FINAL REPORT TO

DESK BASED REVIEW OF CURRENT KNOWLEDGE ON PHARMACEUTICALS IN DRINKING WATER AND ESTIMATION OF POTENTIAL LEVELS

Watts and Crane Associates

November 2007

Desk based review of current knowledge on pharmaceuticals in drinking water and estimation of potential levels

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Final Report

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Executive Summary

The Drinking Water Inspectorate commissioned this review to identify all relevant, robust studies that investigate pharmaceutical concentrations in raw or treated water, or factors affecting those concentrations. This summary of existing knowledge will be taken forward and used for the systematic evaluation of the potential for different pharmaceuticals to reach water.

There are about 3000 pharmaceuticals registered in the UK and approximately 5000 substances listed as human pharmaceuticals were sold over the counter in the UK in 2004. Consumption of active pharmaceutical ingredients in industrial countries is estimated to be between 50 and 150 g per person per year, with fewer than 50 compounds making up 95% of the total amount of active pharmaceutical ingredient consumption. In addition to the consumption of drugs for health care, there is also significant consumption of 'illegal' drugs due to both recreational consumption and drug addiction, and for enhancement of sporting performance.

The observed concentrations of pharmaceuticals in raw wastewater indicate that the major source of pharmaceuticals to the environment is via sewage treatment works effluent. Sewage treatment works use a wide range of processes, e.g. primary screening, biological filtration, and anaerobic digestion, and these are considered in detail in this report. Reported removal rates for pharmaceuticals vary considerably between and within studies. In addition, concentrations of some compounds have been found to increase during the treatment process, probably as a consequence of the transformation of conjugates back to the parent compound. As well as the variances that can be ascribed to differences in process type and sewage treatment works configuration, other factors, such as heavy rainfall and seasonality, have been shown to confound interpretation of removal rate efficiency.

Drinking water treatment works use a wider and technically more advanced range of processes, but again these are not specifically designed to remove pharmaceuticals and several compounds have been reported in finished drinking water in different parts of the world. Although no clear quantitative structural relationships have been determined that describe the degree of removal of a pharmaceutical during treatment processes, it is clear that the structure and nature of individual compounds are key parameters in determining the efficiency of removal. Only a few pharmaceuticals are oxidised to smaller molecules by chlorine or chlorine dioxide, but for those pharmaceuticals containing amino or phenolic moieties a complete oxidative degradation can be expected. Most non-polar organic compounds are the best candidates for the removal by activated carbon but the removal rate may depend on the age of the carbon. Neutrally charged pharmaceuticals are well removed from water using an oxidant such as ozone or ultraviolet radiation. Reverse osmosis has been shown to be a particularly effective process for removing a wide range of pharmaceuticals but is an energy-intensive process. Removal of pharmaceuticals by drinking water treatment works processes was significant for almost all of the pharmaceuticals studied when the treatment process included ozonation and activated carbon. This combination, together with the more conventional DWTW processes, can result in removal rates of >90% for a wide variety of pharmaceuticals.

Very limited data were available for the concentrations of pharmaceuticals or illegal drugs in UK drinking waters, but data from the rest of Europe and the USA have

shown that concentrations in finished drinking water at treatment works are generally =100 ng.l^{1}. Data for UK rivers and streams has shown that median concentrations of pharmaceuticals are almost always =100 ng.l^{1}.

Five drinking water treatment works scenarios based on UK catchments were used for deterministic and probabilistic modelling to estimate concentrations in UK drinking waters. The model was based on the simple approach developed by the European Medicines Agency (EMEA) for estimating concentrations of pharmaceuticals in surface waters. Exposure ratios based on comparison of the estimated concentrations with the minimum therapeutic dose were used to determine the significance of the model outputs for pharmaceuticals and illegal drugs.

Worst-case modelling showed that even in the scenario with the highest estimated concentrations, the exposure ratios (comparison of the minimum therapeutic dose to the estimated intake from drinking water) for most of the major used pharmaceuticals and illegal drugs were significantly greater than 1000 and provided a high safety margin. Only 10 substances produced exposure ratios less than 1000 and four of these were illegal drugs. In only one case was the exposure ratio less than 100 and this was the special case, using a combined total for all NSAIDs at the lowest minimum therapeutic dose. It therefore appears that even in this worst case situation there is no significant risk from pharmaceuticals discharged to drinking water sources.

The use of probabilistic modelling provided a more realistic estimate of likely concentrations in drinking water and showed that, as expected, the estimated concentrations for all except one substance were significantly lower than the estimated concentrations from the worst case (deterministic model). Using the mean concentrations from the probabilistic model, all of the substances have exposure ratios significantly greater than 100 and only tetrahydrocannabinol also has an exposure ratio less than 1000. It therefore appears that this more realistic worst case probabilistic modelling confirms that there is no significant risk from pharmaceutical usage.

Recommendations

The accuracy of the estimates of usage for the illegal drugs is unknown and since many of them produced some of the lowest exposure ratios it would be appropriate to revisit estimates of usage. In addition, since they were assigned nominal, very low, minimum therapeutic doses it would also be appropriate to search for data to provide more realistic estimates. In addition it would be useful to collate data on the percentage of active ingredients in cannabis that are absorbed during use in order to obtain a better estimate of the quantities of tetrahydocannabinol that might be available to reach wastewater.

Some pharmaceuticals produce significant quantities of metabolites which are excreted and enter the environment via sewage treatment. Worst case modelling of these metabolites for major use pharmaceuticals would be worthwhile to determine their exposure ratios.

In view of the dearth of measured data on the concentrations of pharmaceuticals and illegal drugs in UK drinking waters it would be prudent to carry out a small scale survey. This survey could be guided by the findings from this report and address

those substances that have the lowest exposure ratios, the highest predicted concentrations and substances of potentially high public perception of hazard such as cytotoxic drugs, depending on the available analytical methodology. In addition, the monitoring could be carried out in the catchments that provided the scenarios with the highest estimated concentrations or where there is reason to believe that there may be a particular hotspot.

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1 Objectives

The detailed objectives from the project tender for the research project identified by DWI were to:

1) identify all relevant studies, in the published and grey literature, that investigate pharmaceutical concentrations in raw or treated water, or factors affecting those concentrations;

2) assess broadly the quality of the studies identified, in terms of the scope of the study and the performance of the analytical methods used;

3) summarise the findings of the studies, their relevance to England and Wales and identify any factors that may lead to high concentrations;

4) devise a systematic evaluation of the potential for all pharmaceutical and recreational drugs used in England and Wales to reach raw and treated water;
   - the evaluation may group together compounds with similar properties based on mode of action or chemical functionality;
   - the evaluation should start by obtaining relevant usage data for each pharmaceutical or group of pharmaceuticals and then based on knowledge of the properties estimate degradations/dilution for each group or individual compound through each stage from use of the compound through to water treatment; and
   - the evaluation should consider at least four scenarios. Two where there are significant inputs of treated sewage effluent into the water sources, one with more "advanced" treatment and one with conventional treatment. Two more scenarios where inputs are lower but again with different levels of treatment. All scenarios should be based on real sites in England or Wales;

5) consider the potential for unusually high inputs from, for example, inappropriate disposal of old pharmaceuticals and from normal discharges from areas of potential high use such as hospitals or old people's homes;

6) conclude on the likely levels in raw and treated water and comment, in broad terms, on the health significance of the estimated levels.

7) where appropriate, recommend areas for future research

These objectives were considered in the technical proposal and were divided into a series of milestones with target dates (Annex 1).

2 Introduction

There are about 3000 pharmaceuticals registered in the UK and approximately 5000 substances listed as human pharmaceutical preparations were sold in the UK in 2004. The Medicines Act 1968[1] defines three legal categories of medicines viz:

- general sale list medicines,
- pharmacy medicines, and
- prescription only medicines.

Some prescription only medicines are further classified as controlled drugs - these categories are briefly described below.

General sale list medicines (GSL)

General sale list medicines may be sold from a wide range of shops such as newsagents, supermarkets and petrol stations. Often only a small pack size of the medicine may be sold. For example, the largest pack size of paracetamol that may be sold from a shop is 16 tablets, whereas packs of 32 tablets may be sold from a pharmacy. Usually only low strengths of the medicine may be sold. For example, the highest strength of ibuprofen tablets that may be sold from a shop is 200mg whereas tablets containing 400mg may be sold from a pharmacy.

Pharmacy medicines (P)

Pharmacy medicines may only be sold from a pharmacy. A pharmacist must make or supervise the sale. Before being sold a pharmacy medicine the consumer will usually be asked if they have any medical conditions and if they take any other medicines.

Prescription only medicines (POM)

Prescription only medicines can only be obtained with a prescription, usually from a General Practitioner or dentist, but in some cases, a nurse, pharmacist or other healthcare professional.

Some medicines may be reclassified from Prescription only to Pharmacy or from Pharmacy to General Sale List. This can happen after several years on the market, when it is known that the medicine is safe for most people to use. For example, aciclovir cream, which can be used to treat cold sores, was first available as a Prescription only medicine. After a few years, it was reclassified to a Pharmacy medicine and recently, it has been reclassified again to a General sale list medicine.

Controlled drugs

Some prescription only medicines are further classified as Controlled drugs, such as morphine, pethidine and methadone. In some cases, these medicines may be misused or sold illegally, so there are stricter legal controls on their supply.

[1] http://www.nhsdirect.nhs.uk/articles/article.aspx?articleId=1325

Many commonly used pharmaceuticals, e.g. paracetamol, acetylsalicylic acid, and ephedrine are General sale list but are also supplied on prescription. Lists of these substances are available at the MHRA website[2]

Estimation of levels present in waters is difficult for such a wide range of chemicals, but substantial work of relevance to this project has already been carried out by the Environment Agency (EA) and is currently in press. One EA project provided estimated concentrations in river water for the 300 human pharmaceuticals used in the greatest amounts in the UK in 2004 (Watts et al., 2005). There are also measured data on concentrations of specific pharmaceuticals in wastewater, surface water and, to a much lesser extent, drinking water. Comparison of measured concentrations in river and drinking water with the estimated concentrations in river water and potable water can provide an indication of the utility of the estimation method. Estimation of concentrations can be done using data on amounts of pharmaceuticals used in the UK and knowledge of removal in sewage and drinking water treatment processes. Where possible, concentrations estimated in potable water were set against the clinical doses to provide a suitable context as to potential concerns and whether the concentrations are likely to be of concern.

It is important to understand what is meant by removal in the context of this report and the literature information that has been reviewed. Substances may be removed from water by three basic processes: physical, chemical and biological. Physical processes include sorption (e.g. onto sludge solids), volatilisation (e.g. air stripping) and ultrafiltration and their effect is to remove the substance from the water phase into another phase. Chemical and biological processes remove a substance by changing its chemical structure and this process may lead to the production of degradation products and metabolites, or can result in complete mineralisation. The data reported in the literature usually only reveal changes in concentration of the substance of interest to determine extent of removal, so it is not possible to say whether metabolites or degradation products are formed and/or mineralisation occurs as a consequence of the removal process.

This final report covers the whole project (milestones 1-11 in Annex 1) and consists of a literature review, carried out in three stages as below, and estimation of potential UK drinking water concentrations.

The first stage of the review developed a structured search strategy to identify and obtain relevant publications from the open international literature. Wherever possible recent reviews were sought as an efficient way of gathering the information required for the project. Several relevant reviews on pharmaceuticals have been published recently, for example, a review of pharmaceuticals and personal care products in the water cycle by the Global Water Research Coalition (GWRC, 2004). It was also important in the first stage of this project to gather information from key papers on removal mechanisms for pharmaceuticals, such as the report on the POSEIDON project (Ternes et al., 2005).

The second project stage trawled the grey literature, such as the study carried out by the EA on prioritisation of pharmaceuticals (Watts et al., 2005), and the study by KIWA in the Netherlands (Mons et al., 2003), which is not publicly available.

[2] http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=728.

Attempts were also made to obtain internal reports from other organisations that are active in this field and some of the papers from Zucatto et al. and the US Geological Survey fall into this category. It must be remembered that there are significant differences in the use of pharmaceuticals between different countries and between Europe and the USA, so some data from other countries may not be relevant to the UK situation.

The third project stage involved contacting workers in the field to discuss the latest data and what this might be indicating, in order to evaluate properly the published and grey literature and to put any conclusions into a suitable context.

The data from the review were used in a simple deterministic model to estimate worst case concentrations of the major used pharmaceuticals in selected UK drinking waters, and then for more detailed probabilistic modelling when appropriate.

3 Pharmaceutical Use

Consumption of active pharmaceutical ingredients in industrial countries is estimated to be between 50 and 150 g cap^{-1} a^{-1} with less than 50 compounds making up 95% of the total amount of active pharmaceutical ingredient consumption (Alder et al., 2006). Prescription drugs are generally sold in quantities that are at least an order of magnitude lower than non-prescription drugs. Trends in the use of various pharmaceuticals tend to vary between countries and over time, due to differences in regulations and approvals, prescribing practices and health care systems. Although the consumption patterns of many pharmaceuticals are similar between the different EU countries, significant differences can be found for individual compounds.

In addition to the consumption of drugs for health care, there is also significant consumption of 'illegal' drugs due to both recreational consumption and drug addiction, and for enhancement of sporting performance. Naturally, it is more difficult to obtain accurate information on the amounts of such illegally supplied and used drugs in the UK and Europe, but the available information is provided in section 6.

Possibly the first report of pharmaceuticals in environmental samples in the open scientific literature was that of the antibiotics tetracycline and theophylline in river water in 1983 (Watts et al., 1983) and was related to the use of these pharmaceuticals to treat infection in fish farms. Earlier reports from UK Department of the Environment (DoE) funded research also found some pharmaceuticals and related compounds in river and drinking water (Fielding et al., 1981). Steroids were the first physiologically active compounds to be reported to be present in sewage effluent (Daughton and Ternes, 1999). Estrogenic drugs, primarily synthetic xenoestrogens, are used extensively in estrogen–replacement therapy and in oral contraceptives, in veterinary medicine for growth enhancement, and in athletic performance enhancement. The synthetic oral contraceptive (17a-ethynylestradiol), for example, occurs generally at low concentration (< 7 ng l^{1}) in sewage treatment works (STW) effluent. Although these steroidal compounds are an important subgroup of pharmaceuticals there are already a large number of studies and reviews on this topic (Andersen et al., 2003; Shi and Kujawa-Roeleveld, 2007; SCOPE/IUPAC, 2003; Ternes et al., 1999) and it will not be covered in detail in this review.

3.1 UK Usage

3.1.1 Over-the-counter (OTC) and Prescribed Pharmaceuticals

IMS (http://www.imshealth.com) hold information on the total amounts of active ingredients in human pharmaceutical preparations sold in the UK. The data from IMS used in the current work covered the total amounts supplied in 2004 of active ingredients (salts, bases and acids) in generic and branded human pharmaceutical preparations. Data are available for total amounts issued by hospitals and purchased by community pharmacies and dispensing doctors, but not for the following:

1. OTC-only medicines (e.g. Gaviscon can be prescribed and given over the counter; the IMS data do not discern what is dispensed against a prescription and what is bought by the consumer, so the data will for be all of the sales). Likewise it used to be the case that some "brands" had a prescription pack

and an OTC pack (e.g. Clarityn 28 was only able to be given out against a prescription, and Clarityn 7 tablets were able to given out against prescription and OTC – the IMS would include both Clarityn packs in their data). On the other hand if there was a wholly OTC brand (i.e. no pack could be reimbursed against a prescription) then there would be none of that product's data in the IMS usage data).

2. Private hospitals - IMS do not collect data from private hospitals, e.g. from Priory Health or BUPA (The British United Provident Association). However some National Health Service (NHS) Trusts have a private ward, or will treat patients privately. The IMS data include that usage.

3. Within the NHS, IMS estimate that the volume going direct from the manufacturer to hospitals is about 60% of the whole, and the published IMS data used here does not include all of that direct supply.

4. Supermarket pharmacies - the data from IMS do not include data from supermarkets that do not have a pharmacy license, i.e. those that only sell GSL medicines, unless that supermarket has a pharmacy that belongs to one of the pharmacy chains. For example, Tesco uses Lloyds Pharmacies, in which case those data are included.

5. Direct supply to the community: For example the IMS data do not include direct manufacturer sales of either vaccines to General Practitioner practices, or contraceptives to family planning clinics. For IMS to capture the data the sale has to go through a wholesaler or pharmacy.

6. Since most anaesthetics are sold to hospital pharmacies the IMS data coverage for these substances should be good. Similarly about 70% of x-ray contrast media also goes via that route.

By examining the data for certain specific medicines in detail, one can get some idea of the overall percentage of the market that the IMS usage data covers. Several commonly used pharmaceuticals have prescription and OTC packs, e.g. ranitidine is available both on Prescription and OTC as Zantac 75 or a generic equivalent. Both the Prescription and OTC packs are included in the IMS data where they were distributed through hospitals, community pharmacy or dispensing doctors.

Guaifenesin is included in several OTC medicines like Benylin and Tixylix. Where guiafenesin is included within a product that also has a prescription medicine within it, e.g. paracetamol, then the data on guaifenesin will also appear in the IMS data. Where it is combined in a product that has no prescription medicines within it, then it will not.

