

Investigating the environmental transport of human pharmaceuticals to streams in the United Kingdom

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Received 3 October 2003; received in revised form 21 April 2004; accepted 23 April 2004

Abstract

The occurrence of 12 selected pharmaceutical compounds and pharmaceutical compound metabolites in sewage treatment works (STW) effluents and surface waters was investigated. The substances selected for the monitoring programme were identified by a risk ranking procedure to identify those substances with the greatest potential to pose a risk to the aquatic environment. STW final effluent and surface water samples were collected from Corby, Great Billing, East Hyde, Harpenden and Ryemeads STWs. Ten of the 12 pharmaceutical compounds were detected in the STW effluent samples: propranolol (100%, median = 76 ng/l), diclofenac (86%, median = 424 ng/l), ibuprofen (84%, median = 3086 ng/l), mefenamic acid (81%, median = 133 ng/l), dextropropoxyphene (74%, median = 195 ng/l), trimethoprim (65%, 70 ng/l), erythromycin (44%, < 10 ng/l), acetyl-sulfamethoxazole (33%, median = < 50 ng/l), sulfamethoxazole (9%, median = < 50 ng/l), tamoxifen (4%, median = < 10 ng/l). In the corresponding receiving streams, fewer compounds and lower concentrations were found: propranolol (87%, median = 29 ng/l), ibuprofen (69%, median = 826 ng/l), mefenamic acid (60%, median = 62 ng/l), dextropropoxyphene (53%, median = 58 ng/l), diclofenac (47%, median = < 20 ng/l), erythromycin (38%, median = < 10 ng/l), trimethoprim (38%, median = < 10 ng/l), acetyl sulfamethoxazole (38%, median = < 50 ng/l). Four human pharmaceutical compounds were detected in samples upstream of the STWs sampled: ibuprofen (57%, median = 181 ng/l), trimethoprim (36%, median < 10 ng/l), erythromycin (17%, median = < 10 ng/l), propranolol (14%, median = < 10 ng/l), suggesting that longer range stream transport of some compounds is possible.

The particular STW that was sampled and the month that it was sampled significantly influenced the measured concentrations of several, but not all, substances. There was no significant relationship between usage data and the overall frequency with which different substances were detected. There was however, some evidence to suggest that usage data are positively associated with concentrations of pharmaceuticals in effluent and, particularly, with concentrations measured in surface waters below STWs.

These results suggest that most sewage treatment works in England and Wales are likely to be routinely discharging small quantities of pharmaceuticals into UK rivers. None of the pharmaceuticals were found at concentrations that were high enough to cause acute toxic impacts to aquatic organisms. However, insufficient data were available to be able to comment

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on whether the concentrations measured have the potential to result in more subtle long-term effects on aquatic organisms (e.g. effects on growth, ability to reproduce).

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Keywords: Pharmaceutical compounds; Environmental occurrence; Trimethoprim; Diclofenac; Sulfamethoxazole; Acetyl-sulfamethoxazole; Paracetamol; Mefenamic acid; Ibuprofen; Erythromycin; Dextropropoxyphene; Lofepamine; Tamoxifen; Propranolol

1. Introduction

Increased attention is currently being played to pharmaceutical substances as a class of environmental contaminants (Daughton and Ternes, 1999; Kümmerer, 2001). Pharmaceutical substances are used in human and veterinary medicine and can enter the aquatic environment following manufacture, use or ingestion/excretion (see Halling Sørensen et al., 1998 for review). The majority of human pharmaceutical compounds enter aquatic systems after ingestion and subsequent excretion in the form of the non-metabolised parent compounds or as metabolites. Inputs of pharmaceutical substances into aquatic systems have led to their occurrence being reported in sewage treatment works (STW) effluent, river and marine surface water and ground water (Stan and Heberer, 1997; Ternes, 1998; Buser et al., 1998; Heberer et al., 1998; Hirsch et al., 1998; Stumpf et al., 1999; La Farre et al., 2001; Ollers et al., 2001; Kolpin et al., 2002). Much of this work has been conducted in continental Europe and the United States with very little or no recent work being performed in the UK. The absence of data for the UK is significant since use patterns and volumes differ from country to country and occurrence data obtained in Europe may not be applicable to the UK. Occurrence data are therefore required for human pharmaceuticals in aquatic systems in the UK. In order to address this gap in knowledge the Environment Agency of England and Wales (EA) commissioned a study to conduct targeted monitoring of pharmaceutical compounds in STW effluents and receiving waters.

Approximately 2000 different human pharmaceutical substances are registered for use in the UK. Prior to conducting a targeted monitoring study it is therefore necessary to rank substances on their relative risk, enabling those substances with the greatest potential to pose a risk to the aquatic environment to be

identified. The Environment Agency conducted a ranking procedure using a combination of traditional risk assessment procedures, persistence, bioaccumulation and toxicity (P,B,T) data, occurrence data from other countries, whether suitable analytical methods were available and whether the compound was representative of different therapeutic classes (Thomas and Hilton, 2003). The approach adopted highlighted substances which are used in relatively large quantities, but also identified substances which were either acutely toxic, persistent or bioaccumulative. The potential impact of substances that are not acutely toxic, but which exert other harmful impacts such as endocrine disruption were not specifically addressed in this ranking procedure. In addition, substances which may only have a low tonnage usage, such as the contraceptive pill and certain anti-cancer drugs, will not have been captured by the ranking procedure adopted. As the contraceptive pill and natural female hormones are subject to detailed investigation by the Environment Agency as part of an extensive research programme, it was decided therefore to focus on other general human pharmaceuticals.

2. Materials and methods

2.1. Risk prioritisation

Pharmaceutical sales data for the year 1999 for the top 500 substances (in terms of tonnage) were obtained from the British Pharmaceutical Industry-audit of purchases by retail pharmacies and dispensing doctors of registered pharmaceutical products. Sales to hospitals and sales of over-the-counter (OTC) products in to outlets such as supermarkets, garages, etc., are excluded. The data covered the whole of the UK, including Northern Ireland.

An initial screen of the substance list removed a number of classes whose compounds were believed to

pose minimal hazard to the environment. These included:

- Substances naturally occurring in the environment;
- Inorganics;
- Polymers;
- Gaseous compounds.

In addition, substances whose main use is in other sectors were removed from the list, these included:

- Veterinary medicines;
- Agricultural pesticides;
- General chemicals.

