.3	<1	<1
diclofenac	<1	8.3	<1	<1	1.8	<1	<5	<5	<5	<5	2.7	<5	<5	4.2	<5	<1	4.0	<1	0.9	3.4	<1
fluoxetine	2.3	0.6	0.9	0.3	<5	0.2	<2	<2	<2	<1	1.1	<1	<5	<5	<5	1.8	2.0	2.7	7.6	0.8	3.0
furosemide	<1	13.2	<1	<1	1.7	<1	<1	1.1	<1	<1	2.1	<1	<2	2.6	<2	<5	2.0	<5	<1	0.8	<1
ibuprofen	<1	17.6	<1	<1	2.8	<1	<1	3.1	<1	<2	9.0	<2	<1	7.6	<1	<1	6.0	<1	<1	2.7	<1
ketoprofen	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
naproxen	<1	16.3	<1	<1	3.9	<1	<1	2.7	<1	<1	7.2	<1	<1	8.5	<1	<1	6.7	<1	<1	4.6	<1
norfluoxetine	10.3	<5	6.7	1.7	<10	0.9	<2	<2	<2	<5	<5	<5	<5	<5	<5	3.0	<5	2.6	6.9	2.4	3.6
trimethoprim	0.5	8.8	0.1	0.5	3.9	<1	<1	2.8	<1	<1	10.6	<1	<1	7.3	<1	<5	19.0	<5	2.7	9.1	<2

Table C2. Mass (ng) of pharmaceuticals recovered in the receiving phase of the deployed Chemcatcher samplers for Site 3. Values for raw water (RW) and treated water (TW) are means of three replicates. Only one sample blank was used. Underlined values are indicative values only.

	May/Jun			Jun/Jul			Jul/Aug		
	blank	**RW**	**TW**	**blank**	**RW**	**TW**	**blank**	**RW**	**TW**
atenolol	<1	<1	<1	<1	<1	<1	<1	<1	<1
benzoylecgonine	<1	<1	<1	<1	<1	<1	<1	<1	<1
caffeine	<2	3.3	2.8	<2	3.2	1.7	<5	9.9	2.1
carbamazepine	<1	0.8	8.6	<1	7.9	<1	<1	13.9	<1
cocaine	<1	<1	<1	<1	<1	<1	<1	<1	<1
diclofenac	<5	<5	<5	<2	<2	<2	<1	<1	<1
fluoxetine	<2	<2	<2	1.84	<1	2.4	<1	0.8	<1
furosemide	<2	<2	<2	<2	<2	<2	<1	<1	<1
ibuprofen	<1	<1	<1	<1	<1	<1	<1	<1	<1
ketoprofen	<1	<1	<1	<1	<1	<1	<1	<1	<1
naproxen	<1	<1	<1	<1	<1	<1	<1	<1	<1
norfluoxetine	<10	<10	<10	2.4	<2	<2	2.3	<5	<5
trimethoprim	<2	<2	1.2	2.7	<1	<1	<2	<2	<2

APPENDIX D: ESTIMATED CONCENTRATIONS FROM CHEMCATCHERS

Table D1. Mean estimated water concentrations of diclofenac detected in Chemcatcher® passive samplers and spot samples

Site	Sample	Sampling duration (d)	Period SS	Concentration [ng L^{-1}]	
				PS (TWA)	SS*
1	RW	28	Feb/Mar	n.d.	14
1	TW	28	Feb/Mar	n.d.	n.d.
1	RW	28	Mar/Apr	63	11
1	TW	28	Mar/Apr	n.d.	n.d.
1	RW	28	Apr/May	n.d.	n.d.
1	TW	28	Apr/May	n.d.	n.d.
1	RW	29	May/Jun	n.d.	n.d.
1	TW	29	May/Jun	n.d.	n.d.
1	RW	23	Jun	96	n.d.
1	TW	23	Jun	n.d.	n.d.
1	RW	32	Jun/Jul	42	n.d.
1	TW	32	Jun/Jul	n.d.	n.d.
1	RW	28	Jul/Aug	56	n.d.
1	TW	28	Jul/Aug	n.d.	n.d.
2	RW	28	May/Jun	n.d.	15[c]
2	TW	28	May/Jun	n.d.	n.d.
2	RW	32	Jun/Jul	n.d.	n.d.
2	TW	32	Jun/Jul	n.d.	n.d.
2	RW	28	Jul/Aug	n.d.	n.d.
2	TW	28	Jul/Aug	n.d.	n.d.