An estimate of the volume of the substance going through OTC in retail pharmacies depends on whether the OTC product is available as a P or a GSL medicine. If the former, then 100% of the product will go through retail pharmacies, e.g. Zantac 75. If it is also available as GSL, e.g. paracetamol, aspirin and ibuprofen, then approximately 50-60% will go through retail pharmacy. Most of the remainder is probably going through grocers (ca. 30%) and some through other outlets like petrol forecourts. The following data from IMS provides some information on paediatric

forms of paracetamol and ibuprofen sales through retail pharmacies, which demonstrates that supply is not constant and supermarket share is likely to increase:

Paediatric paracetamol	**Yr to 9/04**	**Yr to 9/05**	**Yr to 9/06**
	82%	80%	69%
Paediatric ibuprofen	**Yr to 9/04**	**Yr to 9/05**	**Yr to 9/06**
	71%	79%	75%

Despite these limitations, the usage data from IMS represents the most comprehensive data that are available on UK pharmaceutical usage in relation to amount of active ingredient and is probably within a factor of two of the total usage. This uncertainty in the usage data was taken into account within the worst case deterministic modelling by using twice the IMS value for each pharmaceutical
A recent project carried out for the Environment Agency in 2005 (Watts et al., 2005) used the 2004 IMS database which had data for approximately 5000 substances. From that list an initial screening based on expert judgement identified a number of classes of compound which were subsequently removed. These substances were believed either to pose minimal hazard to the environment and humans, to be present already in the environment or to be present in many effluents (from other sources) in far greater amounts than would arise from pharmaceutical use. The types of substances (active ingredients and additives) present in medicines that were excluded from further consideration are shown below (together with an example of each type):

- plant products and extracts (e.g. *Coriandrum sativum* which is used as a laxative and *Ricinus communis* which is used as an emollient);
- animal products and extracts (e.g. cod liver oil used as a vitamin supplement and lanolin which is used in skin preparations);
- inorganics (e.g. calcium and magnesium used as mineral supplements);
- vaccines (e.g. hepatitis B and influenza vaccines);
- undefined mixtures or solutions (e.g. 'Special Diet Preparations' and 'Dialysis/Haemodialysis Solutions')
- natural and synthetic polymers (e.g. dimethicone, a silicone polymer used in skin creams and laxatives and tannins used as antiseptics); and
- gaseous substances (e.g. nitrous oxide used as an anaesthetic and oxygen used as a therapeutic aid).

Once these substances had been removed, the remaining 394 substances were ranked according to the amount of active ingredient sold in 2004. The UK top 50 pharmaceuticals used in 2004 based on the IMS use data are shown in Table 3.1.

Table 3.1 The UK top 50 used pharmaceuticals in 2004 (based on IMS data)

Compound	GSL P POM	Amount used in 2004 Kg (active ingredient)	Molecular Formula	Pharmaceutical Product Group	Chemical Group
Paracetamol (acetaminophen)	GSL	3,534,737	$C_8H_9NO_2$	Analgesic	Phenols
Metformin	POM	497,453	$C_4H_{11}N_5$	Antidiabetic – lipid lowerer	Neutral organics
Ibuprofen	GSL	330,292	$C_{13}H_{18}O_2$	Analgesic	Neutral organics, carboxylic acid
Acetylsalicylic acid (aspirin)	GSL	177,623	$C_9H_8O_4$	Analgesic	Aromatic carboxylic acid
Amoxicillin	POM	141,287	$C_{16}H_{19}N_3O_5S.3H_2O$	Antibiotic	Aliphatic amines, carboxylic acid
Valproic acid	POM	72,953	$C_8H_{16}O_2$	Anticonvulsant - CNS	Neutral organics – carboxylic acid
Mesalazine	POM	65,088	$C_7H_7NO_3$	Anti-inflammatory - gastrointestinal	Phenol amine and carboxylic acid
Sulfasalazine	POM	61,414	$C_{18}H_{14}N_4O_5S$	Anti-inflammatory - gastrointestinal	Phenol, sulphonamide, carboxylic acid
Flucloxacillin	POM	57,551	$C_{19}H_{17}ClFN_3O_5S$	Antibiotic	Tetracyclic, carboxylic acid, amide, organohalogen, ß-lactam
Carbamazepine	POM	52,245	$C_{15}H_{12}N_2O$	Antiepileptic, psychotropic	Neutral organics – carboxamide Dibenzazepine derivative
Atenolol	POM	49,547	$C_{14}H_{22}N_2O_3$	CV beta blocker	Aliphatic amines
Erythromycin	POM	48,654	$C_{37}H_{67}NO_{13}$	Antibiotic	Aliphatic amines
Gabapentin	POM	48,468	$C_9H_{17}NO_2$	Anticonvulsant - CNS	Aliphatic amines, carboxylic acid
Ranitidine	POM & GSL	48,087	$C_{13}H_{22}N_4O_3S$	H2 antagonist - gastrointestinal	Aliphatic amines
Codeine	POM & P	42,198	$C_{18}H_{21}NO_3$	Analgesic	Aliphatic amines

Compound	**GSL P POM**	**Amount used in 2004 Kg (active ingredient)**	**Molecular Formula**	**Pharmaceutical Product Group**	**Chemical Group**
Povidone-iodine	GSL	37,935	(polyvinylpyrrolidone-iodine)	Antibacterial	Neutral organics, organohalogen
Salicylic acid	GSL	36,573	$C_7H_6O_3$	Kerotic agent	Phenols, carboxylic acid
Diclofenac	POM & P & GSL	35,361	$C_{14}H_{11}NCl_2O_2$	Anti-inflammatory	Neutral organics, carboxylic acid
Naproxen	POM	33,580	$C_{14}H_{14}O_3$	Anti-inflammatory	Neutral organics, carboxylic acid
Dextropropoxyphene	POM	32,820	$C_{22}H_{29}NO_2$	Analgesic	Aliphatic amines
Penicillin V	POM	32,472	$C_{16}H_{18}N_2O_5S$	Antibiotic	Tricyclic, carboxylic acid, amide
Quinine	POM & GSL	32,394	$C_{20}H_{24}N_2O_2$	Antimalarial	Aliphatic amines
Diltiazem	POM	31,645	$C_{22}H_{26}N_2O_4S$	Calcium channel blocker - CV	Aliphatic amines - benzothiapine
Iohexol	POM	31,136	$C_{19}H_{26}I_3N_3O_9$	X-ray contrast medium	Neutral organics, organohalogen
Oxytetracycline	POM	30,078	$C_{22}H_{24}N_2O_9$	Antibiotic	Aliphatic amines
Allopurinol	POM	29,989	$C_5H_4N_4O$	Anti-gout agent	Purine derivative
Gliclazide	POM	28,027	$C_{15}H_{21}N_3O_3S$	Antidiabetic	Tricyclic, sulphonamide, amide
Tramadol	POM	24,678	$C_{16}H_{25}NO_2$	Analgesic	Aliphatic amines
Furosemide	POM	23,744	$C_{12}\ H_{11}N_2ClO_5S$	Diuretic - antihypertensive	Neutral organics, carboxylic acid
Chlorhexidine	GSL	23,245	$C_{22}H_{30}Cl_2N_{10}$	Antiseptic – mouth wash	Neutral organics
Cefalexin	POM	23,169	$C_{16}H_{17}N_3O_4S$	Antibiotic	Aliphatic amines, carboxylic acid
Mebeverine	P	22,946	$C_{25}H_{35}NO_5$	Gastrointestinal – muscular spasmolytic	Aliphatic amines
Cimetidine	POM & P	21,884	$C_{10}H_{16}N_6S$	Antihistamine – H2	Imidazoles

Compound	GSL P POM	Amount used in 2004 Kg (active ingredient)	Molecular Formula	Pharmaceutical Product Group	Chemical Group
				antagonist	
2-phenoxyethanol	POM & P	21,123	$C_8H_{10}O_2$	Bacteriacide –skin cream	Neutral organics
Metronidazole	POM	20,975	$C_6H_9N_3O_3$	Antibiotic - antiprotozoal	Imidazoles
Iopromide	POM	19,848	$C_{18}H_{24}I_3N_3O_8$	X-ray contrast medium	Neutral organics, organohalogen
Caffeine	GSL	16,825	$C_8H_{10}N_4O_2$	CNS stimulant	Imides
Mefenamic acid	POM	16,425	$C_{15}H_{15}NO_2$	Anti-inflammatory - antipyretic	Neutral organics, carboxylic acid
Diatrizoic acid	P	16,020	$C_{11}H_9I_3N_2O_4$	X-ray contrast medium	Amide, carboxylic acid, organohalogen
Levodopa	POM	15,809	$C_9H_{11}NO_4$	Dopamine prodrug - CNS	Aliphatic amines, carboxylic acid
Dipyridamole	POM	15,171	$C_{24}H_{40}N_8O_4$	Platelet inhibitor - CV	Neutral organics
Simvastatin	P	14,596	$C_{25}H_{38}O_5$	Metabolism – lipid lowerer	Esters
Irbesartan	POM	14,529	$C_{25}H_{28}N_6O$	Angiotensin II receptor antagonists - CV	Neutral organics
Tranexamic acid	POM	14,468	$C_8H_{15}NO_2$	Antifibrogenic - CV	Aliphatic amines, carboxylicacid
Ciprofloxacin	POM	14,128	$C_{17}H_{18}FN_3O_3$	Antibiotic	Aliphatic amines, carboxylic acid
Venlafaxine	POM	14,025	$C_{17}H_{27}NO_2$	Antidepressant - CNS	Aliphatic amines
Levetiracetam	POM	13,361	$C_8H_{14}N_2O_2$	Antiepileptic	Neutral organics
Theophylline	P & GSL	12,532	$C_7H_8N_4O_2$	Smooth muscle relaxant - respiratory	Imides

Compound	GSL P POM	Amount used in 2004 Kg (active ingredient)	Molecular Formula	Pharmaceutical Product Group	Chemical Group
Guaifenesin	GSL	12,006	$C_{10}H_{14}O_4$	Expectorant	Neutral organics
Isosorbide Mononitrate	P	11,741	$C_6H_9NO_6$	Vasodilator	Neutral organics

GSL = General Sales List; P = Pharmacy; POM = Prescription Only Medicines (status in 2004)

3.1.2 Other High Usage Situations

The majority of the pharmaceuticals that have been considered during the course of this project are used year round with a few being used more frequently in some seasons (notably winter) than in others. However, there is one potential application of pharmaceuticals that could result in very large concentrations over a limited time period, and that is the use for pandemics and epidemics. As an indication of the possible concentrations that may arise, the anti-viral drug Tamiflu is considered below. Tamiflu was not on the list of the highest used pharmaceuticals in the UK in 2004.

A number of anti-viral pharmaceuticals have been developed to target influenza viruses and three are available in the UK, namely amantidine (Synmetrel, Lysovir), oseltamivir (Tamiflu), and zanamivir (Relenza). Tamiflu is proposed to be used as an anti-viral agent in the event of an outbreak of bird flu and a recent paper (Singer et al., 2007) has suggested that this use would result in very high concentrations (µg l^{-1}) for several weeks in UK waters.

The chemical structure of Tamiflu (oseltamivir) is shown in Figure 3.1.

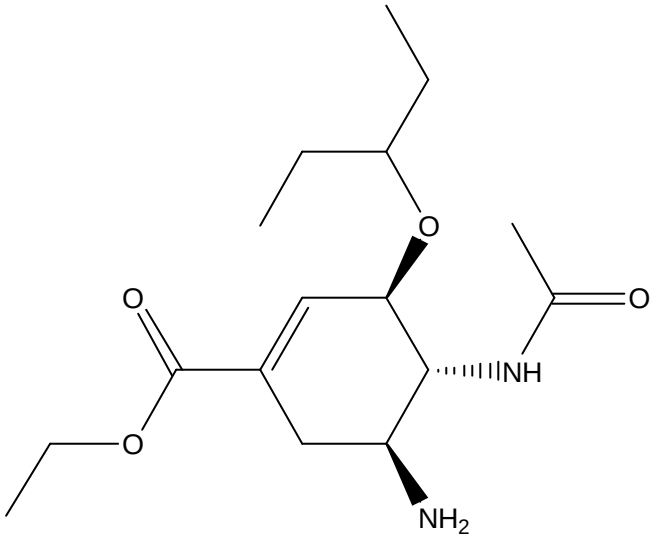


Figure 3.1 Oseltamivir

The compound is administered as the phosphate salt and is extensively metabolized in humans to the carboxylate anion [OC] which provides the anti-viral activity (Figure 3.2).

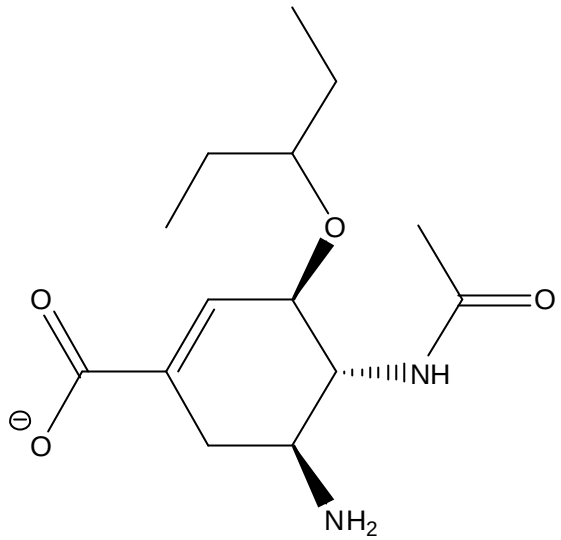


Figure 3.2 Carboxylate metabolite of oseltamivir (OC)

About 95% of the administered Tamiflu is excreted, with the majority of this (71% of dose) excreted as the carboxylate and the remainder as Tamiflu itself (RxList, 2007a; Johnson et al., 2007). The pKa of the carboxylic acid was estimated using the on-line version of SPARC [http://ibmlc2.chem.uga.edu/sparc/] to be 3.5, which means that at a typical environmental pH of = 6 the metabolite will exist almost exclusively as the carboxylate anion. The published experimental data for Tamiflu gives a log Kow of 1.1 and a water solubility of 588 $mg.l^{1}$ at 25 ^{o}C (American Hospital Formulary Service, 2006). Some fate and effect data are available and oseltamivir has been found to be not readily biodegradable in a carbon dioxide evolution test (EMEA, 2005a).

Little information is available regarding the properties of the carboxylate metabolite and EPIWIN v 3.20 was therefore used to generate the key environmental information for this chemical (Table 3.2).

Table 3.2 Key Physicochemical and Fate Parameters Estimated for Tamiflu Carboxylate

Parameter	Value
Octanol-water partition (Log Kow)	0.18
Water solubility ($mg.l^{1}$)	523.8
Biodegradability	Not readily biodegradable
Organic carbon partitioning (Log Koc)	1.54
Bioconcentration Factor (BCF)	3.2
Removal in Wastewater Treatment	<2%

These parameters suggest that the carboxylate will be predominantly present in the aqueous phase of wastewater after excretion (high water solubility, low Log Koc), will be persistent through conventional sewage treatment (not readily biodegradable, low predicted removal), but will not bioaccumulate (very low BCF).

Tamiflu is taken orally as capsules, each containing 75mg of oseltamivir, and a treatment for a fully grown, healthy adult consists of 10 capsules administered as a single capsule twice daily over 5 days (RxList, 2007b). The World Health Organisation has issued guidelines on the prophylactic use of oseltamivir to assist in

the control of an avian flu outbreak (WHO, 2006). Mass prophylaxis is an exceptional measure to be used in Phase 2 if the Phase 1 measures have been unsuccessful and WHO suggests two methods for this outbreak control:

1. mass prophylaxis of the affected population within a radius of 5-10km from each detected case, or

2. targeting administrative areas to cover the 'at risk' population (10000 – 50000). Each individual is given a single course of oseltamivir for a duration of 10 days.

In the event that more cases arise among the targeted population, a second round of prophylaxis is administered. Mass anti-viral prophylaxis ceases automatically ten days after the date of symptom onset in the last reported case. Examination of the data for numbers of tablets required suggests that the WHO recommended prophylaxis uses the administration of a single tablet each day for the 10 day period, as opposed to the normal treatment dose of 2 tablets per day for 5 days.

The modelling reported by Singer et al. (2007) gave the number of days that river water concentration would be above pre-defined amounts in four English rivers, the greatest amount being 50nM oseltamivir carboxykate (OC) (equivalent to 14.22 µg.l^{1}). The 50nM concentration would only be exceeded in the river Lee of the English rivers they modelled (Lee, Don, Mersey, Nene and Thames).

Modelling in this work was carried out using the drinking water scenarios adopted for the other pharmaceuticals, but simulating an outbreak prophylactic treatment situation in respect of the amounts used. The results obtained give peak concentrations that could be reached in drinking water assuming a worst case situation with no metabolism (this is fairly realistic for Tamiflu which is only partially metabolized), no removal in STW (again realistic for Tamiflu), 10%ile river flow and no removal in the DWTW (this is realistic unless the DWTW was using ozonation when there would be some removal). The results obtained show that in the worst case scenario, B, the maximum concentration reached with 90% of the population being treated continuously would be about 148 µg.l-1 which is about an order of magnitude higher than the Singer at al worst case (>14.22 µg.l^{1} for the river Lee). The results from the probabilistic modelling in the current study showed the highest mean estimated concentration (for scenario B) to be 107 µg.l^{1}, which is within an order of magnitude of the Singer et al value. .

3.2 Usage in the rest of Europe

3.2.1 Over-the-counter (OTC) and Prescribed Pharmaceuticals

Table 3.3 shows the annual prescribed consumption of several drugs for selected countries. This shows that there are significant differences in usage of pharmaceuticals across Europe that are not solely related to population numbers. These differences are probably most influenced by differences in prescription practices rather than differences in disease patterns. For example, in Austria the non-steroidal anti-inflammatory drug, diclofenac is prescribed in similar quantities to

ibuprofen, but in all of the other countries in this Table (and in the UK) significantly greater quantities of ibuprofen than diclofenac. are prescribed.