2.2. Risk characterisation ratios

Risk characterisation ratios were determined for the remaining substances on the list. Predicted Environmental Concentrations (PECs) were derived for the substances based on the approach detailed in the EU technical guidance on risk assessment (1996) (Eq. (1)). The calculation uses a simple equation based on usage, population and wastewater production to generate the PEC_w and provides a likely ‘worst case’ concentration for the pharmaceuticals in surface waters. It was assumed that there was no removal during sewage treatment and that the effluent is diluted by a factor of 10 in receiving waters.

$$PEC_w = \frac{A \times (100 - R)}{365 \times P \times V \times D \times 100} \quad (1)$$

where PEC_w is the predicted concentration in surface water; A is the amount of substance used per year (mg year^{-1}); R is the removal rate in sewage treatment (set to 0); P is the population under consideration (i.e. England (55,000,000)); V is the volume of waste water produced per capita per day (assumed to be 150 l) and D is the dilution factor in the environment (default of 10).

2.3. Prediction of no-effect concentrations (PNEC)

Toxicity data were collected from the open literature on properties and effects of the substances. Due

to the lack of experimental data in the public domain on the ecotoxicity and environmental behaviour of substances, it was not possible to prioritise the substances based on experimental data alone. Two approaches were therefore used to predict the no effect concentrations.

- (1) A therapeutic dose approach. This method was used to provide an indication of relative potency of individual substances. This method used a simple equation using the maximum therapeutic dose/1000 to produce a $PNEC_D$.
- (2) An approach using experimental ecotoxicology data and Quantitative Structure–Activity Relationships (QSAR) predictions to generate a single acute ecotoxicity value for each compound, to which a safety factor of 100 was applied to produce a $PNEC_T$. The software used in this study was the Syracuse Research Corporation’s ECOSAR (Meylan and Howard, 1998).

To enable the substances to be prioritised, a single concentration value was chosen to represent acute toxicity. The value was selected from either the predicted or experimental acute toxicity data. The lowest value for fish, daphnids or green algae was used in the prioritisation. Very little chronic toxicity data was publicly available so for consistency acute toxicity data were used for the prioritisation of substances in this study.

2.4. Risk characterisation

The potential risk of the substances to the environment was characterised by comparing the PEC_w value with the PNEC values (Eq. (2)).

$$\text{Risk characterisation ratio} = \frac{PEC_w}{PNEC_D \text{ or } PNEC_T} \quad (2)$$

Risk characterisation ratios were obtained for each type of PNEC ($PNEC_D$ and $PNEC_T$). The resulting ratios were then used to produce two priority lists, one based on dose, the other based on experimental data and/or QSAR predictions for ecotoxicity.

Table 1
Risk characterisation ratios of the top 10 compounds

Substance	Risk characterisation ratio	Therapeutic class
Lofepramine	1.99	Anti-depressant
Dextropropoxyphene	1.67	Analgesic
Procyclidine	1.60	Anti-depressant
Tramadol	0.97	Analgesic
Paracetamol	0.83	Analgesic
Clotrimazole	0.71	Antifungal
Thioridazine	0.60	Anti-depressant
Mebeverine	0.54	Gastrointestinal
Aminophylline	0.45	Respiratory
Tamoxifen	0.32	Anticancer

2.5. Results

Substances with a risk characterisation ratio greater than 1 are deemed to be “of potential concern” (EU, 1996). Using the PNEC_D approach no substances fall into this bracket whilst for the PNEC_T approach three substances had a ratio greater than one, lofepramine (anti-depressant), dextropropoxyphene (analgesic) and procyclidine (anti-depressant), indicating that they could potentially be of concern in the aquatic environment.

A single ranking list combining both of the PNEC approaches was produced to enable all factors (toxicity, usage and dose) to be taken into consideration.

The final ranking was based on the risk characterisation ratio of the substances; the higher of the two values produced for each substance (PNEC_T and PNEC_D) was used in the final ranking. The top 10 substances produced by this process are outlined in Table 1).

The potential persistence, bioaccumulation, and toxicity, (P,B,T) of the top 10 substances and a selection of the other substances near the top of the ranking were examined by applying the OSPAR dynamic selection and prioritisation mechanism for hazardous substances (DYNAMEC) (OSPAR Commission, 2002) criteria. A substance must satisfy all three criteria to be considered to fall under the OSPAR DYNAMEC. Although none of the substances examined were bioaccumulative according to the criteria, several were found to be either toxic or persistent or both. This highlighted a number of substances in addition to the top 10 compounds that could be of potential concern—fluoxetine, trimethoprim, sulfamethoxazole, fenofibrate and diclofenac (Table 2).

A literature review determined that few of the substances near the top of the prioritisation list had reliable analytical methods that could be used in a monitoring programme. In many cases methods could be adapted from existing methods to enable surface water and/or sewage effluent samples to be

Table 2
Summary data on P,B,T and analytical method availability

Substance	Risk characterisation ratio	Therapeutic class	Detected?	Method?	Method development possible?	OSPAR, p = persistence, t = toxicity
Lofepramine	1.99	Anti-depressant	×	×	✓	
Dextropropoxyphene	1.67	Analgesic	×	×	✓	✓t
Procyclidine	1.60	Anti-depressant	×	×	No data	
Tramadol	0.97	Analgesic	×	×	Not easy	
Paracetamol	0.83	Analgesic	✓	✓		
Clotrimazole	0.71	Antifungal	×	×	No data	
Thioridazine	0.60	Anti-depressant	×	×	Not easy	✓p,t
Mebeverine	0.54	Gastrointestinal	×	×	✓	
Aminophylline	0.45	Respiratory	×	×	No data	
Tamoxifen	0.32	Anticancer	×	×	✓	
Fluoxetine	0.07	Anti-depressant	×	×	Not easy	✓p,t
Trimethoprim	0.01	Anti-infective	✓	✓		✓t
Sulfamethoxazole	0.001	Antibiotic	✓	✓		✓t
Fenofibrate	0.04	Metabolism	✓	✓		✓t
Diclofenac	0.01	Anti-inflammatory	✓	✓		✓t

Table 3
Pharmaceutical compounds selected for targeted monitoring

Pharmaceutical	Therapeutic class	Chemical abstracts service (CAS) no.	Structure
Trimethoprim	Antibiotic	738-70-5	
Diclofenac	Anti-inflammatory	15307-86-5	
Sulfamethoxazole	Antibiotic	723-46-6	
Paracetamol	Analgesic	103-90-2	
Mefenamic acid	Anti-inflammatory	61-68-7	
Ibuprofen	Analgesic	15687-27-1	
Erythromycin	Antibiotic	114-07-8	
Dextropropoxyphene	Analgesic	469-62-5	
Lofepramine	Anti-depressant	23047-25-8	
Tamoxifen	Anti-cancer	10540-29-1	
Propranolol	Antihypertensive	525-66-6	

analysed (Table 2). The lack of available methods for many of the top 10 compounds (Table 1) reduced the feasibility of their inclusion on a final list, despite these substances being potential priorities for a monitoring programme.