***- SPOT SAMPLER DATA ESTIMATED FROM DATA FOR CONSECUTIVE MONTHS**

Table D2. Mean estimated water concentrations of atenolol detected in Chemcatcher® passive samplers and spot samples

Site	Sample	Sampling duration (d)	Period SS	Concentration [ng L^{-1}]	
				PS (TWA)	SS
1	RW	28	Feb/Mar	118	29
1	TW	28	Feb/Mar	n.d.	n.d.
1	RW	28	Mar/Apr	63	59
1	TW	28	Mar/Apr	n.d.	n.d.
1	RW	28	Apr/May	17	46
1	TW	28	Apr/May	n.d.	n.d.
1	RW	29	May/Jun	65	40
1	TW	29	May/Jun	n.d.	n.d.
1	RW	23	Jun	105	38
1	TW	23	Jun	n.d.	n.d.
1	RW	32	Jun/Jul	48	30
1	TW	32	Jun/Jul	n.d.	n.d.
1	RW	28	Jul/Aug	23	21
1	TW	28	Jul/Aug	n.d.	n.d.
2	RW	28	May/Jun	n.d.	46[c]
2	TW	28	May/Jun	n.d.	n.d.
2	RW	32	Jun/Jul	n.d.	11
2	TW	32	Jun/Jul	n.d.	n.d.
2	RW	28	Jul/Aug	n.d.	10
2	TW	28	Jul/Aug	n.d.	n.d.

Table D3. Mean estimated concentration of caffeine detected in Chemcatcher® passive samplers and spot samples

Site	Sample	Sampling duration (d)	Period SS	Concentration [ng L^{-1}]	
				PS (TWA)	SS[a]
1	RW	28	Feb/Mar	234	233
1	TW	28	Feb/Mar	n.d.	21
1	RW	28	Mar/Apr	122	227
1	TW	28	Mar/Apr	n.d.	19
1	RW	28	Apr/May	80	192
1	TW	28	Apr/May	32	15
1	RW	29	May/Jun	118	123
1	TW	29	May/Jun	16	12
1	RW	23	Jun	182	124
1	TW	23	Jun	24	14
1	RW	32	Jun/Jul	53	135
1	TW	32	Jun/Jul	9	15
1	RW	28	Jul/Aug	68	108
1	TW	28	Jul/Aug	55	15
2	RW	28	May/Jun	38	163[c]
2	TW	28	May/Jun	17	3[c]
2	RW	32	Jun/Jul	27	77
2	TW	32	Jun/Jul	10	3
2	RW	28	Jul/Aug	69	98
2	TW	28	Jul/Aug	n.d.	6

Table D4. Mean estimated water concentrations of carbamazepine detected in Chemcatcher® passive samplers and spot samples

Site	Sample	Sampling duration (d)	Period SS	Concentration [ng L^{-1}]	
				PS (TWA)	SS
1	RW	28	Feb/Mar	559	55
1	TW	28	Feb/Mar	38	12
1	RW	28	Mar/Apr	147	61
1	TW	28	Mar/Apr	37	12
1	RW	28	Apr/May	80	71
1	TW	28	Apr/May	92	12
1	RW	29	May/Jun	865	103
1	TW	29	May/Jun	63	13
1	RW	23	Jun	1485	132
1	TW	23	Jun	194	15
1	RW	32	Jun/Jul	2013	167
1	TW	32	Jun/Jul	133	17
1	RW	28	Jul/Aug	1403	167
1	TW	28	Jul/Aug	373	17
2	RW	28	May/Jun	13	164[c]
2	TW	28	May/Jun	154	n.d.
2	RW	32	Jun/Jul	183	502
2	TW	32	Jun/Jul	15	n.d.
2	RW	28	Jul/Aug	166	544
2	TW	28	Jul/Aug	n.d.	n.d.

Table D5. Mean estimated water concentrations of ibuprofen detected in Chemcatcher® passive samplers and spot samples

Site	Sample	Sampling duration (d)	Period SS	Concentration [ng L^{-1}]	
				PS (TWA)	SS
1	RW	28	Feb/Mar	90	29
1	TW	28	Feb/Mar	n.d.	n.d.
1	RW	28	Mar/Apr	39	28
1	TW	28	Mar/Apr	n.d.	n.d.
1	RW	28	Apr/May	16	192
1	TW	28	Apr/May	n.d.	n.d.
1	RW	29	May/Jun	44	14
1	TW	29	May/Jun	n.d.	n.d.
1	RW	23	Jun	69	13
1	TW	23	Jun	n.d.	n.d.
1	RW	32	Jun/Jul	27	9
1	TW	32	Jun/Jul	n.d.	n.d.
1	RW	28	Jul/Aug	14	9
1	TW	28	Jul/Aug	n.d.	n.d.
2	RW	28	May/Jun	n.d.	21[c]
2	TW	28	May/Jun	n.d.	n.d.
2	RW	32	Jun/Jul	n.d.	n.d.
2	TW	32	Jun/Jul	n.d.	3
2	RW	28	Jul/Aug	n.d.	2
2	TW	28	Jul/Aug	n.d.	n.d.