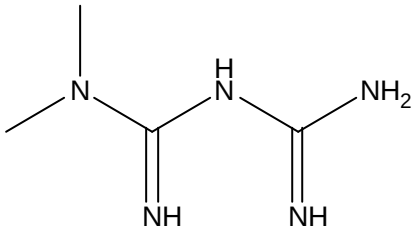
Table 3.3 Annual prescribed consumption in kg a^{-1} per million people for various countries (modified from Alder et al., 2006)

	Austria	France	Finland	Germany	Poland	Switzerland	Spain	Sweden
	1997	1998	1999	2001	2000	2000	2003	2005
Compound	Population (m)							
	8	58.5	5.2	82.4	38.6	7.3	40.3	9
Bezafibrate	550	590	115	316	23	216	n.a.	67
Carbamazepine	804	602	1019	947	1130	557	496	820
Diazepam	16	7	38	5	14	5	22	20
Diclofenac	832	255	154	595	570	532	801	376
Ibuprofen	825	2,841	11610	1,553	1600	2,153	6,851	7864
Iopromide	788	126	n.a.	1,578	276	1,507	n.a.	n.a.
Roxithromycin	48	159	77	75	56	20	7	2
Sulfamethoxazole	104	383	n.a.	570	874	352	315	160

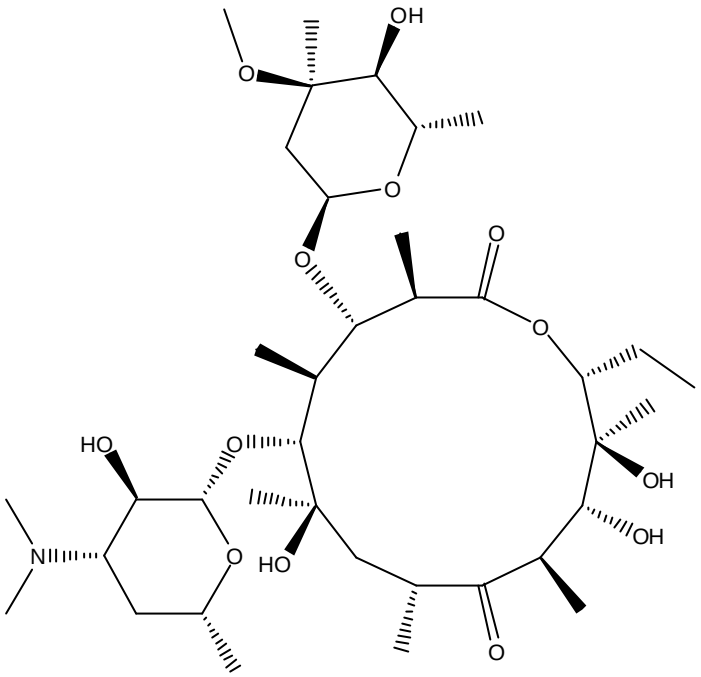
n.a data are not available

3.3 Structures of the UK High Usage Pharmaceuticals

The pharmaceuticals in major use in the UK have a wide range of structures and this can be exemplified by considering the smallest (metformin) and the largest (erythromycin) in the high usage list (Table 3.1). The structures of these compounds are shown below:

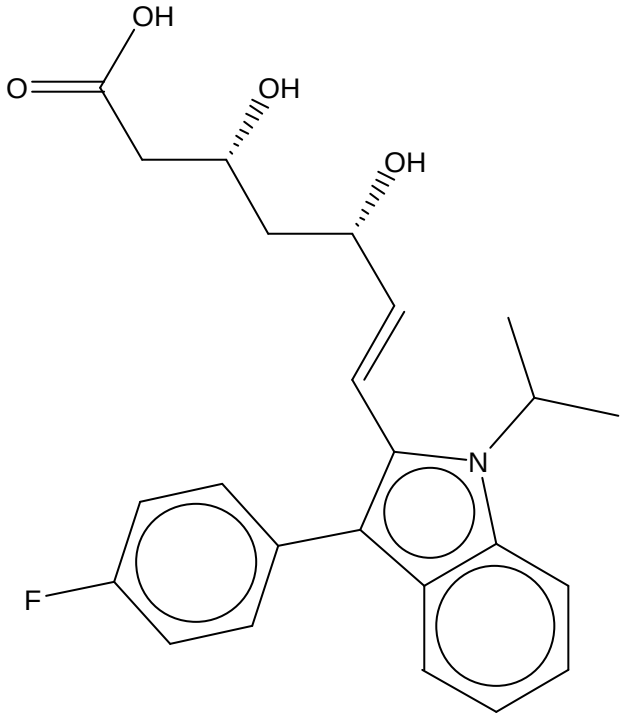


Metformin, $C_4H_{11}N_5$, is a small molecule with an unusual structure with five nitrogen atoms, three of which are amines and two of which are guanidines.

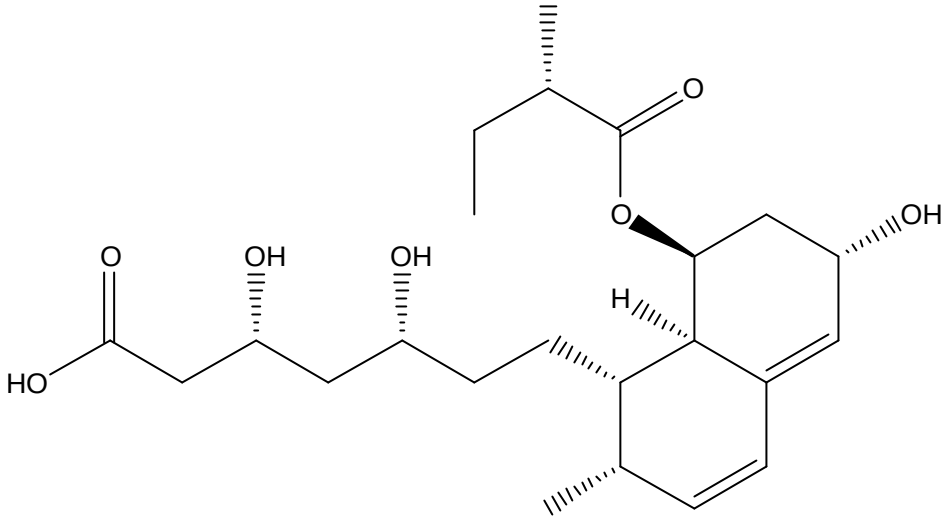


Erythromycin, $C_{37}H_{67}NO_{13}$, is a large molecule with two six-membered rings and one macrocycle and it also has 5 hydroxyl groups, 5 ether groups, one ketone group and an amine group. This is a very complex molecule and it is difficult to predict its fate and behaviour in the environment and in STW and DWTW processes.

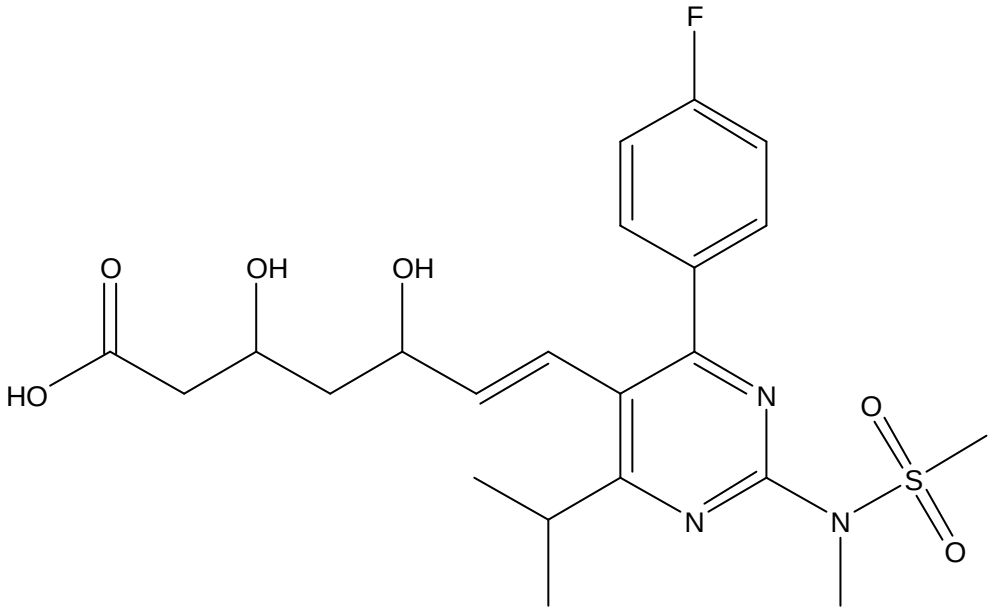
Even for chemicals with the same therapeutic mode of action, the structures can be quite different, as is shown by the following statins:



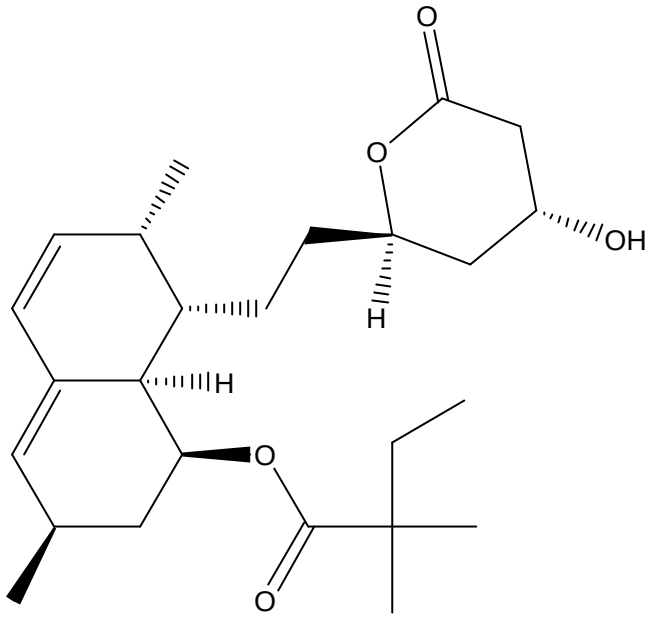
Fluvastatin



Pravastatin

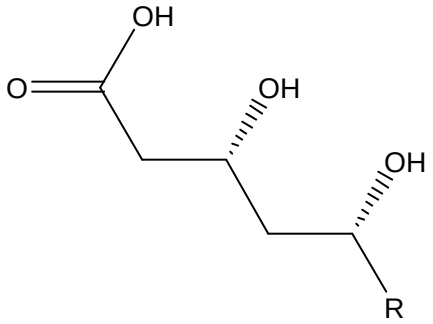


Rosuvastatin



Simvastatin

It is clear that three of these statins have a similar structural feature, namely the following group:



However the other parts of these molecules are very different in structure and the fourth, simvastatin, appears to have little in common structurally with the other three. Two of the statins, rosuvastatin and fluvastatin have a fluorine substituted benzene ring, but the other two do not even have an aromatic ring.

This illustrates the diversity in structure of pharmaceuticals even for those with a similar mode of action and shows that it is very difficult to group them into similar structures that will behave similarly in STW and DWTW processes unless some experimental data are available.

4 Occurrence and Behaviour of Pharmaceuticals in the Aquatic Environment

This section of the report concentrates on the major used substances in the UK, but brings in additional information where this helps to explain the likely behaviour of different types of pharmaceuticals.

4.1 Sources and Routes of Pharmaceuticals to the Environment

Pharmaceuticals are continually released into the environment as a result of

- their manufacture (amounts discharged are controlled and should be small in the UK);
- use (via excretion in urine and faeces, together with metabolites); and
- disposal of unused, unwanted or 'out-of-date' drugs (via the sewer or possibly from historical bulk disposal via landfill leachate).

The amount of pharmaceuticals introduced into the environment is a function of the quantity of drugs manufactured, the dosage frequency and amount, the metabolism excretion efficiency of the parent compound and metabolites, propensity of the drug to sorb to solids, and the biological transformation capability of subsequent sewage treatment (or landfill) microorganisms.

Additionally, consumption patterns may change depending on the season (Castiglioni et al., 2006). McArdell et al. (2003) found that during the winter season loads of macrolide antibiotics in STWs were twice as high as in the summer months. Seasonal differences are due to either the elimination of pharmaceuticals in STWs and/or during transport through the sewage system being less efficient in winter due to lower biological activity, or because the input in winter is higher. Monthly sales data showed that the sales of macrolide antibiotics are twice as high in January/February as in summer because they are mainly used to cure infections of the respiratory tract which are more prevalent in the colder, wetter winter months.

In order to understand and estimate the amounts of pharmaceuticals that may pass through the aquatic environment, an understanding of sources and routes to the environment is required. Figure 4.1 shows the three primary routes by which human-use pharmaceuticals enter into wastewaters and the aquatic environment. This is further broken down in Figure 4.2, which illustrates more specifically the detailed 'domestic' use pathways.

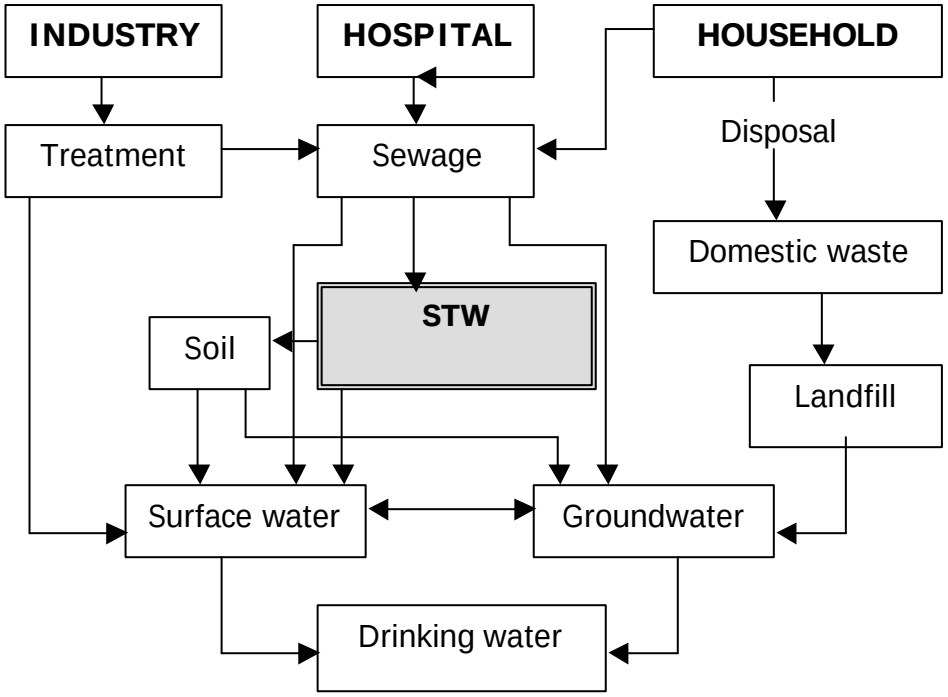


Figure 4.1 Overview of exposure routes of human-use pharmaceuticals into wastewaters and the aquatic environment (taken from Alder et al., 2006)

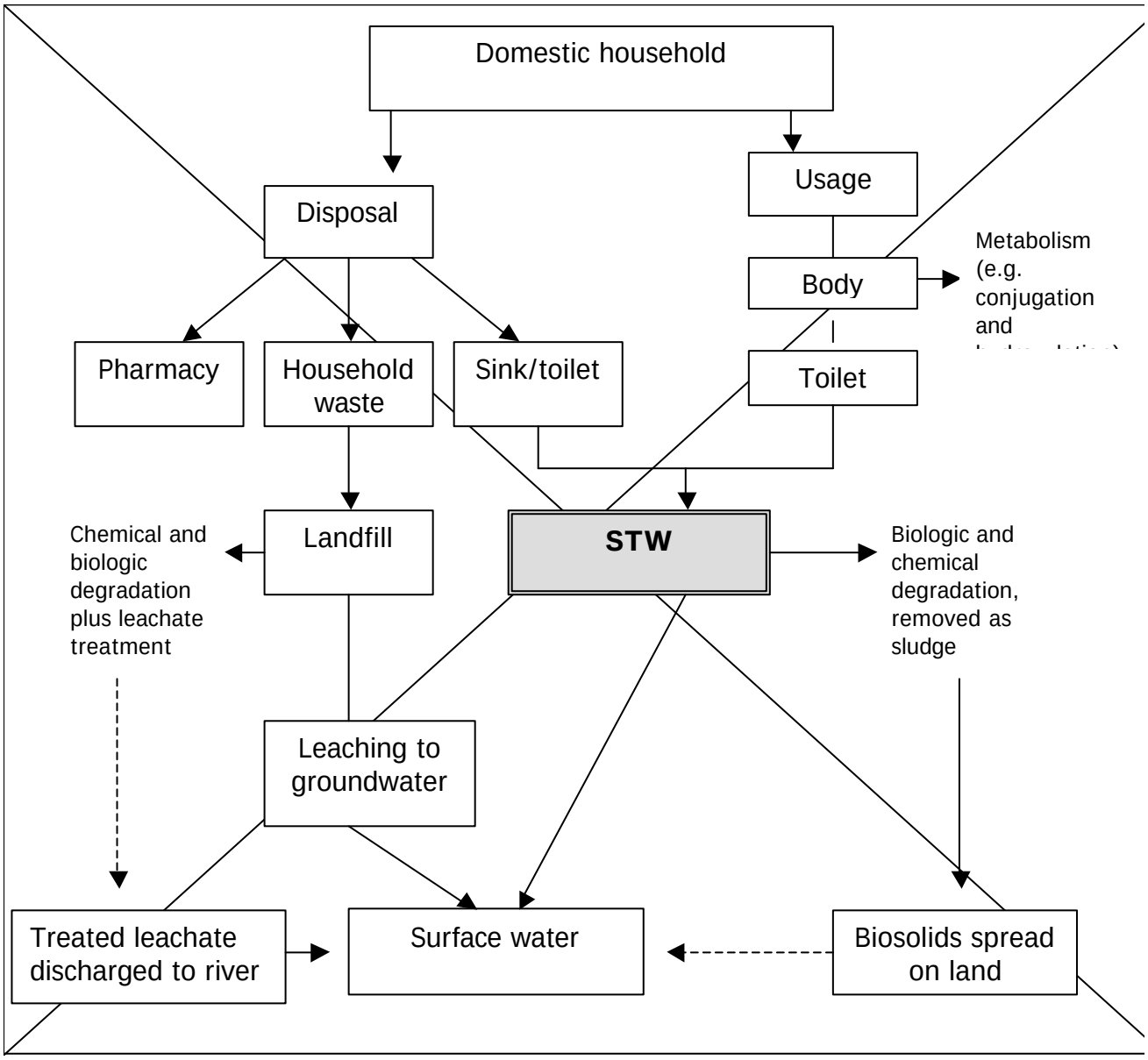


Figure 4.2 Overview of exposure routes of human-use pharmaceuticals from domestic households into the environment (taken from Bound and Voulvoulis, 2005)

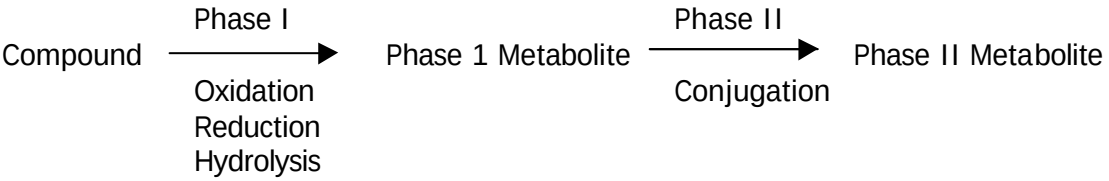
4.1.1 Manufacture

While manufacture of pharmaceuticals does not form a major part of this review, it is useful to consider potential inputs from this source. Input into the environment can occur at the manufacturing plant where small quantities of pharmaceuticals may be present in solid waste or in wastewater effluent. Pharmaceuticals disposed with solid waste by incineration can be assumed to be destroyed, due to chemical oxidation during the burning process. Waste disposal in landfills may lead to reappearance of active pharmaceutical ingredients in the aquifer via landfill leachate or in water drained from the landfill. Effluents are invariably treated in industrial or municipal wastewater treatment plants. However, disposal of waste from the manufacture of

pharmaceuticals is tightly regulated in the UK and is therefore unlikely, under normal circumstances, to be a significant contributor to the concentration of these compounds in the environment. However, there may be some historical disposal of waste that can eventually break through in leachate.