2.6. Compilation of a final list for monitoring

Table 3 outlines the final list of substances chosen for the targeted monitoring programme. All of the substances were ranked close to the top of the prioritisation list produced during the screening process. It includes substances from a range of different therapeutic classes; where the top ranked substance from a particular class was unsuitable (no analytical method), the next ranked substance was chosen. With the exception of tamoxifen, dextropropoxyphene and lofepramine, all the substances have analytical methods and have previously been detected in either sewage effluent or surface waters. The assumptions used in this process are highly conservative and therefore this process is only suitable for relative risks to be identified and conclusions should not be drawn about the potential risk of individual substances.

Ibuprofen, diclofenac, paracetamol and propranolol have all been reported to either biodegrade or to be removed during sewage treatment (Richardson and Bowron, 1985; Ternes, 1998; Stumpf et al., 1999). The percentage removal varies, and all substances have been reported in monitoring studies, justifying their inclusion on the list. As part of the EA study analytical methods were developed for three substances, tamoxifen, dextropropoxyphene and lofepramine (Hilton and Thomas, 2003).

Once a drug is ingested and metabolised in the body a variable proportion is excreted as a conjugate, very little is excreted as the free compound. Studies on the fate of these conjugates indicate that the glucuronide forms can rapidly break down to form the free compounds again (Ternes et al., 1999). In addition to the parent compound, the original aim of the project was to semi-quantify those substances known to metabolise (sulfamethoxazole, paracetamol, ibuprofen, diclofenac, propranolol, lofepramine, dextropropoxyphene and tamoxifen). In practice, analytical methods for all but one of the metabolites could not be developed to sufficient quality for use within the programme.

Table 4
Details of the STWs chosen for this study

STW	Treatment process	Population equivalent (PE)	Trade PE	Mean flow during study (l s^{-1})
Corby	Inlets works: 6 mm screens, 4 mm drum screens, Kaldnes (Moving Fixed Film biological treatment process), intermediate settlement tanks, oxidation ditch (suspended biological treatment process), final settlement tanks and tertiary treatment (sand filter). [Ferric chloride is dosed in the ISTs and the oxidation ditch for phosphate removal. All return liquors are returned post screening]	150,000	105,000	284
Gt. Billing	Combination of filter and activated sludge plant with 40% of flows receiving biological P removal, flows are settled in conventional humus tanks, before being discharged to river. Secondary treatment only.	296,100	67,400	820
East Hyde	Oxidation ditch, final tanks then tertiary sand filters.	143,801	35,478	608
Harpenden	Primary sedimentation tanks then half of the plant is double biological filtration and the other half is alternate double filtration. Both followed by tertiary sand filters	31,905	324	138
Ryemeads	Conventional aeration, final tanks then tertiary lagoons	365,071	44,377	977

2.7. Monitoring sites

The STWs chosen for this study were Corby, Northamptonshire; Great Billing, Northamptonshire; East Hyde, Bedfordshire; Harpenden, Hertfordshire and Ryemeads, Hertfordshire. Details of these STWs are shown in Table 4 and Fig. 1. To ensure the degradation of the pharmaceutical compounds within the water samples was kept to a minimum, the samples were collected and returned to the laboratory the same day. The laboratory conducting the analysis was based in the Southeast of England; the geographical location of the sites was therefore restricted to this area. The sites chosen have previously been used in similar monitoring studies for trace organic compounds and crucially support was forthcoming from the relevant local water companies. Finally, the majority of the STWs selected had a predominantly domestic input. Such sites provide information on the levels of pharmaceuticals via

general use in the population rather than from industrial point sources.

2.8. Sample schedule and collection

Sampling was conducted monthly during May, June and July 2002 at all five sites. Three discrete final effluent samples were taken at hourly intervals on each visit to be analysed independently of each other. Based on data provided by the STW operators, the first sample was taken 1 h before the peak flow through the works, at the point of peak flow, and an hour after peak flow. One sample was also taken 1 km upstream and 1 km downstream of the discharge point at each site during the course of each sampling event. Discharge flow rates were obtained at the time of sampling in order to calculate the overall load of pharmaceutical discharging input from each STW. The pH of each individual sample was also measured, whilst the temperature, and salinity of each effluent/



Fig. 1. Location of sewage treatment works sampled.

water sample was also measured and assumed to be constant.

Samples were taken in May, June and July 2002 when surface water flows were predicted to be low due to low precipitation. Periods of low rainfall were targeted since the dilution of effluent through the STWs would be low and river flows would be correspondingly low. Sampling was performed around the time of peak flow from the STW (information provided by the STW operators). It was anticipated therefore that the concentrations of any compounds detected would represent a ‘worst case’, as dilution would be kept to a minimum. However, heavy rain during July made it impossible to collect samples during dry periods (particularly for Corby and Billing).

Samples (2.7 l) were collected directly into a silanised, clean amber glass winchester, using a stainless steel water sampler (Law et al., 1994) or via a stainless steel bucket dependent on the effluent sampling points available at each STW.

2.9. Analysis

Analysis of all compounds was performed using liquid chromatography coupled to electrospray mass spectrometry or tandem mass spectrometry as described by Hilton and Thomas (2003). Analysis followed extraction and pre-concentration of the samples by solid phase extraction (SPE), following the addition of an internal standard (^{13}C -phenacetin). A summary of the performance data for these methods is shown in Table 5. Low recoveries for lofepramine and tamoxifen meant that the methods were not suitable for environmental monitoring.

2.10. Statistical analysis

Concentration data were log-transformed before analysis and approximate normality confirmed visually by probability plotting. Values $< \text{lod}$ were input as $0.5 \times \text{lod}$. Attempts were made to use more sophisticated distributional techniques for gap-filling (as given in Newman, 1995), but these could not be justified given the small sample sizes and the occasionally large number of values $< \text{lod}$. There were no detections of paracetamol or lofepramine at concentrations above the detection limit; these substances

Table 5

Performance data for analysis of selected pharmaceuticals

Compound	% Recoveries ^a (RSD)	LOD ^b (ng/l ⁻¹)
Sulfamethoxazole	120 (16)	50
Acetyl-sulfamethoxazole	56 (5.4)	50
Trimethoprim	123 (2.5)	10
Erythromycin	73 (30)	10
Paracetamol	75 (6.9)	50
Ibuprofen	117 (22)	20
Mefenamic acid	24 (7.9)	50
Diclofenac	62 (20)	20
Clofibric acid	83 (7.0)	50
Propranolol	45 (5.6)	10
Dextropropoxyphene	63 (3.9)	20
Lofepramine	4.2 (35)	10
Tamoxifen	42 (40)	10

^a Calculated using: $\text{Recovery} = 100(X_S - X_U)/K$, where X_S = concentration measured in spiked sample, X_U = concentration measured in unspiked sample and K = known value of the spike in the sample. $n = 3$. 100 ng spiked into each sample.

^b Limit of detection (LOD) calculated using a signal to noise ratio of 10.

were therefore not statistically analysed. There were also very few detections of tamoxifen and sulfamethoxazole, so these substances were excluded from further analysis of individual compounds.