Table D6. Mean estimated water concentrations of naproxen detected in Chemcatcher® passive samplers and spot samples

Site	Sample	Sampling duration (d)	Period SS	Concentration [ng L^{-1}]	
				PS (TWA)	SS
1	RW	28	Feb/Mar	97	23
1	TW	28	Feb/Mar	n.d.	n.d.
1	RW	28	Mar/Apr	64	23
1	TW	28	Mar/Apr	n.d.	n.d.
1	RW	28	Apr/May	16	18
1	TW	28	Apr/May	n.d.	n.d.
1	RW	29	May/Jun	41	13
1	TW	29	May/Jun	n.d.	n.d.
1	RW	23	Jun	91	12
1	TW	23	Jun	n.d.	n.d.
1	RW	32	Jun/Jul	35	13
1	TW	32	Jun/Jul	n.d.	n.d.
1	RW	28	Jul/Aug	27	13
1	TW	28	Jul/Aug	n.d.	n.d.
2	RW	28	May/Jun	n.d.	18[c]
2	TW	28	May/Jun	n.d.	n.d.
2	RW	32	Jun/Jul	n.d.	9
2	TW	32	Jun/Jul	n.d.	n.d.
2	RW	28	Jul/Aug	n.d.	9
2	TW	28	Jul/Aug	n.d.	n.d.

APPENDIX E: CHEMCATCHER CALIBRATION DATA

Table E1. Chemcatcher® calibration results

Compound[a]	Time [d]	Water conc. [ng L^{-1}]	Slope [ng d^{-1}]	r^2adj	Lack of fit p	*R*s [ml d^{-1}]
Atenolol	6 - 30	43.1	0.2846	32.6	0.393	7
Benzoylecgonine	1 - 30	71.8	0.2391	58.9	0.029[b]	3
Caffeine	2 - 30	40.3	0.2808	42.0	0.170	7
Carbamazepine	6 - 30	139.7	0.4151	24.0[c]	0.107	3
Cocaine	2 - 30	156.1	0.2117	34.8	0.117	1
Diclofenac[d]	1 - 30	73.4	0.2139	26.0	<0.001	3
Ibuprofen	1 - 30	128.3	0.8743	84.7	0.137	7
Ketoprofen	1 - 20	152.4	1.790	89.8	0.799	12
Naproxen	2 - 30	108.3	0.3751	52.7	0.198	6

APPENDIX F: FLOW DATA FOR STUDY SITES

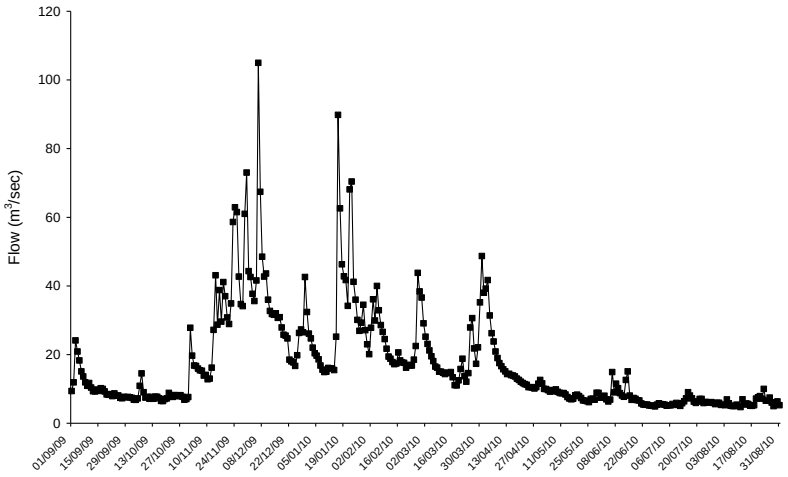

Figure F1 Gauged daily flow data for closest gauging site to water abstraction point for site 1 during the study period.

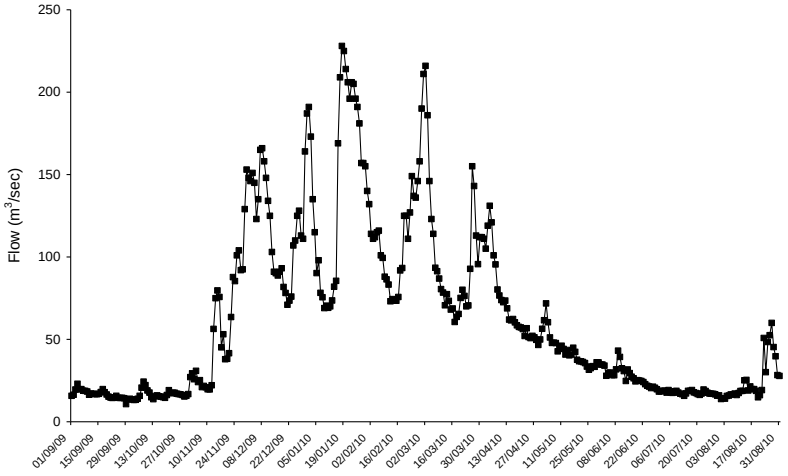

Figure F2 Gauged daily flow data for closest gauging site to water abstraction point for site 2 during the study period.