4.1.2 Metabolism and Excretion

The amounts of human pharmaceuticals reaching the environment are influenced to a large extent by their metabolism and excretion in humans. The vast majority of drugs will enter the body and will ultimately be excreted in urine or faeces either unaltered or as metabolites that may or may not closely resemble the parent compound (Mückter, 2006). The phases of metabolism can be considered as follows:



Phase 1 reactions involve the formation of new or modified functional groups which usually have increased polarity compared to the starting compound. In phase II, the metabolites are conjugated with endogenous molecules to increase their water solubility. The most important conjugation for xenobiotics is glucuronidation.

Table 4.1 shows different urinary excretion rates for a number of commonly used pharmaceuticals. Since many pharmaceuticals are excreted as metabolites, compound fate studies need to include consideration of the principal metabolites. Ester conjugates formed with glucuronic acid or sulphate as part of drug metabolic pathways are likely to be cleaved during sewage treatment to yield the non-conjugated (free) pharmaceuticals, and this process may increase the environmental concentrations of the original compounds.

Table 4.1 Urinary excretion rates of unchanged active ingredient for selected pharmaceuticals.

Compound	Pharmaceutical Product Group	Parent Compound Excreted (%)	Reference
Amoxycillin	Antibiotic	60	Bound & Voulvoulis, 2005
Atenolol	Beta-blocker	90	Bound & Voulvoulis, 2005
Bezafibrate	Lipid regulator	50	Bound & Voulvoulis, 2005
Carbamazepine	Antiepileptic	3	Bound & Voulvoulis, 2005
Cetirizine	Antihistamine	50	Bound & Voulvoulis, 2005
Clofibric acid	Active metabolite[3]	6	Alder et al., 2006
Diclofenac	Anti-inflammatory	15	Alder et al., 2006
Erythromycin	Antibiotic	25	Bound & Voulvoulis, 2005
Felbamate	Antiepileptic	40-50	Bound & Voulvoulis, 2005
Ibuprofen	Analgesic	10	Bound & Voulvoulis, 2005

[3] Clofibric acid is the active metabolite of the blood lipid regulators clofibrate, etofibrate, etofyllinclofibrate.

Compound	Pharmaceutical Product Group	Parent Compound Excreted (%)	Reference
Indometacin	Anti-inflammatory	10-20	Alder et al., 2006
Metoprolol	Beta-blocker	10	Bound & Voulvoulis, 2005
Paracetamol	Painkiller	4	Bound & Voulvoulis, 2005
Propranolol	Beta-blocker	<1	Alder et al., 2006
Sulfamethoxazole	Antibiotic	15	Bound & Voulvoulis, 2005

The available metabolic data does not always differentiate between faecal and urinary metabolites, but the bulk of metabolites are water soluble and excreted via urine, as metabolism acts as a detoxification mechanism. Unchanged pharmaceuticals that are sufficiently water soluble will also be primarily excreted in urine and only the less soluble pharmaceuticals are likely to be excreted in faeces. However, partitioning will also occur during transport in sewers and in sewage treatment works that will lead to some transfer from the aqueous phase to the sewage sludge solids and this will be driven primarily by water solubility.

4.1.3 Disposal of unused, unwanted or 'out-of-date' pharmaceuticals

Most pharmaceutical companies and pharmacists operate a returns scheme for unwanted/unused pharmaceuticals and these are disposed of by incineration. However, there is evidence that large quantities of prescription and 'over-the-counter' drugs that are never consumed are eventually disposed down toilets or via domestic refuse (Daughton and Ternes, 1999). A recent survey carried out in southeast England suggests that two-thirds of people dispose of unwanted pharmaceuticals in household waste, with the remainder either returning them to the pharmacist (22%) or emptying them into the sink or toilet (12%) (Bound and Voulvoulis, 2005). The data showed that consumption and disposal strategy varies with respect to drug type. For example, approximately 80% of respondents said they consumed all painkillers, whether bought over the counter or prescribed, whereas the corresponding percentage for antibiotics was only 18%. The latter result is surprising when general practitioners stress that patients should always consume the entire course of a treatment of antibiotics. In order to allow for this in the modelling the worst case scenario assumed there was no metabolism of the pharmaceuticals in humans - this is equivalent to the entire amount of the drug being disposed to sewer.

4.1.4 Input from Sewage Treatment Works (STWs)

The major source of pharmaceuticals to the environment is via STW effluent (Daughton and Ternes, 1999). Sewage Treatment Works use a wide range of processes, e.g. primary screening, biological filtration, anaerobic digestion and, while these are not specifically designed to remove pharmaceuticals, they may effect some removal. For example, both biodegradation of some pharmaceuticals (which may occur in aerobic and anaerobic biological treatment processes) and sorption of hydrophobic pharmaceuticals to sewage sludge may reduce concentrations present in the treated STW effluent. Sorption occurs by partitioning between the water and solids phases and depends in part on the degree of polarity of the particular compound. Sludge biosolid material has a high organic content and is a likely sink for

less polar or non-polar substances, whereas polar substances are expected to remain primarily in the aqueous phase. Some pharmaceuticals will be excreted as conjugates that will be broken down in sewage treatment to release the less soluble parent compound. Some pharmaceuticals are not susceptible to biodegradation and are hydrophilic, so the elimination of pharmaceuticals in municipal STWs is often incomplete. In addition, substances with low solubility can bypass STWs due to colloid-facilitated transport during periods of high effluent turbidity. Overflow due to technical problems, floods or high influent loads may also cause substances with low solubility to shortcut or completely bypass the STWs (Bendz et al., 2005).

Pharmaceuticals that are removed from wastewater by adsorption onto sludge solids may enter the aquatic environment, in particular groundwaters, via sewage sludge application to (agricultural) land, land filling, or soil erosion (Jones et al, 2005) although there are few actual data to support this contention.

4.1.4.1 Removal by Sorption onto sludge

As mentioned above, sorption onto particulate biosolids in sewage sludge can be an important removal mechanism in municipal wastewater treatment, depending on the tendency of micropollutants to partition onto the primary and secondary sludge. This is likely to be a particularly important process for pharmaceuticals that have low water solubility and lipophilic properties since the sewage sludge is comprised primarily of biosolids, which have a very high organic content.

The concentration of a substance sorbed per litre of wastewater (C_{sorbed}) can be expressed as a simplified linear equation:

$$C_{sorbed} = K_d \times SS \times C_{dissolved}$$

where K_d is the sorption constant, defined as the partition coefficient of a compound between sludge and the water phase; SS is the concentration of suspended solids in the raw wastewater; and $C_{dissolved}$ is the dissolved concentration of the substance (Ternes et al., 2004a).

Sorption behaviour can be estimated using the sorption coefficient (K_d), which depends mainly on characteristics of the compound but is also influenced by the nature of the sludge. Ternes et al. (2005) found no correlation of the observed K_d values for a number of pharmaceuticals with the literature values for octanol water partitioning, K_{ow}, or partitioning to soil organic carbon, K_{oc}. Although there are a number of relationships that have been established between Kd and Kow, they are compound type specific. Electrostatic interactions are also relevant for sorption of polar pharmaceuticals onto activated sludge. Additionally, for compounds containing functional groups which can be protonated and de-protonated, the pH of the sludge may play a crucial role (Ternes et al., 2004). Experimentation has shown that for compounds with K_d values = 300 l kg SS^{-1} removal by sorption in a municipal STW is negligible (Joss et al., 2005). Ternes et al., (2004) put the figure for negligible sorption to sewage solids at K_d values < 500 l kg SS^{-1}.

4.1.4.2 Removal by Stripping

The amount of a compound being stripped from the water phase into the gas phase during aeration depends on the amount of air in contact with the wastewater (the

latter depending on type of aeration) and the liquid-gas partitioning coefficient – the Henry's Law coefficient in the case of air-water partitioning. This is unlikely to be a very important removal process for pharmaceuticals as they tend to have high water solubility to vapour pressure ratios.

4.1.4.3 Removal by Biological degradation

Biological degradation, either aerobic or anaerobic, by micro-organisms results in a reduction of the parent pharmaceuticals and/or their metabolites during wastewater treatment. Some biodegradation may also occur during in-pipe transport to the sewage treatment plant, but most will probably occur in the secondary stage of treatment when the compound is exposed to large concentrations of micro-organisms. Molecules with long, highly branched side chains are generally less amenable to biodegradation than unbranched compounds with shorter side chains. Unsaturated aliphatic compounds are generally more accessible to biodegradation than saturated analogues or aromatic compounds with complicated aromatic ring structures and sulphate or halogen substituent groups. Examples of the latter are the X-ray contrast media which have been shown to be resistant to biodegradation.

By weight, X-ray contrast media are one of the most intensively used compounds in hospitals. These are all iodinated compounds that are derivatives of 2,4,6-triiodobenzoic acid (Haiss and Kümmerer, 2006). Some are ionic in character, i.e. have a free carboxylic group such as diatrizoate, others are ester derivatives and, as such, are neutral compounds, e.g. iopromide. The occurrence of four iodinated compounds (diatrizoate, iopamidol, iopromide and iomeprol) in eight German STWs was examined by Ternes et al. (2000). They found that these compounds were not significantly degraded or absorbed during sewage treatment processes and so remained in the aqueous phase. The concentrations of diatrizoate, iopromide and iomeprol frequently exceeded 1 µg l^{1} in the raw sewage influent, and were found at comparable concentrations in the final effluents, with the maximum concentration measured being 15 µg l^{1} for iopamidol.

Sludge age has been shown to be a crucial parameter influencing pharmaceutical removal. Biochemical versatility of activated sludge was shown to increase with sludge age; in a nutrient-removing process (sludge age 10-15 d) the majority of the compounds were at least partly biologically transformed or degraded whereas in COD-removing processes (sludge age = 4 d) almost no biological degradation of pharmaceuticals was observed (Clara et al., 2005). The time required for degradation was compound specific. For example, bezafibrate, sulfamethoxazole, ibuprofen and acetylsalicylic acid required a sludge age of 2 – 5 d for significant degradation; diclofenac, iopromide and roxithromycin needed 5 –15 d and carbamazepine and diazepam remained un-degraded even at a sludge age > 20 d (Ternes et al., 2004a).

4.1.4.4 Advanced treatment

Traditional STW processes have been shown to be ineffective in removing certain pharmaceuticals and highly effective at removing others (see Tables 4.5 and 4.6). More advanced technologies such as ozonation, other oxidation processes or membranes, including membrane filtration and membrane bioreactors, may therefore be necessary if a reduction in the concentration of the widest possible range of pharmaceuticals in effluent discharges is required. However it should be remembered

that at present, none of these advanced methods are in routine use in STW in the UK.

4.1.4.4.1 Ozone

Ozone is a widely used oxidant in drinking water for disinfection and oxidation (e.g. taste and odour control, decolouration, and micropollutant elimination) but is not used routinely for treatment of STW effluent (see Section 4.3.4 for a more detailed discussion). Ozone-based oxidation processes have a high potential for the elimination of many pharmaceuticals. Ternes et al. (2003) showed that for biologically treated wastewater with <8 mg DOC.l^{-1} (DOC = dissolved organic carbon) an ozone dose of 2 – 5 mg l^{-1} and with ~ 23 mg DOC.l^{-1} an ozone dose of 5 – 10 mg.l^{-1} is sufficient for removing most pharmaceuticals by 90 – 99%, the prime exception being iodinated contrast media.

4.1.4.4.2 Other advanced oxidation processes (AOP)

Processes aiming at the formation of highly reactive **?**OH radicals are generally referred to as advanced oxidation processes. The combination of O_3/H_2O_2, UV/H_2O_2 or Fe^{2+}/H_2O_2 (Fenton's reagent – a solution of hydrogen peroxide and an iron catalyst) are most used in AOP for **?**OH formation. **?**OH radicals react unselectively and therefore the efficiency of the reaction is affected by non-target compounds contained within the matrix. The combination of UV and hydrogen peroxide is expected to yield comparable results to O_3/H_2O_2 and the cost competitiveness of the two alternatives is likely to be the determinate of its application (Joss et al., 2006). Fenton's reagent has low efficiency of **?**OH radical formation under neutral pH and is not considered practical as an application in municipal wastewater treatment for the removal of pharmaceuticals (Joss et al., 2006).

Chlorination of wastewater was quite widely practised in the US, but is little used at STWs in the UK, although it is not generally regarded as an advanced oxidation process. Bedner and MacCrehan (2006) demonstrated the potential for the common analgesic paracetamol to form degradation products during wastewater chlorination that are more toxic than the parent compound, i.e. 1,4-benzoquinone and N-acetyl-p-benzoquinone imine. The latter compound is the toxicant associated with lethality in paracetamol overdoses.

4.1.4.4.3 Tight membrane filtration

Nanofiltration and reverse osmosis are membrane filtration processes allowing micropollutant retention by molecular sieving. It is expected that these processes will not be cost competitive with ozonation for removal of pharmaceuticals (Joss et al., 2006). Reverse osmosis is used increasingly in DWTW and is discussed more fully in Section 4.3.6.

4.1.4.4.4 Activated carbon

The efficiency and effectiveness of pharmaceutical removal using activated carbon has been shown for drinking water treatment and is discussed in Section 4.3.3. However, no data could be found in respect of its use for removal of pharmaceuticals from STW effluent.

4.1.5 Hospital wastewater

Hospital wastewater is a significant source of pharmaceuticals, especially antibiotics, anti-cancer agents, and iodinated contrast media containing individual pharmaceuticals at higher concentrations than household effluents due to the lower dilution in the wastewater (Alder et al., 2006). Most hospital sewers are directly connected to the municipal sewer system and no additional treatment is performed prior to disposal to public sewer. Several pharmaceuticals have been detected in hospital wastewater (Kümmerer, 2001; Gómez et al., 2006). Hartmann et al. (1998) measured ciprofloxacin concentrations in the range of 3 to 87 µg l^{-1} in hospital effluent.

Heberer and Feldman (2005) looked at two drugs commonly used both in hospitals and more generally, namely diclofenac and carbamazepine. Their finding, for usage in Berlin, Germany, was that only approximately 10% and 15% respectively was contributed by hospital effluent into STWs.

Table 4.2 Pharmaceutical residues found in hospital effluent wastewaters (n = 6) (Gómez et al., 2006).

Compound	Pharmaceutical Product Group	Concentration range (mean) µg l^{-1}
Acetaminophen	Analgesic	0.5 – 29 (16.02)
Atenolol	Beta-blocker	0.1 – 122 (3.4)
Carbamazepine	Antiepliletic	0.03 – 0.07 (0.04)
Codeine	Analgesic	0.01 – 5.7 (0.9)
Diclofenac	Anti-inflammatory	0.06 – 1.9 (1.4)
Erthromycin	Antibiotic	0.01 – 0.03 (0.019)
Ibuprofen	Analgesic	1.5 – 151 (19.77)
Ketoroloc	Anti-inflammatory	0.5 – 59.5 (4.2)
Metronidazole	Antibiotic	1.8 – 9.4 (5.9)
Propranolol	Beta-blocker	0.2 – 6.5 (1.35)
Ranitidine	H2 antagonist	0.4 – 1.7 (0.98)
Trimethoprim	Antibiotic	0.01 – 0.03 (0.025)

4.1.6 Loss of wastewater in the sewer system

4.1.6.1 Combined sewer overflow

Combined sewer overflow (CSO) is the discharge, during heavy rainfall, of untreated wastewater from a sewer system that carries both sewage and storm water. The increased flow caused by the storm water runoff exceeds the sewerage system's capacity and the sewage is forced to overflow into streams and rivers in the surrounding area through CSO outfalls. For example, London's 140-year-old sewage system is often unable to cope with the combined flow from the city's sewage and storm water system. Of the 57 combined sewer overflows in London, 36 are considered 'unsatisfactory' in terms of frequency of discharge and/or environmental impact. Even during periods of moderate rainfall, the overflows discharge storm water and sewage into the River Thames on average once a week. An average of 20

million cubic metres of untreated sewage is discharged into the Thames every year (http://www.thamesweb.com/page.php?page_id=76&topic_id=2).

The combined sewer system can be equipped with storage tanks where the first highly polluted flush of combined sewage is temporarily stored for subsequent pumping back to the sewer for mechanical and biological treatment. Alternatively excess flow may be directed to sedimentation tanks where the sewage, after partial separation of settable solids, is discharged to the receiving water. While this route may result in higher inputs of pharmaceuticals as the STW processes are by-passed, it is a transient situation and the overall proportion of sewage that reaches surface water by this route is probably small (Joss et al., 2006). During storm water events rivers also have an increased flow that will dilute pharmaceutical concentrations and therefore the effect of this route on the concentrations of pharmaceuticals in surface waters is not thought to be significant.

High input situations may also occur as a consequence of very high rainfall and flooding leading to the by-pass of the normal sewer and STW and direct input of untreated sewage effluent to rivers. While these extreme events are likely to be rare, their incidence is predicted to increase as a consequence of climate change. Since such events are accompanied by very high flows, the loss of STW removal processes will almost certainly be more than compensated for by the much higher than usual dilution.

4.1.6.2 Sewer exfiltration

Sewer exfiltration as a route for pharmaceuticals into the environment has been suggested to be potentially significant (Joss et al., 2006). Leakages from house connection pipes and public sewer systems directly into the subsoil could ultimately contaminate groundwater supplies. The amount of leaking sewage is controlled by the size and geometry of the leak, the water level in the pipe, the chemical composition of the sewage and the existence and condition of a colmation layer. Outside of the pipe, the surrounding material and the seepage distance from the pipe to the groundwater is important in regard to degradation and chemical reactions (Held et al., 2004).