3. Results and discussion

3.1. Targeted monitoring

A summary of the occurrence data generated by this study is presented in Table 6.

3.1.1. Ibuprofen

Ibuprofen was determined at significantly higher concentrations than any other targeted pharmaceutical compound. Ibuprofen was regularly determined in STW effluents at a median concentration $\sim 3 \mu\text{g l}^{-1}$, mean concentration of $4 \mu\text{g l}^{-1}$ and downstream in receiving surface waters at concentrations of between < 0.02 and $\sim 5 \mu\text{g l}^{-1}$ (Table 6). A maximum concentration of $27 \mu\text{g l}^{-1}$ was measured in effluent from Great Billing STW, however the maximum concentration measured downstream of the works was $0.8 \mu\text{g l}^{-1}$ (Fig. 2). The maximum concentration measured in surface waters was in a sample collected downstream of Corby STW dis-

Table 6
Occurrence of selected pharmaceutical compounds in STW effluent and rivers

Compound	Sample type	Mean (ng/l ⁻¹)	Median	Max	Min	Frequency (%) ^a
Ibuprofen	Upstream	432	181	1555	<20	57
	Final effluent	4201	3086	27256	<20	84
	Downstream	1105	826	5044	<20	69
Diclofenac	Upstream	<20	<20	<20	<20	0
	Final effluent	599	424	2349	<20	86
	Downstream	154	0	568	<20	47
Propranolol	Upstream	10	<10	115	<10	14
	Final effluent	93	76	284	16	100
	Downstream	41	29	215	<10	87
Dextropropoxyphene	Upstream	<20	<20	<20	<20	0
	Final effluent	199	195	585	<20	74
	Downstream	147	58	682	<20	53
Mefenamic acid	Upstream	<50	<50	<50	<50	0
	Final effluent	273	133	1440	<50	81
	Downstream	86	62	366	<50	60
Erythromycin	Upstream	<10	<10	57	<10	17
	Final effluent	109	<10	1842	<10	44
	Downstream	159	<10	1022	<10	38
Trimethoprim	Upstream	<10	<10	36	<10	36
	Final effluent	128	70	1288	<10	65
	Downstream	12	<10	42	<10	38
Acetyl-sulfamethoxazole	Upstream	<50	<50	<50	<50	0
	Final effluent	161	<50	2235	<50	33
	Downstream	70	<50	239	<50	38
Sulfamethoxazole	Upstream	<50	<50	<50	<50	0
	Final effluent	<50	<50	132	<50	9
	Downstream	<50	<50	<50	<50	0
Tamoxifen	Upstream	<10	<10	<10	<10	0
	Final effluent	<10	<10	42	<50	4
	Downstream	<10	<10	<10	<10	0

^a Percentage of samples analysed where pharmaceutical was detected.

charge even though the ibuprofen concentration determined in Corby STW effluent was only 3 µg l⁻¹; indicating low levels of dilution. Ibuprofen was present at detectable concentrations in 84% of the effluent samples collected.

A high concentration of ibuprofen in STW effluents is not surprising since it has previously been reported at a concentration of up to 3.4 µg l⁻¹ in STW effluents (Ayscough et al., 2000; Ollers et al., 2001; La Farre et al., 2001; Kolpin et al., 2002). This is probably due to the amount of ibuprofen used as a prescription and an ‘over-the-counter’ anti-inflammatory and painkiller, combined with a low degree of human metabolism. Buser et al. (1999) reported that 70% to 80% of the human therapeutic dose of ibuprofen would be excreted as the parent compound

or as metabolites, whilst it has also been reported as relatively persistent in aquatic systems ($t_{1/2}$ = 50 days; Singer et al., 2002), although a half-life of < 1 day has also been reported (Richardson and Bowron, 1985). Ibuprofen has also been previously reported as inherently biodegradable during the STW process (Ayscough et al., 2000). However, the performance of different sewage treatment processes varies. Data from a study of the removal of 11 pharmaceutical compounds in a Brazilian sewage treatment works suggested that ibuprofen would be more effectively removed by activated sludge treatment (75% removal) than via biological filtration (22% removal) (Stumpf et al., 1999). It is apparent from this study that high concentrations of ibuprofen are present in the STW effluents analysed and that measurable concentrations

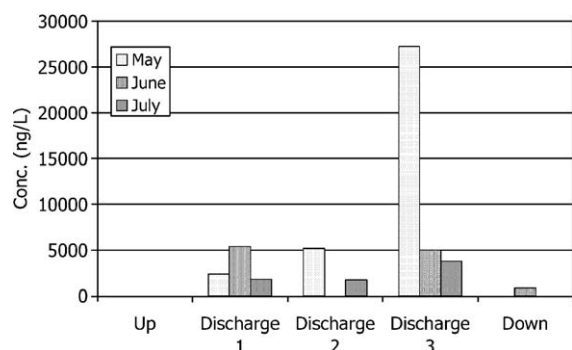


Fig. 2. Monthly concentration of ibuprofen in samples collected from Great Billing STW.

are present in surface waters receiving treated STW effluent.

3.1.2. Diclofenac

Diclofenac was found to have the second highest mean concentration in the effluents collected ($0.6 \mu\text{g l}^{-1}$; Table 6). The highest concentration of diclofenac ($2.3 \mu\text{g l}^{-1}$) was measured in a sample collected from Great Billing STW; as with ibuprofen, however, a low concentration of diclofenac was determined in receiving waters downstream, suggesting high levels of dilution. The highest diclofenac concentration measured in surface waters was $0.5 \mu\text{g l}^{-1}$ in a sample collected downstream of Harpenden STW (Fig. 3). Eighty-six percent of the effluent samples collected tested positive for the presence of diclofenac.

Although no data on the total UK usage of diclofenac were readily available, in 1997 there were over a million prescription items issued (Ayscough et al., 2000). The diclofenac concentrations measured within this study are of the same order as those that have been previously reported in sewage effluents (Ayscough et al., 2000; Ollers et al., 2001; La Farre et al., 2001; Ternes et al., 2003). Diclofenac sodium is known to be eliminated through metabolism and subsequent urinary and biliary excretion of the glucuronide and the sulphate conjugates of the metabolites with <1% of the parent drug excreted unchanged (EMC, 2002). Diclofenac is reported to be non-persistent in the aquatic environment, possessing a short half-life of <1 day and vulnerable to photodegradation ($t_{1/2} = 4 \text{ h}$) (Buser et al., 1998; Ayscough et al., 2000), suggesting that once it enters the environment

it will rapidly degrade. It has also been reported that a 69% reduction in diclofenac concentration occurs following primary sedimentation, aeration and phosphate removal treatment (Ternes, 1998). The available environmental fate data would suggest that diclofenac is environmentally labile, explaining why the concentration of diclofenac downstream of STWs is low and that it was not found in any of the upstream samples even though some of these receive STW effluent from other STWs.