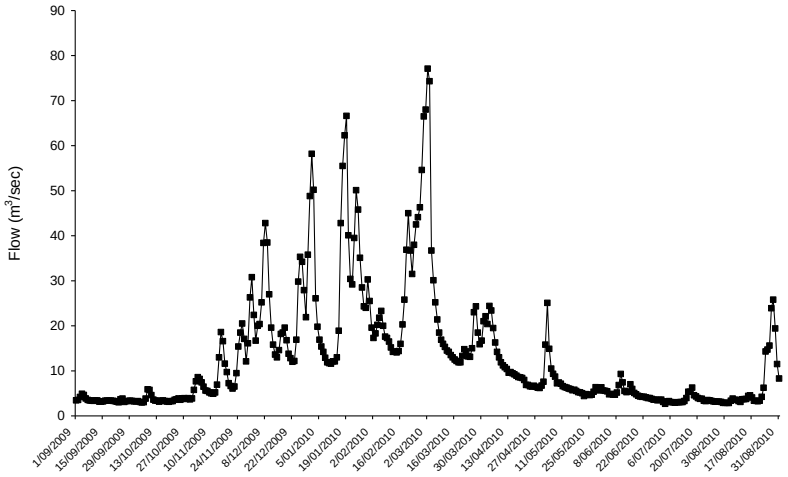

Figure F3 Gauged daily flow data for closest gauging site to water abstraction point for site 3 during the study period.

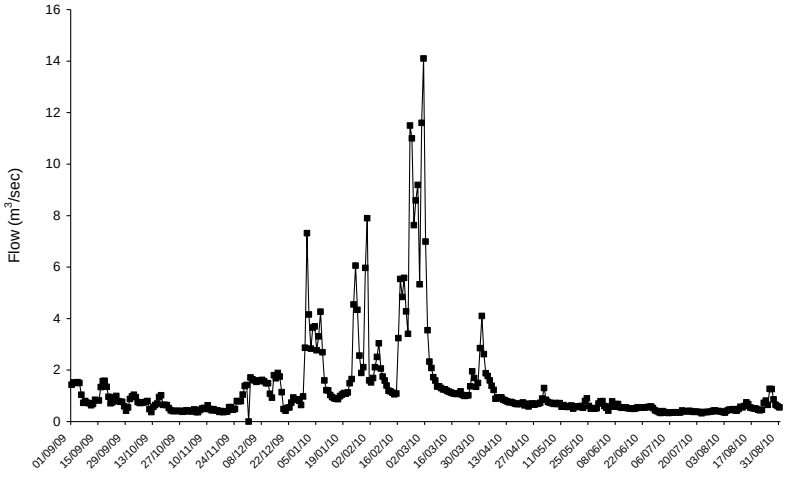

Figure F4 Gauged daily flow data for closest gauging site to water abstraction point for site 4 during the study period.

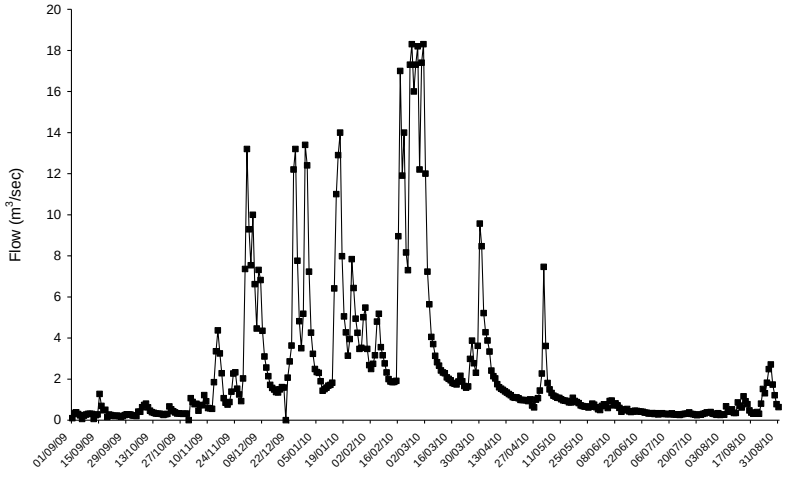

Figure F5 Gauged daily flow data for closest gauging site to water abstraction point for site 4 during the study period.