Since sewer pipe connections to private property are generally in a worse condition than the maintained public sewer system, the total loss by sewer exfiltration is expected to be significantly higher (Joss et al., 2006). In an assessment of the sewer-groundwater interactions in a medium sized city, Rastatt, in Germany a number of potential marker substances were analysed including several pharmaceutical residues. However, none were detected in the groundwater samples analysed, although significant loads were present in wastewater. On the other hand, the iodated x-ray contrast media amidotrizoic acid (66 ng l^{1}) and iothalamic acid (72 ng l^{-1}) were measured, suggesting a possible 5 – 12% of wastewater in the groundwater (Wolf et al., 2003).

A number of studies have identified evidence for groundwater contamination as a result of sewer leakage on a citywide scale in the UK, with an estimated loss of 5% reported for the Greater London Region (Ellis, 2001). Exfiltration rates are difficult to measure accurately and discussion on this subject is often based on anecdotal evidence. Studies carried out in other countries have estimated losses between 5 –

20% lending weight to an average potential exfiltration rate of 3- 5% for pre-1960 sewer pipes (Ellis et al., 2004).

Since this source results in a very diffuse input to the environment, the contribution to the concentration of pharmaceutical concentrations in UK waters is difficult to estimate but is unlikely to be significant except perhaps in some very localised situations.

4.1.7 Leachate from Landfill

Leachate contamination of the groundwater environment is less likely from modern landfills as a consequence of engineered barriers and leachate collection. Seepage water from landfill is often treated by biological or chemical wastewater treatment processes but leachate can also infiltrate the groundwater due to poor or degraded bottom sealing. Schwarzbauer et al. (2002) analyzed a wide array of organic compounds in groundwater-contaminating seepage water of a waste deposit landfill in Germany where a leak in the bottom sealing had been identified. Three pharmaceutical compounds were identified: propyphenazone, a widely used analgesic and antipyretic, at concentrations of 110 – 140 µg l^{-1}, ibuprofen, and clofibric acid, which is an environmental metabolite of the corresponding ethyl ester used as a blood lipid regulator.

4.1.8 Sewage Sludge Disposal

The main disposal routes for sludge are to agricultural land, incineration or sanitary landfill. In the UK approximately 45-50% of sludge is spread on land. Estimated annual sewage sludge production in the UK was 1,583,000 tonnes dry solids (Schowanek et al., 2004). The estimated sewage sludge arisings for 2005, for England and Wales, was 1,369,000 tonnes with the following disposal routes (Defra, 2006).:

- farmland 995,000
- landfill 7,000
- incineration 243,000
- land reclamation/restoration 80,000, and
- other 40,000 tonnes

Sewage sludge is a by-product of the wastewater treatment process and is a combination of organic and inorganic solids from the sewage as well as the biomass formed during aerobic, anoxic, or anaerobic degradation processes. Depending on the type and extent of sludge treatment, organic materials will constitute 40-80% by dry weight, of the mass. Live and dead micro-organisms constitute a large proportion of the organic material and provide a large surface area for sorption of lipophilic organic contaminants in the sludge. In many cases some form of post-treatment is applied to the sewage sludge. This can use a combination of thickening, anaerobic digestion, composting, lime stabilization, disinfection, dewatering and/or thermal drying and can have a significant impact on residual contaminant levels (Schowanek et al., 2004).

In most EU countries the maximum allowable sludge addition rate is around 5 tonnes dry matter/ha year. In practice, however, quantities on crop land usually do not exceed 2-3 tonnes/ha year as they are limited by the restrictions on nutrient addition rates. The potential exposure of sludge on the soil surface is usually short as it is a

general requirement to cultivate within 1-2 days to avoid potential problems of odour, pest attraction and surface run-off. In addition, much sludge is incorporated sub-surface using specialised equipment. Of the many pathways for pharmaceuticals to reach the environment via the spreading of sewage sludge the two pertinent to this review are:

- Sludge→ soil→ surface runoff→ surface water→ human, and
- Sludge→ soil vadose zone→ groundwater→ human.

Water-soluble compounds or metabolites could potentially leach to groundwater but this is unlikely to occur for lipophilic organic chemicals with a high affinity for organic matter or for positively charged compounds with affinity for clay minerals. Run-off to surface water occurs during heavy rainfall. The chemicals can be in a dissolved state but are more usually bound to soil particles and other suspended matter. However, significant run-off events will normally coincide with high discharge in the receiving waters leading to a high degree of dilution.

Göbel et al. (2005) measured five sulphonamide or macrolide anitmicrobials together with trimethoprim (used almost exclusively in combination with sulphonamides) in samples of activated sludge taken from STWs in Germany and Switzerland. The amounts measured varied depending on analytical method and STW. Higher concentrations were generally determined in German activated sludge samples indicating a lower wastewater dilution compared to Switzerland. The ranges of measured concentrations are shown in Table 4.3.

Table 4.3 Range of concentrations of sulfonamides, macrolides and trimethoprim in activated sludge from three different STW plants in German and Switzerland (Göbel et al., 2005)

	Concentration (µg kg^{-1} dw)					
	SPY	**SMX**	**TMP**	**AZI**	**CLA**	**ROX**
Germany	26 – 197	18 – 113	79 – 133	47 – 158	16 – 41	45 – 131
Switzerland	nd – 29	20 – 73	nd – 30	5* - 56	12 – 63	nd

SPY - sulfapyridin; SMX – sulfamethoxazole; TMP – trimethoprim; AZI – azithromycin; CLA – clarithromycin; ROX – roxithromycin; nd – not detected; *estimated concentration <LOQ.

Kinney et al. (2006) determined the presence of organic wastewater contaminants in nine different sludge products produced by STWs in seven different states in the USA. Despite the variety of STW processes found at each site the total number of organic contaminants present in the biosolids was fairly uniform, with some seasonal variation evident with respect to pharmaceutical contaminants. In total 19 different pharmaceuticals were detected in the sludge samples, representing a range of physical chemical properties, including compounds with low log K_{ow} and high water solubility values, such as acetaminophen and caffeine. The presence of compounds in the sludge that have such a wide range of physicochemical properties suggests that multiple mechanisms are operating and that other factors such as total volume of influent, biosolid/liquid ratios and sludge retention time, for example, are influencing final concentrations found in the end product. Biosolid product I, a wet-cake biosolid, had the fewest organic wastewater contaminants detected; a granular, kiln-dried biosolid, biosolid A, had the greatest number of detections. Carbon-

normalised concentrations of each biosolid were compared to the respective log Kow for a number of the wastewater contaminants, but only four of the nine biosolids were significantly ($p = 0.05$) correlated, suggesting that organic carbon content is not the only factor influencing organic contaminant concentrations in biosolids. Table 4.4 provides a summary of the measured concentrations for each pharmaceutical, by sludge sample.

4.1.9. High inputs from pandemic and epidemic situations

High levels of input may also arise when pharmaceuticals are used in pandemic and/or epidemic situations to treat or prevent the spread of diseases such as influenza (Singer et al., 2007). This has been exemplified in detail in section 3.1.2 by the consideration of the potential use of Tamiflu in the UK.

Table 4.4 Summary of detected concentrations for pharmaceuticals measured in nine sludge samples, in µg kg^{-1} dry weight (Kinney et al., 2006)

Compound	Sludge A		Sludge B		Sludge C		Sludge D	Sludge E	Sludge F		Sludge G		Sludge H		Sludge I
	13/5/03	17/11/03	14/5/03	17/11/03	8/8/03	12/11/03	6/11/03	14/5/04	12/9/03	24/11/03	2/6/03	26/1/04	2/6/03	26/1/04	21/4/05
Acetaminophen	200(13)	1400(58)	170(36)	71(11)	28(24)	23(28)	67(5)	75(13)	33(14)	ND	230(34)	130(40)	70(32)	ND	ND
Albuterol	30(22)	850(28)	ND	380(11)	ND	45(18)	51(10)	ND	ND	ND	ND	ND	ND	ND	ND
Carbamazepine	40(29)	33(44)	12(38)	17(17)	9(21)	11(45)	8(16)	19(21)	17(10)	29(7)	21(15)	13(24)	26(3)	44(44)	390(51)
Dehydronifedipine	26(17)	21(45)	ND	26(71)	ND	ND	ND	ND	ND	ND	3(43)	ND	21(15)	ND	ND
Diltiazem	59(34)	49(57)	10(39)	ND	3(29)	ND	ND	ND	ND	ND	ND	ND	ND	6(35)	ND
Erythromycin	ND	ND	ND	41(32)	2(6)	5(2)	26(12)	ND	8(16)	ND	ND	ND	ND	ND	ND
Fluoxetine	32(34)	15(67)	25(33)	19(13)	7(19)	2(19)	5(17)	30(4)	29(5)	38(11)	68(8)	ND	65(16)	25(18)	1500(68)
Gemfibrozil	ND	ND	420(27)	330(19)	120(8)	140(3)	ND	ND	170(11)	ND	ND	ND	ND	ND	ND
Sulfamethoxazole	160(31)	150(36)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Trimethoprim	22(27)	18(35)	ND	ND	2(31)	ND	0.7(8)	ND	ND	ND	ND	3(9)	ND	ND	ND
Cimetidine	14(17)	ND	ND	13(17)	ND	ND	ND	ND	ND	ND	50(18)	53(47)	71(34)	ND	ND
Codeine	22(23)	ND	3(93)	8(17)	ND	ND	ND	ND	5(8)	ND	ND	8(34)	ND	ND	ND
Diphenhydramine	170(19)	190(10)	92(27)	89(8)	23(12)	32(18)	53(8)	15(17)	230(6)	330(21)	230(7)	180(38)	250(12)	250(32)	7000(48)
Miconazole	360(31)	160(10	70(62)	100(56)	14(37)	33(52)	57(6)	92(28)	85(10)	460(20)	340(9)	200(46)	320(14)	330(30)	ND

ND = not detected

Average concentration (n=3) of pharmaceutical in the sludge. Value in ( ) following the average concentration is the percent standard deviation.

4.2 Removal efficiencies of STWs

Reported removal rates for pharmaceuticals vary considerably between and within studies. In addition, concentrations of atenolol, bezafibrate, carbamazepine, crotamiton, diclofenac, metoprolol, propyphenazone and sulfamethoxazole have been found to increase during the treatment process (Bendz et al., 2005; Lindqvist et al., 2005; Lishman et al., 2006; Nakada et al., in press). One possible mechanism for this apparent increase is transformation of conjugates, as discussed in Section 4.1.2. This is an important consideration in a wider context, since most studies infer removal by measuring the concentration of a target substance in influent and effluent waters. Possible precursors, such as conjugates, or metabolites are invariably not analysed so the apparent 'removal' may be by conversion to a metabolite or degradation product rather than complete mineralization.

As well as the variances that can be ascribed to differences in process type and STW configuration, other factors have been shown to confound interpretation of removal rate efficiency. Heavy rainfall has lead to a significant reduction in the removal of naproxen, bezafibrate and diclofenac because of the lower efficiency of the STW (Ternes, 1998). Removal rates have also been found to differ according to season. Castiglioni et al. (2006) monitored six similar STWs in different locations in Italy, in different seasons, with all samples collected in dry weather conditions. Removal rates were higher in summer than winter for a number of pharmaceuticals but this pattern was not uniform throughout (see Table 4.5). Lindqvist et al. (2005) observed lower removal rates of pharmaceuticals from STWs where part of the wastewater originated from industrial sources, i.e. pulp and paper mills and the metal industry.

Table 4.5 Winter and summer removal rates (RR) in STWs Italy (Castiglioni et al., 2006)

Compound	Pharmaceutical Product Group	Winter RR %		Summer RR %	
		median	range	median	range
Amoxycillin	Antibiotic	75	49-100	100	100
Atenolol	Beta-blocker	10	0-21	55	36-76
Bezafibrate	Lipid regulator	15	0-66	87	0-98
Carbamazepine	Antiepileptic	0	0	0	0
Ciprofloxacin	Antibiotic	60	45-78	63	53-69
Clarithromycin	Antibiotic	0	0-24	0	0
Clofibric acid	Lipid regulator metabolite	30	0-30	<0.36	<0.36
Enalapril	ACE inhibitor	18	4-31	100	69-100
Erythromycin	Antibiotic	0	0	0	0
Furosemide	Diuretic	8	0-17	54	15-62
Ibuprofen	Analgesic	38	25-72	93	0-100
Hydrochlorothiazide	Diuretic	24	0-77	44	0-51
Lincomycin	Antibiotic	0	0	0	0
Ofloxacin	Antibiotic	43	0-62	57	33-66
Ranitidine	H2 antagonist	39	0-76	84	72-89
Salbutamol	Beta-blocker	0	0	0	0-12
Spiramycin	Antibiotic	0	0-11	0	0

Compound	Pharmaceutical Product Group	Winter RR %		Summer RR %	
Sulphamethoxazole	Antibiotic	17	0-84	71	71

Table 4.6 summarises the removal efficiencies that have been reported in the literature for the most frequently studied pharmaceuticals.

Table 4.6 Removal efficiency of STW processes for selected pharmaceuticals

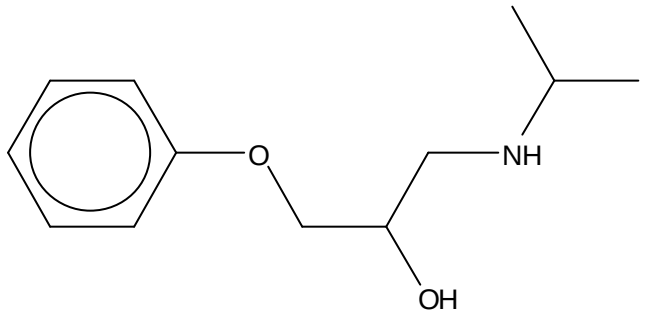
Compound	Pharmaceutical Product Group	% STW removal	Treatment Process	Reference
Acetylsalicylic acid	Analgesic	81	Activated sludge STW	Ternes 1998
		>90	Activated sludge STW	Nakada et al., in press
Betaxolol	Beta-blocker	80	Activated sludge STW	Ternes 2000
Bezafibrate	Lipid regulator	83	Activated sludge STW	Ternes 1998
		50	Activated sludge STW	Stumpf et al., 1999
		27	Biological filter STW	Stumpf et al., 1999
		11 – 100	Activated sludge STW	Lindqvist et al., 2005
Bisoprolol	Beta-blocker	65	Activated sludge STW	Ternes 2000
Carazolol	Beta –blocker	66	Activated sludge STW	Ternes 2000
Carbamazepine	Anti-epileptic	7	Activated sludge STW	Ternes 1998
		30	Activated sludge STW	Bendz et al., 2005
Clofibric acid	Lipid regulator metabolite	15	Biological filter STW	Stumpf et al., 1999
		34	Activated sludge STW	Stumpf et al 1999
		51	Activated sludge STW	Ternes 1998
Diclofenac	Anti-inflammatory	69	Activated sludge STW	Ternes 1998
		75	Activated sludge STW	Stumpf et al., 1999
		9	Biological filter STW	Stumpf et al., 1999
		22	Activated sludge STW	Bendz et al., 2005
		9 – 60	Activated sludge STW	Lindqvist et al., 2005
Dimethylamino-phenazone	Anti-inflammatory	38	Activated sludge STW	Ternes 1998
Fenoprofen		65-95	Activated sludge STW	Nakada et al., in press
Fenofibric acid	Lipid regulator metabolite	6	Biological filter STW	Stumpf et al., 1999
		45	Activated sludge STW	Stumpf et al., 1999
		69	Activated sludge STW	Ternes 1998
Gemfibrozil	Lipid regulator	46	Activated sludge STW	Stumpf et al 1999
		69	Activated sludge STW	Ternes 1998

Compound	Pharmaceutical Product Group	% STW removal	Treatment Process	Reference
		75	Activated sludge STW	Bendz et al., 2005
Ibuprofen	Analgesic	22	Biological filter STW	Stumpf et al., 1999
		65	Biological filter STW	Rodriguez et al., 2003
		75	Activated sludge STW	Stumpf et al., 1999
		90	Activated sludge STW	Ternes 1998
		60-70	Activated sludge STW	Carballa et al. 2004
		78 – 100	Activated sludge STW	Lindqvist et al., 2005
		96	Activated sludge STW	Bendz et al., 2005
		> 90	Activated sludge STW	Nakada et al., in press
Indomethacine	Anti-inflammatory	83	Activated sludge STW	Stumpf et al., 1999
		71	Biological filter STW	Stumpf et al., 1999
		75	Activated sludge STW	Ternes 1998
Ketoprofen	Anti-inflammatory	69	Activated sludge STW	Stumpf et al., 1999
		48	Biological filter STW	Stumpf et al., 1999
		65	Activated sludge STW	Bendz et al., 2005
		51-100	Activated sludge STW	Lindqvist et al., 2005
		15-75	Activated sludge STW	Nakada et al., in press
Metoprolol	Beta-blocker	83	Activated sludge STW	Ternes 1998
Naproxen	Analgesic	78	Activated sludge STW	Stumpf et al., 1999
		15	Biological filter STW	Stumpf et al., 1999
		45	Biological filter STW	Rodriguez et al., 2003
		66	Activated sludge STW	Ternes 1998
		40-55	Activated sludge STW	Carballa et al. 2004
		93	Activated sludge STW	Bendz et al., 2005
		55 – 98	Activated sludge STW	Lindqvist et al., 2005
		0-80	Activated sludge STW	Nakada et al., in press
Paracetamol	Analgesic	98	Activated sludge STW	Ternes 1998
Phenazone	Analgesic	33	Activated sludge STW	Ternes 1998
Propranolol	Beta-blocker	96	Activated sludge STW	Ternes 1998
		32	Activated sludge STW	Bendz et al., 2005

Compound	Pharmaceutical Product Group	% STW removal	Treatment Process	Reference
Salbutamol	?$_2$- sympatho-mimetic	> 90	Activated sludge STW	Ternes 2000
Sulfamethoxazole	Antibiotic	67	Activated sludge STW	Carballa et al. 2004
Terbutalin	?$_2$- sympatho-mimetic	67	Activated sludge STW	Ternes 2000
Trimethoprim	Antibiotic	49	Activated sludge STW	Bendz et al., 2005

Concentrations of pharmaceuticals in the sludge were not determined, therefore it is not possible to allocate removal between biodegradation or adsorption to the sludge.