3.1.3. Propranolol

Propranolol was detected in every STW effluent sample collected. The mean propranolol concentration in effluent was $0.09 \mu\text{g l}^{-1}$ with a maximum concentration of $0.28 \mu\text{g l}^{-1}$ determined in a sample collected from Harpenden STW (Table 6). The concentration of propranolol in samples collected downstream of the selected works was <0.01 and $0.2 \mu\text{g l}^{-1}$. Using a Pearson's Correlation there was a significant ($P < 0.0001$) positive correlation between the concentrations of propranolol found in effluent and those found downstream. These data compare well with the concentration of propranolol determined in effluent samples collected from German STWs and surface waters (Hirsch et al., 1996; Ternes et al., 2003). In the UK, approximately 12 tonnes/annum of propranolol is used (Ayscough et al., 2000). Once consumed, propranolol is extensively metabolized in the liver and is excreted from humans via the urine largely as metabolites with very little unchanged propranolol (Martindale, 2002). No data are readily available on its environmental persistence.

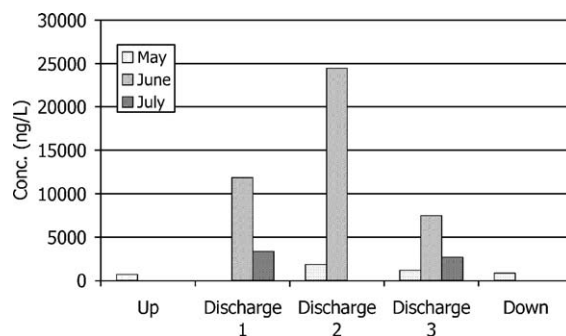


Fig. 3. Monthly concentration of diclofenac in samples collected from Harpenden STW.

3.1.4. Dextropropoxyphene

Dextropropoxyphene was determined in 74% of the effluent samples collected at a mean concentration of $0.2 \mu\text{g l}^{-1}$ (Table 6). A maximum concentration of $0.59 \mu\text{g l}^{-1}$ was measured in a sample collected from Rye Meads STW, whilst samples collected downstream of STWs contained between <0.02 and $0.6 \mu\text{g l}^{-1}$, the highest concentration being measured downstream of Corby STW. Studies in the UK during the early 1980s reported dextropropoxyphene to be present in certain rivers at concentrations of up to $1 \mu\text{g l}^{-1}$ (Richardson and Bowron, 1985). The mean downstream dextropropoxyphene concentration in this study was $0.15 \mu\text{g l}^{-1}$, which is an order of magnitude lower. Approximately 43 tonnes of dextropropoxyphene is used in the UK annually (Ayscough et al., 2000) and is excreted in urine mainly in the form of metabolites (Martindale, 2002). Any dextropropoxyphene that does pass through the body unchanged is likely to persist since it possesses a half-life ≥ 1 year (Richardson and Bowron, 1985).

3.1.5. Mefenamic acid

Mefenamic acid was also detected in a high number (80%) of the effluent samples collected (Table 6). A maximum concentration of $1.4 \mu\text{g l}^{-1}$ was measured in a sample collected from Great Billing STW with a mean concentration of $0.27 \mu\text{g l}^{-1}$ for all of the effluent samples collected. The mean concentration measured downstream of the STWs was $0.09 \mu\text{g l}^{-1}$, with a maximum concentration of $0.3 \mu\text{g l}^{-1}$ also measured downstream of Great Billing STW. All of the samples collected upstream of the selected STW discharges were $<0.01 \mu\text{g l}^{-1}$. To our knowledge no previous data have been reported on the concentration of mefenamic acid in STW effluents. These data compare with mefenamic concentrations of $\sim 0.01 \mu\text{g l}^{-1}$ reported in samples collected from Upper Austria (Ahrer et al., 2001). Mefenamic acid is also mainly excreted in urine as metabolites (EMC, 2002), whilst little information is available on its fate in STWs and the environment.

3.1.6. Trimethoprim

Trimethoprim was the most frequently occurring antibiotic analysed in this study, being detected in 65% of the effluent samples collected at a mean concentration of $0.1 \mu\text{g l}^{-1}$ and a maximum con-

centration of $1.3 \mu\text{g l}^{-1}$ (Table 6). The maximum concentration was measured in a sample collected from Great Billing STW. Trimethoprim was also detected in surface waters at a maximum concentration of $0.04 \mu\text{g l}^{-1}$ downstream of Great Billing STW. The median surface water concentration, however, was below the method LOD of $0.01 \mu\text{g l}^{-1}$. There was a significant (Pearson's Correlation, $P < 0.0001$) positive correlation between the concentrations of trimethoprim found in effluent and those found downstream. Trimethoprim has previously been reported in German STW effluents at concentrations of up to $0.66 \mu\text{g l}^{-1}$ (median $0.3 \mu\text{g l}^{-1}$) and up to $0.2 \mu\text{g l}^{-1}$ (median $<0.02 \mu\text{g l}^{-1}$) in German surface waters and up to $0.7 \mu\text{g l}^{-1}$ (median $0.15 \mu\text{g l}^{-1}$) in US surface waters (Hirsch et al., 1999; Kolpin et al., 2002). These data compare with those reported in the current study. Trimethoprim is mainly excreted in urine unchanged (Martindale, 2002). Little data on the fate of trimethoprim in STW are available, although an environmental half-life of 20–100 days has been reported (Zuccato et al., 2001).

3.1.7. Erythromycin

Erythromycin occurred less frequently (44%) than trimethoprim in the samples collected but was sometimes found at higher concentrations (Table 6). A maximum concentration of $1.8 \mu\text{g l}^{-1}$ was measured in a sample collected at Rye Meads STW, with an overall mean concentration of $0.1 \mu\text{g l}^{-1}$ being calculated for STW effluents. Erythromycin was detected in up and downstream surface water samples at a maximal of $1 \mu\text{g l}^{-1}$. There was a significant (Pearson's Correlation, $P < 0.0001$) positive correlation between the concentrations of erythromycin found in effluent and those found downstream. A comparable concentration of up to $6 \mu\text{g l}^{-1}$ has been reported in effluents from German STWs and up to $0.7 \mu\text{g l}^{-1}$ in German and US surface waters (Hirsch et al., 1999; Kolpin et al., 2002). Richardson and Bowron (1985) have also reported a nominal concentration of $1 \mu\text{g l}^{-1}$ in UK rivers. UK usage of erythromycin is high at 48 tonnes/annum.

3.1.8. Sulfamethoxazole

Sulfamethoxazole and its metabolite acetyl-sulfamethoxazole were irregularly detected in the final

effluent samples collected (Table 6). Acetyl-sulfamethoxazole occurred at a higher frequency (33%) when compared with sulfamethoxazole (9%). Acetyl-sulfamethoxazole was measured at a maximum concentration of $2.2 \mu\text{g l}^{-1}$ in STW effluents, whilst sulfamethoxazole was only detected at a maximal of $0.1 \mu\text{g l}^{-1}$ in samples collected from Corby and East Hyde STWs. There was a significant (Pearson's Correlation, $P < 0.0001$) positive correlation between the concentrations of acetyl-sulfamethoxazole found in effluent and those found downstream. Sulfamethoxazole has been detected in sewage discharge by Ternes et al. (2003) at a mean of $0.62 \mu\text{g l}^{-1}$ and by Hirsch et al. (1999) in surface waters at a concentration of $0.03 \mu\text{g l}^{-1}$, while Kolpin et al. (2002) detected sulfamethoxazole in 12.5% of surface water samples at a median concentration of $0.15 \mu\text{g l}^{-1}$. It is apparent that the concentration of sulfamethoxazole in UK STW effluents is lower than that observed in the US and Germany, whilst the majority of the compound occurs as its principal metabolite acetyl-sulfamethoxazole. No previous studies have assessed the occurrence of acetyl-sulfamethoxazole.

3.1.9. Tamoxifen, paracetamol and lofepramine

Of the remaining targeted pharmaceutical compounds, tamoxifen was detected twice in STW effluent samples, at concentrations of 0.02 and $0.04 \mu\text{g l}^{-1}$ in samples collected from Corby and East Hyde STWs, respectively, but was not detected in surface water samples. Paracetamol and lofepramine were not detected in either STW or surface water samples. No previous data have been reported on the occurrence of tamoxifen and lofepramine.

Paracetamol has been reported to occur at concentrations of up to $6 \mu\text{g l}^{-1}$, but this result was not wholly representative since both the reported median and 90th percentile data were both less than $0.5 \mu\text{g l}^{-1}$ (Ternes, 1998). Previous occurrence data therefore support the results of this study. In addition, paracetamol is known to be excreted as glucuronide and sulphate conjugates with only 5% excreted as the parent compound (Martindale, 2002). It is also readily degradable in the environment ($t_{1/2} < 1$ day) (Richardson and Bowron, 1985).

3.2. Inter-site differences

Significant variability was seen in the occurrence and concentration of the targeted pharmaceutical compounds in the samples collected. The particular STW that was sampled and the month in which it was sampled influenced the measured concentrations of several, but not all, substances. In particular, Great Billing STW effluent contained significantly higher concentrations of mefenamic acid, propranolol, dextropropoxyphene, erythromycin and trimethoprim. There was no significant overall effect of time of sample, and although month had a significant effect on concentrations, no consistent monthly pattern emerged across all substances. Variation in the concentration of compounds found in STW effluents has been observed in previously reported studies (Williams et al., 2003). In a study investigating the fate of steroid oestrogens the variable concentration of steroid oestrogens could not be correlated to flow. It was assumed that inputs of natural steroids are related to the (constant) population served by the works and that the variations in steroid concentrations indicate variations in STW plant performance, which in turn may be an important factor in determining final effluent concentrations (Williams et al., 2003). Plant performance may control some of the variability observed in the concentration of targeted pharmaceutical compounds, but it is likely that the input of pharmaceutical compounds and their metabolites into STW will be highly variable. The input into a works will be affected by a number of factors; for example, use patterns, amount used, the presence of hospitals and the presence of pharmaceutical manufacturing sites. It is therefore unsurprising that this has been detected in the samples collected for this study. Sebastine and Wakeman (2003) have reported information on the use of human pharmaceuticals in the UK. The annual consumption of pharmaceuticals on a weight basis was calculated based on prescription data obtained from the Department of Health (UK). Tonnage data is reported for nine of the substances analysed in the present study, a significant correlation (Spearman Rank Correlation, $P = 0.015$) existing between the two data sets. There was however, no significant relationship between the usage data derived for the present study and the overall frequency

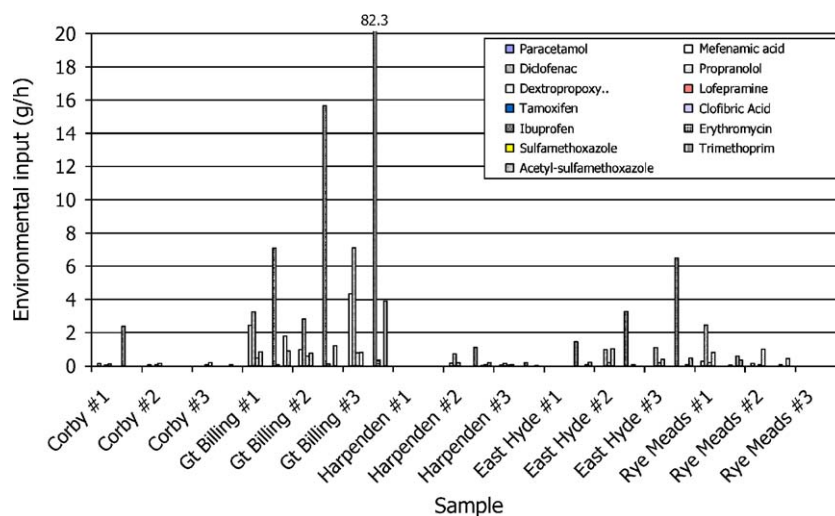


Fig. 4. Pharmaceutical compound inputs from (g h^{-1}) from five selected UK STW effluents during May 2002.

with which different substances were detected in effluent. However, there was some evidence to suggest that usage data are positively associated

with concentrations of pharmaceuticals in effluent and, particularly, with concentrations measured in surface waters below STWs.