The data clearly show that for substances that are removed in STWs, activated sludge plants are always more efficient at removal than simple biological filters. It also shows that prediction of removal for STWs is possible for pharmaceuticals with very similar chemical structures, eg the ß blockers betaxolol, bisprolol, carazolol, metprolol, and propranolol which all share the common structural fragment shown below:



All of these substances are significantly removed by activated sludge plants with the reported removal rate varying from 65 to 96 %, but with one report for propranolol where the removal was only 36%. Hence even with compounds of very similar structure, which are significantly removed by STW, there are difficulties in predicting amounts of removal between different activated sludge plants.

4.3 Removal in Drinking Water Treatment Works

Drinking Water Treatment works use a wide range of processes, but these are not specifically designed to remove pharmaceuticals that may be present in source waters. However biodegradation on slow sand filters and/or sorption to particles removed by coagulation may reduce concentrations present in the treated effluent for some substances. The increasingly prevalent use of Granular Activated Carbon (GAC) and Powdered Activated Carbon (PAC) as a final finishing treatment to remove pesticides and taste and odour causing compounds may also lead to removal by sorption (or biodegradation on GAC) of some pharmaceuticals. As with 'removal' rates measured in STWs, some caution has to be applied in interpreting the literature data since generally only the concentrations of target compounds in influent and effluent streams are measured. If the process that is used effects removal by physical means, e.g. sorption or filtration, there is no problem, but if the removal is by chemical or biological degradation or metabolism then the apparent removal rate

measured may be an over-estimate. This will be the case if there is not complete mineralization and there is no measurement of the concentration of likely metabolites and/or degradation products.

However, there is evidence that some compounds are unaffected by such processes (Jones et al., 2005). Table 4.7 lists some of the pharmaceuticals that have been measured in finished drinking water worldwide. Iodinated contrast media are particularly persistent such that diatrizoate, iopromide and ioxithalamic acid have been detected at up to 45 µg l^1 after final disinfection and in tap water (Wenzel et al., 2003).

Groundwater used for drinking water production is typically low in concentrations of particles and organic matter and, therefore, drinking water treatment is mostly single-stage, with the main objective being disinfection. Leakages in landfill sites, sewer drains and STWs are potential sources for groundwater contamination and, in highly populated areas, groundwater has to be artificially recharged usually by a pre-treatment of surface water followed by a passage through soil.

About 30% of Britain's public water supplies come from wells or boreholes that draw groundwater from water-bearing rocks called aquifers. The principal British aquifers are the Chalk, the Permian and Triassic sandstones, and Jurassic limestones, which together underlie much of southern and eastern England and large parts of the Midlands. Many communities in these areas, for example, Brighton and Cambridge, are totally dependent on groundwater for potable water supplies.
(http://www.bgs.ac.uk/hydrogeology/PollProb.htm)

Table 4.7 Concentrations of pharmaceuticals found in finished drinking water (taken from Jones et al., 2005)

Compound	Pharmaceutical Product Group	Maximum concentration detected ng l^{-1}	Country
Bezafibrate	Lipid regulator	27	Germany
Bleomycin	Anti-neoplastic	13	UK
Clofibric acid	Lipid regulator	+ve identification	UK
		70	Germany
		165	Germany
		270	Germany
		170	Germany
		5.3	Italy
Carbamazepine	Anti-epiletic	24	Canada
		258	USA
Diazepam	Psychiatric drug	10	UK
		23.5	Italy
Diclofenac	Analgesic and anti-pyretic	6	Germany
Gemfibrozil	Lipid regulator	70	Canada
Ibuprofen	Analgesic and anti-pyretic	3	Germany
Phenazone	Analgesic and anti-pyretic	250	Germany
		400	Germany

Compound	Pharmaceutical Product Group	Maximum concentration detected ng l^{-1}	Country
Propylphenazone	Analgesic and anti-pyretic	80	Germany
		120	Germany

Where surface waters are used as a potable resource, a multistage treatment is typically implemented to guarantee a drinking water that fulfils the requirements with regard to hygienic parameters, turbidity, DOC and micropollutants. The major treatment steps are:

- Clarification (flocculation/settling and filtration)
- Direct coagulation or flotation
- Disinfection
- Polishing treatment (oxidation with ozone, GAC filtration, membranes, or membranes with PAC addition).

The processes by which pharmaceuticals may be removed can be separated into two categories:

- Removal processes: physical barrier membranes, or physical retention by adsorption on a solid phase with activated carbon (either a granular activated carbon (GAC in filters, or as powdered activated carbon (PAC) in conventional clarification processes or combined with membranes);
- Transformation processes: chemical oxidations with ozone or chlorine are most commonly applied, but also UV irradiation can lead to some direct or indirect phototransformation. Advanced oxidation processes (AOPs) can be applied for compounds which react only slowly with ozone or chlorine. A more detailed description of each process is given below.

4.3.1 Coagulation

Coagulation is the process of adding chemical reagents (iron or aluminium salts) in a mixing tank to destabilise colloidal particles and allow them to agglomerate or flocculate with other suspended particles to form larger, more readily settled particles (Droste, 1997).

Vieno et al. (2006) carried out a number of jar test experiments using spiked deionized water, lake water and commercial humic solutions using aluminium (pH 6) and ferric sulphate (pH 4). In deionised water, less than 10% of the pharmaceuticals were removed by coagulation with the exception of diclofenac, which was removed up to 66% with ferric sulphate. This was also the only pharmaceutical removed during the coagulation of lake water with ferric sulphate (see table 4.8). The coagulation of pharmaceuticals was impaired by the presence of natural organic matter (NOM). It is thought that lower molecular weight (MW) organic matter is responsible for this impairment and that high concentrations of high MW NOM may enhance coagulation of pharmaceuticals up to 50%. Neutral pharmaceuticals such as carbamazepine and sulfamethoxazole cannot be removed by coagulation.

Table 4.8 Removal of pharmaceuticals by coagulation using ferric sulphate (50 mg l^{-1}) (Vieno et al., 2006)

Source Water	Compound	Concentration in source water (µg l^{-1})	Removal (%)
Lake Roine*	Diclofenac	30-40 µg/L	30
	Ibuprofen	30-40 µg/L	10
	Bezafibrate	30-40 µg/L	<5
	Carbamazepine	30-40 µg/L	<5
	Sulfamethoxazole	30-40 µg/L	<5

* - samples were spiked with each pharmaceutical

A study by Westerhoff et al. (2005) revealed that coagulation by aluminium and ferric salts at pH 6.8 resulted in an average of 6% (SD ±8%, range 0-28%) removal of pharmaceuticals and endocrine disrupting chemicals (EDCs). They concluded that chemical precipitation processes achieve minimal removal of most pharmaceuticals and EDCs examined. It should be noted that here the dominant mechanism of removal is precipitation rather than coagulation, which would occur at pH 4-5.

4.3.2 Filtration

Filtration provides polishing of a potable water supply and is required for every surface water. Filtration follows sedimentation if that is provided. Water moves through tanks that contain sand and other types of media. Fine solids that did not settle out in a sedimentation basin will be entrapped in the filter. There will also be significant removal of bacteria in a filter but not enough to provide safe drinking water (Droste, 1997).

Table 4.9 Removal of phenazone type pharmaceuticals and their metabolites by aeration and filtration (Reddersen et al., 2002)

Source water and treatment	Compound	Concentration in source water (ng l^{-1})	Removal by DWTW (%)
Polluted groundwater, Germany (aeration followed by biologically active clay and sand filters)	Phenazone	3950	90
	Propiphenazone	1230	90
	Dimethylamino-phenazone	400	>95
	AMDOPH	1200	25
	AMPH	20-100	Nd
	DMOAS	Nd	Nd

AMDOPH – 1-acetyl-1-methyl-2-dimethyl-oxamoyl-2-phenylhydrazide
AMPH – 1-acetyl-1-methyl-2-phenylhydrazide
DMOAS – dimethyloxalamide acid-(*N'*-methyl-*N*-phenyl)-hydrazide
Nd – Not detected

Removal of the phenazone pharmaceuticals reported by Redderson et al. (2002) appears very good (Table 4.9). However removal of the phenazone metabolite, AMDOPH was poor. Since no phenazone residues, apart from AMDOPH could be detected in the sludge the authors concluded that the three parent phenazones were

removed, or degraded to other metabolites, during filtration by microbiological processes.

4.3.3 Activated Carbon

Activated carbon is a broad-range adsorbent of dissolved substances. Dissolved, colloidal and particulate substances are attracted and attached to the surface of the carbon particles. It is used to remove taste and odour causing compounds as well as toxic organic chemicals. Precipitation and other chemical reactions also occur on the carbon surface. A variety of carbon adsorbers can be designed, including batch and continuous flow units. The adsorption capacity of the carbon is eventually exhausted and the carbon is regenerated by heating, which oxidises and volatilises the substances accumulated on it. The activated carbon can take the form of granules (granular activated carbon – GAC) or powder (powdered activated carbon – PAC) (Droste, 1997).

Kim et al. (2007) investigated the treatment efficiency of micropollutants, including a number of pharmaceuticals, in drinking water processes using different purification methods. All compounds were reduced to below the analytical reporting limits in the finished drinking water (see Table 4.10). The observed removal was entirely related to GAC as previous treatment by coagulation and ultrafiltration did not result in any removal of the pharmaceuticals.

Table 4.10 Removal of pharmaceuticals by GAC (Kim et al., 2007)

Source Water	Compound	Concentration in source water (ng l^{-1})	Removal (%)
Paldang Lake	Iopromide	143	100
	Ibuprofen	15	100
	Carbamazepine	4.8	100
	Caffeine	45	100

Westerhoff et al. (2005) carried out a series of bench-scale experiments to simulate individual treatment processes in a DWTW. They found that the addition of 5 mg l^{1} PAC with a 4 h contact time removed 10% to >98% of the compounds (see Table 4.11). The removal of pharmaceuticals by activated carbon may be influenced by many factors (carbon age, contact time, size of the pharmaceutical, competition for sites on the carbon). Westerhoff et al. (2005) concluded that the octanol-water partition coefficient was a reasonable indicator of compound removal under controlled PAC test conditions, except for pharmaceuticals that were protonated or deprotonated at the test pH and some that contained heterocyclic or aromatic nitrogen. They also noted that higher PAC dosages improved removal rates.

Table 4.11 Removal of pharmaceuticals by PAC (dose 5 mg l-1) (Westerhoff et al., 2005)

Source Water	Compound	Concentration in source water	Removal (%)
Suwannee River Water –	Diclofenac	Total spiked into source water = 1789 ng l^{1} for 64 compounds giving an average of 28 ng l^{1} for each	44
	Ibuprofen		35
	Meprobamate		44
	Androstenedione		96

Source Water	Compound	Concentration in source water	Removal (%)
freeze dried and reconstituted	Testosterone	compound	47
	Progesterone		91
	Ethynylestradiol		97
	Estradiol		97
	Oxybenzone		92
	Fluoxetine		96

In the literature different approaches have been used to predict the removal performance for individual compounds, but no quantitative predictive relationship could be established. However, the adsorption isotherms obtained in deionised water show that the compounds can be classified into two categories:

?? Carbamazepine and diazepam are very easily adsorbable (< 0.2 ppm activated carbon for 99% removal): these compounds are neutral and have K_{ow} values higher than 2 (log K_{ow} of 2.45 and 2.82 respectively);

?? Ibuprofen, roxithromycin, sulfamethoxazole and iopromide are either charged compounds at pH 7-8 (ibuprofen, roxithromycin), or compounds with low K_{ow} values (log K_{ow} of 0.89 and –2.1 for sulfamethoxazole and iopromide, respectively) (von Gunten et al., 2006).

Furthermore, the following generalisation can be concluded for waters with DOC contents between 1 and 1.5 mg l^{1}:

?? 5 mg l^{1} PAC enabled the target of 90% removal to be reached,
?? 10 to 15 mg l^{1} PAC enabled a target of 99% removal to be reached (von Gunten et al., 2006).

4.3.4 Oxidants – Ozone and Chlorine dioxide

The oxidants commonly used in drinking water are ozone, chlorine, chlorine dioxide and chloramine. Ozone (O_3) is a more powerful oxidising agent than chlorine and a very effective biocide. Ozone reacts with most organic matter either by direct attack or indirectly through the formation of hydroxyl radicals (•OH) formed from ozone.

McDowell et al. (2005) spiked several neutral pharmaceuticals into flocculated and sand filtered water taken from the River Rhine, Germany (see Table 4.12). The neutral pharmaceuticals that exhibit a high rate of oxidation from ozone do so because their structures contain fast reacting double bonds (caffeine, propyphenazone), and tertiary amine groups (phenazone, dimethylaminophenazone, pentoxifylline). The slower oxidation of ifosfamide, cyclophosphamide and diazepam is due to a lack of susceptible functional groups in these three compounds, which hinders a fast electrophilic attack by ozone, meaning that the oxidation occurs mainly through reactions with OH radicals (McDowell et al., 2005).

Table 4.12 Removal of pharmaceuticals by ozonation (McDowell et al., 2005)

Source Water	Compound	Concentration in source water (ng l^{-1})	Removal (%)
Spiked Rhine River Water – O_3 dose 1.2 mg l^{-1}	Pentoxyifylline	500	100
	Ifosfamide	500	50
	Cyclophosphamide	500	33
	Carbamazepine	500	100
	Diazepam	500	65
	Caffeine	500	100
	Phenazone	500	100
	Propyphenazone	500	100
	Dimethylamino-phenazone	500	100

Huber et al. (2005) assessed the potential of chlorine dioxide to oxidise pharmaceuticals during wastewater treatment by spiking a number of acidic and neutral pharmaceuticals into drinking water taken from a German DWTW immediately before the disinfectant dosing. Diclofenac and phenazone type compounds were readily oxidisable by chlorine dioxide, however other compounds showed no reactivity at all (see Table 4.13).

Table 4.13 Removal of pharmaceuticals by chlorine dioxide (Huber et al., 2005)

Source Water	Compound	Concentration in source water (ng l^{-1})	Removal (%)
Drinking water spiked – ClO_2 dose 11.5 mg l^{1}	Bezafibrate	1000	0
	Ibuprofen	1000	0
	Diclofenac	1000	100
	Carbamazepine	1000	0
	Diazepam	1000	0
	Cyclophosphamide	1000	12
	Gemifibrozil	1000	41
	Glibenclamide	1000	29
	Phenazone	1000	100
	Propiphenazone	1000	100
	Dimethylamino-phenazone	1000	100

Ozone has been found to be a more effective oxidiser for a large range of pharmaceuticals. Chlorine dioxide has, however, been shown to be a stronger oxidiser than chlorine (Huber et al., 2005). A comparison of ozonation and chlorination of pharmaceuticals/EDCs has been made (Westerhoff et al., 2005). Some compounds were oxidised to the same degree by ozone and chlorine (>95 %). These compounds had common structural properties such as activated aromatic ring structures (i.e. hydroxyl or amine functionalities) and low pK_a values. De-protonated species react faster with electrophilic ozone because they are stronger nucleophiles. Also typical oxidant exposures during treatment and distribution are higher for chlorine than for ozone. This can partially or fully compensate for the lower reactivity

of most compounds with chlorine compared to ozone and yield similar degrees of transformation in both systems (von Guten et al., 2006).

Another group of compounds identified by Westerhoff et al. (2005) are those that are poorly oxidised by either ozone or chlorine (<20 %). The compounds in this group are aliphatic with polar functional groups (e.g. the fire retardant tris-(2-chloroethyl) phosphate; TCEP). Non-oxidative treatment such as membranes may be required to remove such compounds. The third group of compounds highlighted by Westerhoff et al. (2005) are those that react preferentially with ozone rather than chlorine. These include carbamazepine, caffeine, ibuprofen, meprobamate and iopromide. These compounds contain nucleophilic sites that will react with either ozone or chlorine. However, it is thought that the hydroxyl radicals produced when ozonating are responsible for the higher reactivity observed with ozone. Hydroxyl radicals are powerful oxidants that react non-selectively with most organic compounds.

Further studies using ozone to destroy pharmaceuticals in surface water have found that an ozone dose of 0.2 mg l^1 can remove >97 % of pharmaceuticals with the exception of bezafibrate. The ozone dose required for oxidation will be influenced by the ozone demand of the water. The ozone rate constant for bezafibrate is at least 100 times lower than those for the other compounds studied (carbamazepine, diazepam, diclofenac, ibuprofen, iopromide, sulfamethoxazole and 17a-ethinylestradiol) and oxidation of bezafibrate cannot compete with the initial ozone demand of the water (Huber et al., 2003).

In a study of the ozonation of two antibiotics (Qiang et al., 2004), it was observed that the rate of degradation was related to the solution pH. The antibiotics were lincomycin and spectinomycin. The reaction rates increased with increasing pH. The hydroxyl radical (•OH) would most probably be generated at alkaline pH in the ozonation process. Ozone primarily attacks the free amino group in the structure of these antibiotics with a high reactivity. Once protonated, the amine group is non-reactive towards ozone.

A study on the kinetic rate of depletion of clofibric acid by ozonation (Andreozzi et al., 2003) supports the information provided by Qiang et al. (2004) that the reactivity of clofibric acid increases with increasing pH. Andreozzi et al. (2003) attributed the increased reactivity to clofibric acid dissociating in water and becoming de-protonated.

The reappearance of 17a-ethinylestradiol (EE2) after ozonation has been reported (Huber et al., 2004). The reappearance was less pronounced at higher ozone doses (4800 mg l^1) treating ~3000 mg l^1 EE2. These ozone doses and EE2 concentrations are very high and are unlikely to be seen in water treatment.

4.3.5 Ultraviolet

Ultraviolet (UV) radiation is widely used for disinfection although more powerful doses have been shown to reduce species such as bromate to bromide. By combining UV with hydrogen peroxide (H_2O_2), •OH is produced and acts as a powerful, non-specific oxidising agent (Parsons and Jefferson, 2006).

UV radiation combined with hydrogen peroxide has been used to degrade clofibric acid (Andreozzi et al., 2003). Experiments were carried out at initial concentrations of 5-10 mg l^{1} clofibric acid. The UV lamp had a power of 17 W and emitted light at 254 nm. At doses of 1020 mg l^{-1} H_2O_2, 90% reduction was achieved after 110 seconds. At lower concentrations of clofibric acid (~10 µg l^{1}), the concentration was reduced by 80 %. There was no influence of pH on the kinetic rate constant of •OH attack with UV/H_2O_2.

Treatment with UV alone is ineffective with a low pressure UV lamp (Rosenfeldt and Linden, 2004). A medium pressure lamp emits light at more wavelengths and is therefore more effective at destroying the endocrine disruptors than the low pressure lamp. When H_2O_2 is added to the water, the oxidation process becomes very efficient regardless of the lamp used as the main method of oxidation becomes •OH mediated advanced oxidation (see Table 4.14). The use of UV for drinking water treatment either on its own or in combination with H_2O_2 is not widespread in the UK.

Table 4.14 Removal of pharmaceuticals by UV/H_2O_2 (Rosenfeldt and Linden, 2004)

Source Water	Compound	Concentration in source water (ng l^{-1})	H_2O_2 dose (mg l^{-1}) and lamp pressure	Removal (%)
Spiked milliQ water	17a-ethinylestradiol	Not given	0 (low) 0 (medium) 15 (low) 15 (medium)	3 22 >95 >95
	17ß-estradiol	Not given	0 (low) 0 (medium) 15 (low) 15 (medium)	5 18 >95 >95

UV dose is 1000 mJ cm^{-2}

UV-phototransformation is considered a fairly inefficient process under conditions typical for UV disinfection, i.e. 400 J m^{-2} (von Guten et al., 2006).

4.3.6 Reverse Osmosis

Reverse osmosis (RO) is used for the removal of high concentrations of dissolved solids. RO essentially 'filters' dissolved solids from the water by forcing the water through a membrane by applying pressure in excess of the osmotic pressure of the dissolved components in solution. Suspended solids must be removed to a low level before water is subjected to RO to prevent fouling of the membrane.

Heberer et al. (2002) tested mobile drinking water purification systems using water taken from The Tetlowkanal in Germany. This canal is highly polluted with municipal sewage effluents. Reverse osmosis proved effective at removing pharmaceuticals by greater than 95% (Table 4.15). This was due to the size of the membrane pores that do not permit chemical species to pass through the membrane that are of a certain molecular size.

Table 4.15 Removal of pharmaceuticals by reverse osmosis (Heberer et al., 2002)

Source Water	Compound	Concentration in source water (ng l^{-1})	Removal (%)
Tetlowkanal, Germany	Propylphenazone	170	>99.4
	Naproxen	38	>95.0
	Diclofenac	329	>99.7
	Clofibric acid	155	>99.4
	Carbamazepine	330	>99.7
	Caffeine	430	>99.8

Kimura et al. (2004) examined the ability of reverse osmosis membranes to retain neutral compounds. The rejection of the pharmaceuticals is dependent on their size and physico-chemical properties. Rejection by the XLE membrane was largely related to molecular weight. Rejection by the SC-3100 membrane was highly dependant on polarity. It was hypothesised that the dominant rejection mechanism for reverse osmosis membranes would be different depending on membrane material and the physico-chemical properties of target compounds (Kimura et al., 2004).

Table 4.16 Removal of pharmaceuticals by reverse osmosis (Kimura et al., 2004)

Source Water	Compound	Concentration in source water (ng l^{-1})	Removal (%)[1]	Removal (%)[2]
Spiked milliQ water	Phenacetine	100000	74	10
	Primidone	100000	87	85
	Isoproplantipyrine	100000	78	69
	Sulfamethoxazole	100000	70	82
	Carbamazepine	100000	91	85
	Caffeine	100000	70	44

1 – XLE – polyamide membrane with molecular weight cut-off (MWCO) of <200 and salt rejection of 90%
2 – SC-3100 – cellulose acetate membrane with MWCO of 200-300 and salt rejection of 94%

4.3.7 General removal by entire DWTWs

There are a few papers that do not list the removal by single water treatment processes. Instead they show removal by an entire treatment works or from process to process (Boyd et al., 2003). Conventional drinking water processes, i.e. coagulation, flocculation and sedimentation together with the continuous addition of PAC (2 mg l^{1}) did not remove naproxen from Mississippi River waters. However, chlorination, ozonation and dual media filtration processes reduced the concentration of naproxen to below the limits of detection in both river waters tested (Boyd et al., 2003). Table 4.17 summarises the results.

Table 4.17 Removal of pharmaceuticals by DWTW processes (Boyd et al., 2003)

Source Water	Compound	Concentration in source water (ng l^{-1})	Removal %
Detroit River	Clofibric acid	103	100 (O_3 + coag + sed + Cl_2)
Detroit River	Naproxen	63	100
Mississippi River	Naproxen	64	0 (PAC + coag + sed)
Mississippi River	Naproxen	64	100 (Cl_2)

Ternes et al. (2002) investigated the elimination of a number of pharmaceuticals during drinking water processes both at laboratory and pilot scale and in DWTWs. They found similar removal efficiencies in DWTWs as observed under experimental conditions. In particular ozonation filtration with GAC proved to be very effective in removing the pharmaceuticals under investigation (Tables 4.18 and 4.19).

Hua et al. (2006) sampled influent and effluent at a DWTW in Ontario, Canada, in order to assess the efficiency of the treatment processes. Only carbamazepine (antiepileptic), caffeine (stimulant), cotinine (a metabolite of nicotine) and atrazine were consistently detectable in the raw water intake (low to sub-ng l^{-1} level). Regardless of the seasonality, the flocculation-coagulation and dual media filtration steps without ozone treatment resulted in no decrease in analyte concentrations, while decreases of 66–100% of the analyte concentrations were observed when ozone treatment was part of the water processing (Table 4.20).

Table 4.18 Concentration of pharmaceuticals (ng l^{-1}) through waterworks 1 (WW1), Germany – Ternes et al. (2002)

Compound	Source water (ng l-1)	After pre-O3	After flocculation	After main O3	After GAC
Clofibric acid	10	10	5	4	nd
Diclofenac	35	nd	Nd	nd	nd
Carbamazepine	80	5	4	nd	nd

WW1 – Pre-O_3 (0.7-1.0 mg $l^{1}$for 3 minutes), flocculation with iron(III) chloride, main O_3 (1.0-1.5 mg $l^{1}$for 10 minutes), multiple layer filter and a final GAC filtration

Table 4.19 Concentration of pharmaceuticals (ng l^{-1}) through waterworks 2 (WW2), Germany – Ternes et al. (2002)

Compound	Source water (ng l^{-1})	After flocculation	After GAC	After bank filtration	After slow sand filtration
Clofibric acid	13	13	5	nd	nd
Diclofenac	66	60	Nd	nd	nd
Bezafibrate	82	75	Nd	nd	nd
Carbamazepine[1]	180	180	10	50	30
Carbamazepine[2]	140	105	Nd	25	10

Compound	Source water (ng l^{-1})	After flocculation	After GAC	After bank filtration	After slow sand filtration
Primidone	17	17	5	9	10

WW2 – Sedimentation, flocculation with FeCl3/CaOH, GAC filtration, underground passage, bank filtration and slow sand filtration

Table 4.20 Removal of pharmaceuticals by WTW1 and WTW2 (Hua et al., 2006)

Source Water	Compound	Concentration in source water (ng l^{-1})	Removal (%)1	Removal (%)2
Detroit River O_3 dose 1.5-2.0 mg/L	Cotinine	0.5	0	83-93
	Carbamazepine	1.5	0	78-99
	Caffeine	10	0	67-81

1- WTW1 – coagulation/flocculation followed by sedimentation, then filtration by dual media

2- WTW2 – as WTW1 but with ozonation before coagulation and before filtration

Generally when traditional processes are used, the removal is very low. When ozonation is added to these processes, the removal is vastly improved.

Seitz et al. (2006) investigated the removal of five iodinated X-ray contrast media (ICM) during drinking water production from surface water at a full-scale water works, which comprised coagulation/flocculation, intermediate ozonation, in-line filtration and adsorption with activated carbon. The elimination rates over all treatment units for the non-ionic ICM (iomeprol, iopromide, iohexol and iopamidol) were determined to be approximately 70%. In particular, intermediate ozonation removed 30% on average of the non-ionic ICM, whereas it could not remove the ionic diatrizoic acid, and the granulated activated carbon filters achieved a further 50% removal of non-ionic ICM. However, over 100 ng l^{1} of ionic diatrizoic acid and 40-100 ng l^{-1} of non-ionic ICM were found in the produced drinking water.

4.3.8 Novel processes

Electrolysis of water containing 3200 ng l^{1}ethinyl estradiol (EE2) removed 97% at a current of 2 amps (Pauwels et al., 2006). Complete oxidation of EE2 in lake water by ferrate (Fe (IV)) occurred after 30 minutes exposure at pH 8 and at 25 °C (Lee et al., 2005). Other novel processes include catalytic absorption onto titanium dioxide (TiO_2) followed by separation of the TiO_2 by microfiltration (Doll and Frimmel, 2005). This pilot study showed promise for degrading pharmaceuticals but would be expensive to operate due to the separation of powdered TiO_2.

4.3.9 Overview of Removal by WTW Processes

Although no clear quantitative structural relationships have been determined to-date, the degree of removal during treatment of a pharmaceutical is dependent on the structure and nature of that pharmaceutical. Von Gunten et al. (2006) list the following key parameters:

- The acid dissociation constant (pKa = -log *Ka* +pH log([A^-]/[AH])) is important for all removal processes since the neutral and the ionic forms of a compound typically behave differently. pKa is a measure of the strength of an acid relative to the acid-base pair H_3O^+/H_2O. At a pH = pKa, the organic acid is present in equal amounts as the dissociated and non-dissociated forms, i.e. [A^-]=[HA], at a pH<pKa the non-dissociated form [HA] predominates and at pH>pKa the dissociated form [A^-] predominates.
- Second-order rate constants for the reaction of the compounds with a particular oxidant have to be known for oxidation processes.
- For activated carbon filtration, a parameter describing the affinity towards activated carbon has to be determined (K_{AC}); the partitioning coefficient between water and octanol, K_{ow}, can be a good surrogate indicator for activated carbon adsorption.
- For the photolysis processes, the quantum yield and the molar absorption coefficient have to be determined.
- For filtration by membranes, it is important to know the molecular weight cut-off and the surface charge of the membrane, but also the molecular weight, charge and shape of the pharmaceutical.

Most non-polar organic compounds are the best candidates for removal by activated carbon. For polar compounds, other mechanisms may enable adsorption as well, but the prediction is not straightforward (von Gunten et al., 2006)

Only a few pharmaceuticals are transformed by chlorine or chlorine dioxide. However, for those pharmaceuticals containing amino or phenolic moieties a complete transformation can be expected (von Guten et al., 2006).

Neutrally charged pharmaceuticals are well removed from water using an oxidant such as ozone or UV/H_2O_2. Charged pharmaceuticals can be removed by coagulation but only under certain conditions (e.g. where there is a high proportion of high MW organic matter). Activated carbon has been very effective in some cases but the removal rate may depend on the age of the carbon. Reverse osmosis is another particularly effective process for removing pharmaceuticals but is an energy intensive process.

DWTWs that treat groundwater have short treatment lines usually consisting solely of disinfection with chlorine or UV. These processes are unable to remove all pharmaceutical residues, particularly polar compounds. However, the contamination load is invariably much lower than for surface waters.

Although there is no 'ideal process' that is effective at removing all pharmaceuticals (as evidenced in Table 4.21) the more advanced DWTW processes such as ultafiltration, nanofiltration and ozonation have been shown to remove a large proportion of a wide range of pharmaceuticals. Table 4.21 summarises the removal efficiencies of the various processes for 10 selected pharmaceuticals.

Table 4.21 Removal efficiency of individual treatment processes for selected pharmaceuticals (Ternes et al., 2005)

Process	Antibiotics		Antiphlogistics		Anti-Depressant	Anti-epliletic	Lipid regulator	Contrast media		
	Roxithr-mycin	Sulfamet-Oxazole	Diclo-fenac	Ibu-profen	Diazepam	Carba-mazepine	Beza-fibrate	Diatri-zoate	Iopa-midol	Iopro-mide
Primary treatment	<10%	<10%	<10%	<10%	<10%	<10%	<10%	<10%	<10%	<10%
COD removal ($?_x$ < 2 d)	10-50%	>90%	<10%	50-90%	<10%	<10%	<10%	<10%	<10%	<10%
Nitrification ($?_x$ 10-15 d)	10-50%	>90%	10-50%	>90%	<10%	<10%	>90%	<10%	<10%	50-90%
Sludge stabilisation, membrane bioreactor ($?_x$ >25 d)	50-90%	50-90%	10-50%	>90%	<10%	<10%	>90%	<10%	<10%	50-90%
Biofilter	10-50%	no data	10-50%	no data	no data	<10%	no data	<10%	<10%	50-90%
Soil, unsaturated zone		<10%	>90%	>90%	no data	<10%	>90%	<10%	<10%	50-90%
Groundwater, saturated zone	50-90%	no data	50-90%	50-90%	10-50%	<10%	no data	no data	no data	no data
Sludge digestion	>90%	>90%	10-50%	10-50%	10-50%	10-50%	no data	no data	no data	10-50%
Fenton process	<10%	<10%	<10%	<10%	<10%	<10%	<10%	<10%	<10%	<10%
Effluent ozonation	>90%	>90%	>90%	10-90%	10-50%	>90%	50-90%	<10%	10-50%	10-50%
Bank filtration	>90%	50-90%	>90%	>90%		<10%	50-90%	<10%	<10%	
Flocculation	<10%	<10%	<10%	<10%		<10%	<10%	<10%	<10%	
Ozonation	>90%	>90%	>90%	10-50%	10-50%	>90%	50-90%	<10%	10-50%	10-50%
Advanced oxidation processes*	50-90%	50-90%	50-90%	50-90%	50-90%	50-90%	50-90%	10-50%	10-50%	50-90%
Granular activated carbon	>90%	50-90%	>90%	>90%	>90%	>90%	>90%	10-50%	10-50%	50-90%
Ultrafiltration/ powdered activated carbon	>90%	50-90%	>90%	>90%	>90%	>90%	>90%	10-50%#	50-90%#	50-90%
Nanofiltration	>90%	>90%	>90%	>90%	>90%	>90%	>90%	>90%#	>90%#	>90%
UV**	no data	>90%	>90%	no data	>90%	no data	no data	no data	no data	>90%
Chlorination	50-90%#	>90%#	50-90%	<10%	<10%	<10%	<10%	<10%#	<10%#	<10%#
Chlorine dioxide	50-90%	>90%	>90%	<10%	<10%	<10%	<10%	<10%	<10%	<10%

$?_x$ suspended solids retention time

* advanced oxidation processes based only on an OH radical is considered (e.g. UV/H_2O_2)

** UV dose about 100 times higher than that used for drinking water disinfection (typically 40,000 compared to 400 mJ cm^{-2})

predicted, based on expert knowledge

5 Amounts Present in the Aquatic Environment

Where pharmaceutical compounds have been reported to occur in surface waters their concentrations are generally very low, in the ng l^{-1} to µg l^{-1} (ppt – ppb) range. It has been noted that even for biodegradable substances, the daily introduction of quantities of drugs from any given STW into receiving waters could result in sustained concentrations in the receiving water course (Daughton and Ternes, 1999). The concentrations in ambient waters are very much dependent on the share of treated wastewater discharge to the receiving waters and therefore of the dilution of the wastewater that occurs. Concentrations of pharmaceuticals in different EU surface waters are comparable to each other when considering the share of treated wastewater discharged into the river due to different dilution factors. For most EU countries wastewater is expected to be diluted between 10 and 100 times in the receiving waters. The dilution factor is a crucial parameter in order to be able to compare different studies and to predict environmental concentrations of pharmaceuticals from amounts used (Alder et al., 2006).

5.1 UK

Ashton et al. (2004) carried out a monitoring programme in the UK focusing on 11 pharmaceutical (or metabolite) compounds. The results showed that a range of pharmaceutical compounds from different therapeutic classes were present in both STW effluents and receiving waters in England. The values reported were within the same range as those reported in continental Europe and the US where more extensive monitoring has been conducted. They also found some evidence to suggest that usage data are positively associated with concentrations of pharmaceuticals measured in effluent and in surface waters below STWs. The anti-inflammatory pharmaceutical ibuprofen was determined at significantly higher concentrations than any of the other targeted pharmaceutical compound. Ibuprofen was regularly found in STW effluents at a median concentration ~3 µg l^{1}. In the EA study (Roberts and Thomas 2006) only paracetamol, of the pharmaceuticals monitored which appear in the top 50 bu usage, was not detected in any of the effluent or receiving water samples collected. However, Paracetamol has been reported in UK waters at a concentration of 555 ng.l^{1} by Bound & Voulvoulis, 2006. Table 5.1 gives details of the pharmaceuticals that have been found in the UK aquatic environment and in drinking water.

Table 5.1 Median (maximum) measured concentrations of pharmaceuticals in the UK aquatic environment in ng l^{-1}.