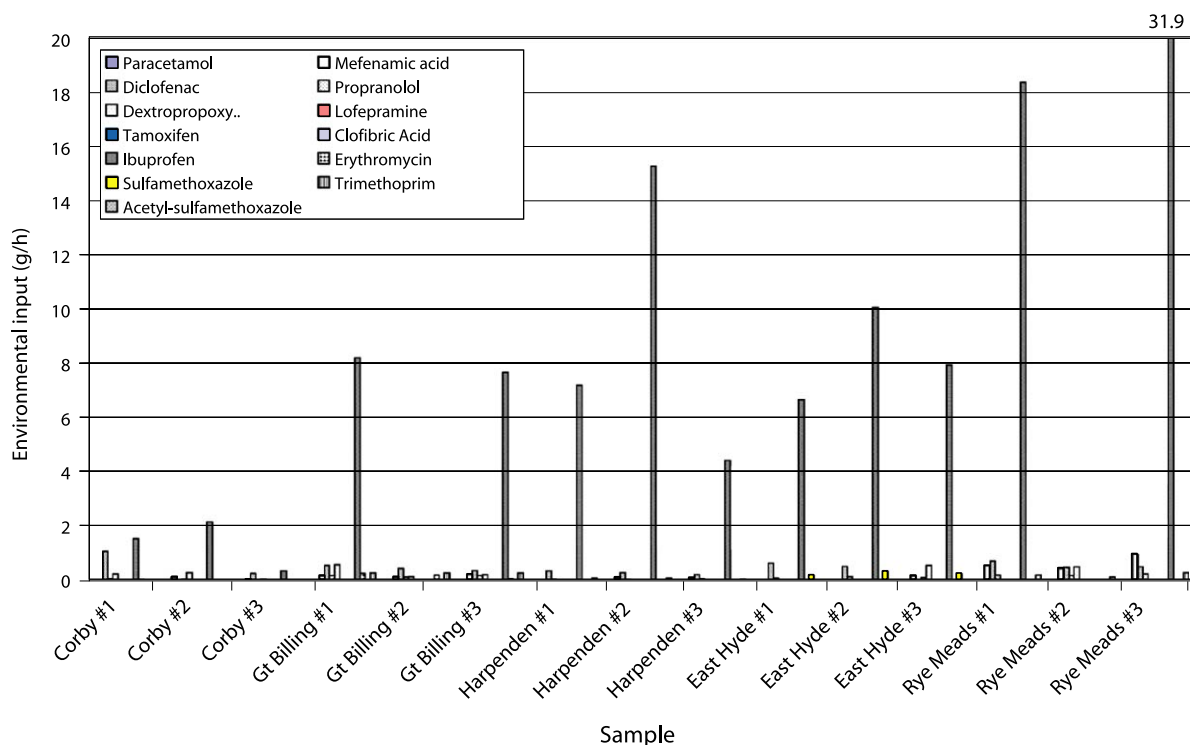


Fig. 5. Pharmaceutical compound inputs from (g h^{-1}) from five selected UK STW effluents during June 2002.

The coefficients of variation for substances ranged from 10.1% (propranolol) to 49.4% (erythromycin), showing that there is a difference in the precision of measured concentrations for different substances. In any future monitoring programme, the sampling strategy would need to take account of the variation reported between substances in this study. Composite sampling may have helped reduce the observed variability, but constraints in access to the sites and the financial implications involved did not allow for this and a pragmatic approach of using grab samples was adopted.

3.3. Environmental load

The environmental input, in g h^{-1} , of each targeted pharmaceutical was calculated for each STW effluent sampling event using effluent flow rates supplied by the STW operators (Figs. 4–6). The data are dependent on the effluent flow rate and concentration of targeted pharmaceutical at the time of sampling. The

time of sampling was around the time of peak flow of the STWs and therefore likely that they are among the highest for the sites monitored. Within the context of this study, Great Billing had both high final effluent flow rates and high concentrations of targeted pharmaceutical compounds. Therefore the highest loads were calculated to be from Great Billing STW. Similarly, the load data for Rye Meads STW are also high due to its high flow rates. Corby and Harpenden STWs provided the lowest load data, Corby STW due to the combination of low concentration of targeted pharmaceuticals determined in the final effluent and low flow rates. The loads of targeted pharmaceuticals from Harpenden STW were low due to correspondingly low flow rates.

Since the environmental load of each targeted pharmaceutical is dependent on its concentration, ibuprofen provides the most significant loads into the receiving waters. These loads are commonly in the low g h^{-1} range, while regularly reaching the order of tens of g h^{-1} . Within the context of this

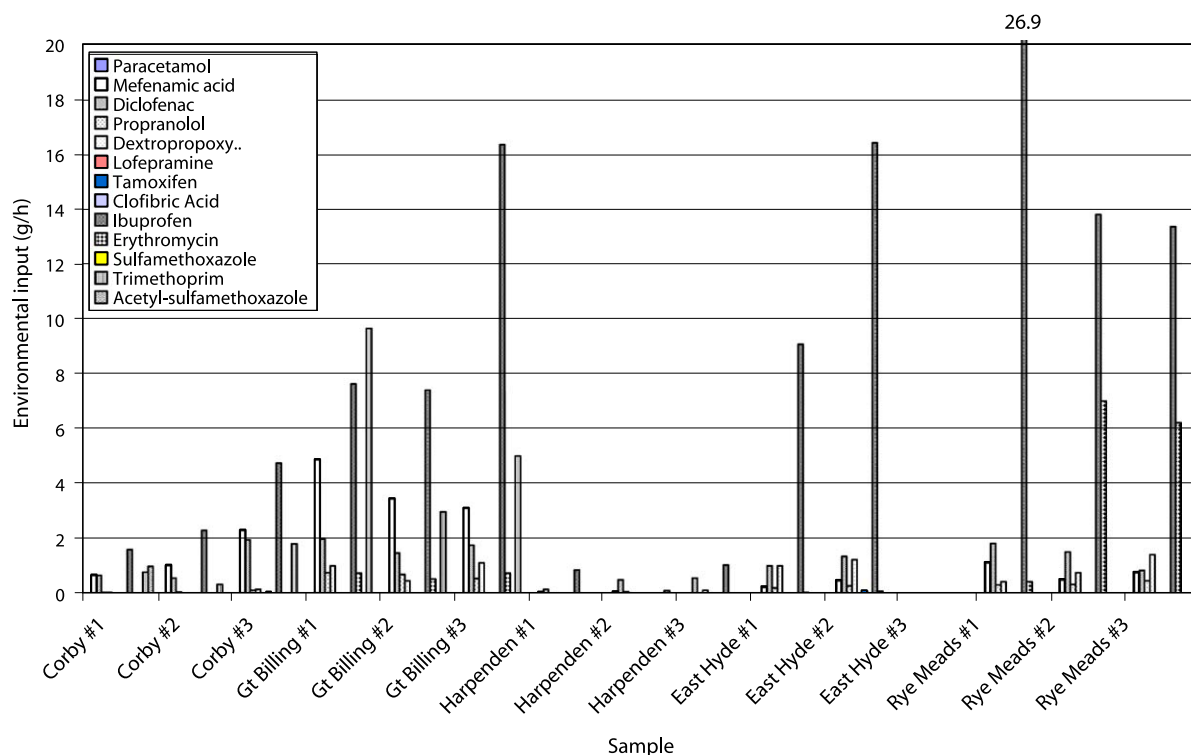


Fig. 6. Pharmaceutical compound inputs from (g h^{-1}) from five selected UK STW effluents during July 2002.

Table 7
Comparison of PECs and measured concentrations

Substance	Therapeutic class	Predicted environmental concentration (ng/l)	Actual concentration measured downstream (mean for five STW) (ng/l)	
			Mean	Maximum
Paracetamol	Analgesic	76400	N/d	N/d
Ibuprofen	Analgesic	10800	1105	5044
Mefenamic acid	Anti-inflammatory	677	86	366
Diclofenac	Anti-inflammatory	1090	154	568
Propranolol	Anti-hypertensive	365	41	215
Dextropropoxyphene	Analgesic	1332	147	682
Lofepramine	Anti-depressant	140	N/d	N/d
Tamoxifen	Anti-cancer	63	N/d	N/d
Erythromycin	Antibiotic	1594	159	1022
Trimethoprim	Antibiotic	289	12	42
Sulfamethoxazole	Antibiotic	40	N/d	N/d

targeted study, mefenamic acid, diclofenac and to a lesser extent dextropropoxyphene are all regularly providing a significant environmental input. However, the concentration of the target compound within the receiving watercourse, and therefore any associated biological effect, is very much dependent on the volume of the receiving waters, the degree of dilution that occurs and the environmental fate properties of the pharmaceutical. Although propranolol was detected in all of the discharge samples collected, an overall mean concentration of $\sim 0.2 \mu\text{g l}^{-1}$ suggests that overall input from individual effluent discharges is low in comparison to the other commonly detected target compounds. However, it would appear that propranolol is ubiquitous in the sewage discharges monitored.

3.4. PEC/PNEC comparisons

Predicted Environmental Concentrations were derived in the initial prioritisation exercise. In all cases the measured downstream concentrations, expressed as an average for all five sewage treatment works examined, are an order of magnitude below the PECs derived as part of the prioritisation process (Table 7). As described previously, the derivation of the PECs was precautionary, with no removal during sewage treatment or human metabolism being included in the calculation. This could have led to the discrepancy between the PECs and the concentrations measured in the field.

Table 8 outlines a comparison of the PNECs derived during the initial screening exercise and the

Table 8
Comparison of PNECs and measured concentrations

Substance	PNEC (ng/l)	Ratio (mean measured concentration/PNEC)	Actual concentration measured downstream (mean for five STW) (ng/l)	
			Mean	Maximum
Paracetamol	92,000	N/d	N/d	N/d
Ibuprofen	115,000	0.01	1105	5044
Mefenamic acid	15,000	0.006	86	366
Diclofenac	99,090	0.002	154	568
Propranolol	23,520	0.002	41	215
Dextropropoxyphene	800	0.18	147	682
Lofepramine	70	N/d	N/d	N/d
Tamoxifen	200	N/d	N/d	N/d
Erythromycin	78,000	0.002	159	1022
Trimethoprim	26,264	0.0005	12	42
Sulfamethoxazole	45,000	N/d	N/d	N/d

concentrations measured at the study sites. The majority of concentrations reported are all significantly lower than the PNEC, often several orders of magnitude lower. The maximum concentration reported downstream for dextropropoxyphene is close to the PNEC derived for this substance and the mean concentration is also within the same order of magnitude. With the exception of paracetamol and ibuprofen, all the derived PNECs were based on predicted traditional toxicity end-point data, whereas the mode of action of these substances may be significantly different and the chronic effects have not been sufficiently taken into account. There is therefore some uncertainty associated with these values.

As the risk prioritisation approach used in this study was precautionary, it is likely that the substances with a risk characterisation ratio greater than 1 could be further reduced using additional information. Human metabolism of substances would provide information on the species of compound being excreted, i.e. parent compound, metabolite or bound conjugate. Improved usage data would provide a better indication of the actual quantities of different compounds being used in the UK. At present, sales to hospitals and sales of over-the-counter (OTC) products in to outlets such as supermarkets, garages, etc., are excluded. These omissions could represent a significant input that at present is not being considered.

Removal/degradation data within STWs will provide an indication of the substances likely to be in the final effluent and thus reaching receiving waters. Recently reported data indicate that many pharmaceuticals are broken down during treatment and the efficiency of removal can be increased by using ozonation (Ternes et al., 2003). The fate of a range of pharmaceutical compounds in STWs has been modelled by Jones et al. (2002). This information will enable monitoring and management actions to be more effectively targeted at the media of concern, i.e. waste water or sewage sludge.

With the exception of oestrogenic compounds, there is little peer-reviewed data on the aquatic toxicity of human pharmaceutical compounds. In addition, the data that is available rarely considers an end point with a relevant mode of action. An increasing number of studies are, however, being reported for a limited number of substances (Brooks

et al., 2003; Pascoe et al., 2003). This data will help to assess the significance of concentrations measured in monitoring programmes, but consideration of the endpoints utilised in such studies needs to be addressed to increase the relevance of the data reported.

4. Conclusions

- Environmental occurrence data has been obtained for 11 pharmaceutical (or pharmaceutical metabolite) compounds in samples collected from STW final effluent discharges and receiving waters at five UK STWs.
- The results indicate that a range of pharmaceutical compounds from different therapeutic classes is present in both STW effluents and receiving waters in England. The values reported are within the same range as those reported in Europe and the US where more extensive monitoring has been conducted.
- Ten pharmaceutical compounds, ibuprofen, mefenamic acid, diclofenac, propranolol, dextropropoxyphene, erythromycin, trimethoprim, tamoxifen, sulfamethoxazole and acetyl-sulfamethoxazole were detected in STW final effluent samples.
- Eight pharmaceutical compounds, ibuprofen, mefenamic acid, diclofenac, propranolol, dextropropoxyphene, erythromycin, trimethoprim, and acetyl-sulfamethoxazole were detected in receiving surface water samples.
- Paracetamol and lofepramine were not detected in any of the effluent or receiving water samples collected.
- The anti-inflammatory pharmaceutical ibuprofen was consistently found to be present in the effluent samples collected at the highest median concentration ($\sim 3 \mu\text{g l}^{-1}$).
- Environmental input data showed that significant amounts of the targeted pharmaceutical compounds are entering UK surface waters from STW effluent discharges.
- There was some evidence to suggest that usage data are positively associated with concentrations of pharmaceuticals in effluent and, particularly, with concentrations measured in surface waters below STWs.

- The occurrence of some pharmaceuticals in upstream samples suggest that longer-range transport is possible for some compounds.
- The risk prioritisation procedure adopted in this study was precautionary and could be refined with additional data concerning human metabolism of substances, fate in STW and more inclusive usage data.
- The paucity of suitable effects data with which to put monitoring data into context prevents the risk of these substances to organisms exposed to low level concentrations over long periods of time to be assessed.

Acknowledgements

This work was funded by the UK Environment Agency (Contract P6-012/6). The work conducted within this programme was assisted greatly by advice and help provided by Simon Bonney (Anglian Region, Environment Agency), and staff at Anglian and Thames Water who provided access to the sampling sites and additional information. Thanks to Jacqui Eggleton for help with sampling. Significant work on the risk prioritisation exercise was conducted by Cranfield University (Alistair Boxall and Chris Sinclair), additional contextual data and interpretation was provided by WRc-NSF (Chris Watts and Neal Sorokin), statistical interpretation was conducted by Dr. Mark Crane.

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