Name	Concentration in STW Effluent	Reference	Concentration in stream or river waters	Reference
Bleomycin	11-19	Aherne et al., 1990	Nd-17	Aherne et al., 1990
Clotrimazole	14 (27)	Roberts & Thomas, 2006	21 (34)	Roberts & Thomas, 2006
			7 (22)	Thomas & Hilton, 2004
Diclofenac	424 (2349)	Ashton et al., 2004	< LOQ (568)	Ashton et al., 2004
	289 (598)	Roberts & Thomas, 2006	< LOQ	Roberts & Thomas, 2006
			< LOQ (195)	Thomas & Hilton, 2004
Dextropropoxyphene	195 (585)	Ashton et al., 2004	58 (682)	Ashton et al., 2004
	37 (64)	Roberts & Thomas, 2006	12 (98)	Roberts & Thomas, 2006
			< LOQ (80)	Thomas & Hilton, 2004
Erythromycin	< LOQ (1842)	Ashton et al., 2004	< LOQ (1022)	Ashton et al., 2004
	202 (290)	Roberts & Thomas, 2006	5 (70)	Roberts & Thomas, 2006
Fluoxetine	7.6 – 52.9	Boucard et al., 2006	2 – 43.7	Boucard et al., 2006
Ibuprofen	3,086 (27,256)	Ashton et al., 2004	826 (5044)	Ashton et al., 2004
	2,972 (4,239)	Roberts & Thomas, 2006	297 (2370)	Roberts & Thomas, 2006
			48 (930)	Thomas & Hilton, 2004
Mefenamic acid	133 (1440)	Ashton et al., 2004	62 (366)	Ashton et al., 2004
	340 (396)	Roberts & Thomas, 2006	< LOQ	Roberts & Thomas, 2006
			< LOQ (196)	Thomas & Hilton 2004

Name	Concentration in STW Effluent	Reference	Concentration in stream or river waters	Reference
Norfluoxetine	5.2- 30.7	Boucard et al., 2006	4.5 – 83.0	Boucard et al., 2006
Paracetamol	<20	Roberts & Thomas, 2006	555	Bound & Voulvoulis, 2006
Propanolol	76 (284)	Ashton et al., 2004	29 (215)	Ashton et al., 2004
	304 (373)	Roberts & Thomas, 2006	61 (107)	Roberts & Thomas, 2006
			< LOQ (56)	Thomas & Hilton, 2004
Sulphamethoxazole	< LOQ (132)	Ashton et al., 2004	< LOQ (< LOQ)	Ashton et al., 2004
Tamoxifen	< LOQ (42)	Ashton et al., 2004	< LOQ (<LOQ)	Ashton et al., 2004
Tetracycline			?1000	Watts et al., 1983
Theophylline			?1000	Watts et al., 1983
Trimethoprim	70 (1288)	Ashton et al., 2004	< LOQ (42)	Ashton et al., 2004
	271 (322)	Roberts & Thomas, 2006	9 (19)	Roberts & Thomas, 2006
			7 (569)	Thomas & Hilton, 2004

Nd = not detected
LOQ = limit of quantification

5.2 Rest of Europe

There are a number of papers and review articles that describe the presence of pharmaceuticals and x-ray contrast media in the aquatic environment in continental Europe (Heberer, 2002; Hernando et al., 2006; Ternes, 1998; Ternes et al., 2005; Zuccato et al., 2005). Table 5.2 gives an example of the types of pharmaceuticals and concentration levels found in five European countries.

Table.5.2 Median (maximum) concentrations found in European surface waters in ng l^{-1} (Ternes et al., 2005)

Compound	Austria	Finland	France	Germany	Switzerland
Bezafibrate	20 (160)	5 (25)	102 (430)	350 (3100)	-
Carbamazepine	75 (294)	70 (370)	78 (800)	250 (110)	30 – 150
Diclofenac	20 (64)	15 (40)	18 (41)	150 (1200)	20 – 150
Ibuprofen	n.d.	10 (65)	23 (120)	70 (530)	n.d (150)
Iopromide	91 (211)	-	7 (17)	100 (910)	-
Roxithromycin	n.d.	-	9 (37)	< LOQ (560)	-
Sulphamethoxazole[1]	n.d.	-	25 (133)	30 (480)	-

n.d. non detectable (< detection limit)[1] includes the human metabolite N^4 –acetyl-sulfamethoxazole

6 Illegal ('Recreational') Pharmaceuticals

Although information on illegally used drugs (sometimes known as recreational drugs and drugs of dependence) is more difficult to obtain, data are beginning to emerge as a consequence of studies of the presence of metabolites of recreational drugs in European rivers (Zuccato et al., 2005a) and STWs (Castiglioni et al., in press). The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has been working with the Member States of the EU for several years and has developed a comprehensive picture of trends in recreational drug use (EMCDDA, 2005). Illegal drug use in the general population is assessed through surveys, which provide estimates of the proportion of the population that has used drugs over defined periods of time: lifetime use (experimentation), last 12 months' use (recent use) or last 30 days' use (current use).

In 2004, the EMCDDA was notified by Member States of six new synthetic drugs, bringing the total number of monitored substances to more than 25. These include ring-substituted phenethylamines, tryptamines and piperazines. Table 6.1 lists the most frequently used illegal drugs.

Table 6.1 Most frequently used illegal drugs

Compound		Molecular Formula
Common name	**Chemical name**	
Amphetamine		$C_9H_{13}N$
Cannabis	tetrahydrocannabinol	$C_{21}H_{30}O_2$
Cocaine	methylbenzoylecgonine	$C_{17}H_{21}NO_4$
Ecstasy	MDMA (N-methyl-3, 4-methylenedioxyamphetamine)	$C_{11}H_{15}NO_2$
GHB	4-hydroxybutanoate	$C_4H_8O_3$
Heroin	diamorphine	$C_{21}H_{23}NO_5$
Ketamine		$C_{13}H_{16}ClNO$
LSD		$C_{20}H_{25}N_3O$
Magic mushroom	Psilocybin	$C_{12}H_{17}N_2O_4P$

Amphetamines

Amphetamines is used as a generic term to describe a number of chemically related drugs which stimulate the central nervous system. The most commonly available is amphetamine but levels of methamphetamine use are increasing. Until recently amphetamines were the second most commonly used illegal substance after cannabis but recent trends suggest that for many countries ecstasy use is the second most prevalent. The average retail purity of amphetamine in 2003 ranged from 7.5% (Germany) to 50% (Norway) (EMCDDA, 2006).

Cannabis

Cannabis is the most commonly used illegal drug in Europe. The potency of cannabis products is determined by their content of tetrahydrocannabinol (THC), the primary active ingredient. Data for 2003 indicates that the THC content of cannabis resin at the retail level ranged from 1% to 25%, while herbal cannabis potency ranged from 1% to 20% (the higher figure relating to home-grown cannabis) (EMCDDA, 2006).

Cocaine

Compared with heroin, the average purity of cocaine at consumer level is high, varying in 2003 from 32% to 83%.

Ecstacy
The most common member of the ecstasy group of drugs is 3,4-methylenedioxymethamphetamine (MDMA), but other related analogues are also sometimes found in ecstasy tablets. The MDMA content of ecstasy tablets can vary greatly from batch to batch both between and within countries, with the average MDMA content ranging from 54 to 78 mg per tablet (EMCDDA, 2006).

GHB and Ketamine
The limited prevalence data available on gamma-hydoxybutanoate (GHB) and ketamine suggest that use of these substances has stabilised at low levels in most countries. Studies of high-prevalence populations suggest that even among regular recreational drug users both of these drugs may be less commonly used than other substances such as amphetamines, ecstasy, LSD and hallucinogenic mushrooms (EMCDDA, 2006).

Heroin
In Europe, heroin occurs in two forms: the commonly available brown heroin, its chemical base form, and the less common salt form, white heroin. The average purity of brown heroin at street level in the EU varied from 6% to 40%, and for white heroin 6% to 70% (EMCDDA, 2006).

LSD
Historically, lysergic acid diethylamide (LSD) has been by far the best-known hallucinogenic drug, but overall consumption levels have been low and somewhat stable for a considerable time. LSD is manufactured and trafficked to a much smaller extent than other synthetic drugs. Since 2002, Germany has been the country seizing the largest quantities of LSD per year, followed by the United Kingdom (EMCDDA, 2006).

Psilocybin
Recently, evidence of increased availability and use of naturally occurring hallucinogenic substances, hallucinogenic mushrooms in particular, has emerged (EMCDDA, 2006). The availability of hallucinogenic mushrooms appears to have increased since the late 1990s, when they began to be marketed alongside other 'natural' products in 'smart shops' in the Netherlands and elsewhere. Psilocybin (also known as psilocybine) is a psychedelic alkaloid of the tryptamine family and is the active hallucinogenic compound found in psilocybin mushrooms.

An indirect indicator of the supply and availability of drugs in any one country is the number of drug seizures that take place. However, the seizure rate will be influenced by law enforcement resources, priorities and strategies, making accurate comparisons between countries difficult. The following reviews the readily available information on the usage of illegal drugs.

6.1 UK Usage

An estimated 25 – 35 tonnes of heroin enters the UK annually. The estimate for cocaine powder entering the UK each year is 35 – 45 tonnes. This supplies both the

cocaine powder and crack cocaine markets. Crack cocaine is rarely imported, but is produced in the UK from cocaine powder. The UK is the third highest consumer of ecstasy in the world Consumption has been estimated at between 500,000 and 2,000,000 tablets per week. The amount of active ingredient in ecstasy has fallen from 100 mg per tablet in 2000 to 65 mg in 2004, and some manufacturers have added ingredients, such as ketamine (SOCA, 2006).

Table 6.2 shows the quantity of drug seizures in England and Wales for 2004; Table 6.3 the purity of the drugs seized and Table 6.4 the estimated number of people who have taken drugs, by type 'recently' and 'currently' in 2005/06. In general, the purity from HM Revenue and Customs seizures is higher than that of the police force seizures, reflecting the fact that their seizures will tend to be made higher in the supply chain and before 'cutting' occurs.

Table 6.2 Quantities of drugs seized, England and Wales, 2004 (HOSB, 2006)

Drug type	Police Forces (including National Crime Squad	HM Revenue and Customs	Total
	Quantity – kg[1]	Quantity – kg[1]	Quantity – kg[1]
Cocaine	1,266	3,306	4,572
Crack cocaine	130	4	134
Heroin	1130	978	2108
LSD	6,194	30,031	36,225
Ecstasy-type drugs	1,676	2,973	4,649
Methadone	59	-	59
Amphetamine	930	276	1,206
Cannabis – herbal	2,789	18,595	21,384
Cannabis – resin	21,675	40,387	62,062
Cannabis – plants	88,674	-	88,674

[1] Quantities for LSD and ecstasy-type drugs are in thousands of doses; cannabis plants = number.

Table 6.3 Average purity of drug seizures in the UK analysed by the Forensic Science Service by drug type and agency for 2003 and 2004 (HOSB, 2006)

Drug	Authority	Purity %	
		2003	2004
Amphetamines	HM R&C	40.0	30.0
	Police	11.0	9.0
Cocaine	HM R&C	69.8	67.9
	Police	50.5	42.6
Crack cocaine	HM R&C	75.5	80.1
	Police	69.5	63.5
Heroin	HM R&C	36.5	45.4
	Police	32.8	39.9

Table 6.4 Estimated numbers of 16 – 59 year olds in England and Wales who have taken drugs in the last year and in the last month, 2005/06 (British Crime Survey, 2006).

Drug	Used last year	Used last month
Cocaine powder	769,000	368,000
Crack cocaine	53,000	25,000
Ecstasy	502,000	216,000
LSD	83,000	25,000
Psilocybin (magic mushrooms)	302,000	68,000
Heroin	39,000	23,000
Methadone	33,000	24,000
Amphetamines	426,000	176,000
Cannabis	2,775,000	1,644,000

Notes: estimates are derived by multiplying the prevalence rate by the estimated population aged 16 – 59 in England and Wales
The figures are calculated using population estimates provided by the Government Actuarial Service

A report produced by the Research, Development and Statistics Directorate (Bramley-Harker, 2001) proposed a methodology for estimating the size of the market for drugs in the UK, which was based upon prevalence and consumption patterns of different types of drug user. Table 6.5 shows the estimates that were derived using 1998 data from the British Crime Survey. However, these estimates should be treated with caution as they are based on experimental methodology that the author considered required refinement.

Table 6.5 Estimates of the size of the UK market for illicit drugs 1998 (Bramley-Harker, 2001)

Drug	'Street quantity'[1] – kg
Amphetamines	25,772
Cannabis	486,224
Cocaine	4,582
Crack cocaine	18,174
Ecstasy	26,786,000 (tablets, not kg)
Heroin	31,257

[1] estimates based on 'street quantity' as purity of substance not known

A report in the Sunday Telegraph[4] outlined the results of a study carried out to measure levels of cocaine in sewage influent and effluent samples that discharge into the River Thames. The reporters extrapolated data from the British Crime Survey, 2003/4 and estimated that Londoners were taking 2,397 doses of 100 mg d^{-1}: the equivalent of 9,588 lines at 25 mg per line. Measured concentrations in the sewage samples indicated that actual cocaine use is far higher, i.e. 37,638 doses of cocaine, equivalent to 150,552 lines consumed in London every day.

6.2 Usage in the rest of Europe

[4] http://www.telegraph.co.uk/news/main.jhtml?xml=/news/2005/11/06/ncoke106.xml

Since direct estimation of illegal drug use is difficult, in some cases it has been estimated indirectly. Zuccato et al. (2005) investigated the levels of cocaine, and its main urinary metabolite (benzoylecgonine (BE)), in water samples taken from the River Po and four urban STWs situated in different Italian cities. They then estimated drug usage based on 'field' evidence by using the following: drug concentration, water flow rate, and population at each site. The largest Italian river, the Po, with five-million people in its catchment basin, carried the equivalent of approximately 4 kg cocaine per day. This would imply an average daily use of at least 27 ± 5 doses (100 mg each) for every 1000 young adults, an estimate that greatly exceeds official national figures. Data from wastewater treatment plants serving medium-size Italian cities were consistent with this figure. The mean concentration of cocaine in the River Po was 1.2 (± 0.2) ng l^{1} and for the BE metabolite, 25 (± 5) ng l^{-1}. Concentration in the STW influent ranged between 42 – 120 ng l^{1} cocaine and 390 – 750 ng l^{-1} BE metabolite. Their indirect estimation from analytical results would suggest that cocaine use greatly exceeds that quoted in official statistics.

In another study influent and effluent samples were collected from two STWs, one in Italy, one in Switzerland, and analysed for a series of illegal drugs (Castiglioni et al., in press). The results are given in Table 6.6.

Table 6.6 Concentrations (ng l^{-1}) of illicit drugs and their metabolites in influents and effluents of the (Milan) and Lugano STWs (Castiglioni et al., in press).

	Milan, Italy		**Lugano, Switzerland**	
	influent	**effluent**	**influent**	**effluent**
	Mean ± SD ng l^{-1}	**Mean ± SD ng l^{-1}**	**Mean ± SD ng l^{-1}**	**Mean ± SD ng l^{-1}**
Cocaine and metabolites				
Cocaine	421.4 ± 83.3	< LOQ	218.4 ± 58.4	10.7 ± 3.2
Benzoylecgonine	1132.1 ± 197.2	< LOQ	547.4 ± 169.4	100.3 ± 28.6
Norbenzoylecgonine	36.6 ± 7.8	< LOQ	18.8 ± 5.6	7.5 ± 2.9
Norcocaine	13.7 ± 5.3	< LOQ	4.3 ± 0.9	0.7 ± 0.5
Cocaethylene	11.5 ± 5.	< LOQ	5.9 ± 2.6	0.2 ± 0.5
Morphine and metabolites				
Morphine	83.3 ± 11.8	< LOQ	204.4 ± 49.9	55.4 ± 11.1
6-acetylmorphine	11.8 ± 8.5	< LOQ	10.4 4.8	< LOQ
Morphine-3ß-D-glucuronide	2.5 ± 7.1	< LOQ	18.1 30	< LOQ
Amphetamines				
Amphetamine	14.7 ± 0.6	< LOQ	< LOQ	< LOQ
Methamphetamine	16.2 ± 7.1	3.5 ± 2	< LOQ	< LOQ
MDA	4.6 ± 7.3	1.1 ± 1.5	< LOQ	0.9 ± 1.9
MDMA	14.2 ± 14.5	4.4 ± 3.7	13.6 ± 12.6	5.1 ± 3
MDEA		< LOQ	< LOQ	< LOQ
Methadone and metabolite				
Methadone	11.6 ± 1.7	9.1 ± 0.5	49.7 ± 9.6	36.2 ± 2.8
EDDP	19.8 ± 3.1	22.6 ± 0.6	91.3 ± 19.2	72.1 ± 8.7
Cannabis				
11-nor-9-carboxy-	62.7 ± 5	< LOQ	91.2 ± 24.7	7.2 ± 3.7

	Milan, Italy		Lugano, Switzerland	
	influent	**effluent**	**influent**	**effluent**
	Mean ± SD ng l^{-1}	**Mean ± SD ng l^{-1}**	**Mean ± SD ng l^{-1}**	**Mean ± SD ng l^{-1}**
?9-THC				

In influents benzoylecgonine and cocaine were the most abundant. Morphine, which was found at relatively high concentrations (80-200 ng l^{1}), may have come from clinical use of morphine or codeine, but might also have come from illicit use of heroin. 6-Acetylmorphine, a metabolite of heroin, was detected in influents from both plants suggesting widespread consumption of heroin. Morphine is excreted in urine mainly as glucuronide metabolites, but morphine-3ß-D-glucuronide was detected at low concentrations thus suggesting cleavage of the conjugated molecule in wastewater. Concentrations of drugs and metabolites were lower in effluents than in influents, particularly in the Milan plant, probably reflecting degradation or sorption of these substances in STWs.

6.3 Estimation of Illegal Drug Usage in the UK for Modelling

Estimation of the amounts of drugs used in the UK is difficult since the available information usually relates to seizures by the Police or HM Revenue and Customs and only provides information on the amount removed from potential use. However, available data suggest that the amount of illegal drugs seized in the UK represents between 5 and 20% of the total amounts in circulation and an average factor of 12% was used for the estimates. The estimates were made by combining the quantities seized in the UK by Police Forces and HM Revenue and Customs, modifying this by an average purity factor (these range from 11.5% for herbal cannabis to 72% for crack cocaine) and multiplying by 100/12. A slightly different approach was used for LSD and ecstasy where the information on seizures relates to number of doses rather than weight and conversion to weight was done using Home Office information on the number of doses equivalent to one kilogram of active substance.

Table 6.7 Estimation of Illegal Drug Usage in the UK in 2004

Seizure Amounts	Police Forces (including National Crime Squad)	HM Revenue and Customs	Total from weight	Total from 'doses'	Purity Factor (%)	Estimate of total active ingredient used in 2004		
Drug type	**Quantity kg[1]**	**Quantity kg[1]**	**Quantity kg[1]**	**Quantity kg**		**Quantity kg**	**Quantity in mg**	**Totals in mg**
Cocaine	1,266	3,306	4,572		58	21983.70	21983700000	
Crack cocaine	130	4	134		72	805.68	805675000	22789375000
Heroin	1130	978	2108		39	6789.52	6789516667	6789516667
LSD[1]	6,194	30,031	36,225	3,6225	na[2]	301875.5	30187500000	30187500000
Ecstasy-type drugs[1]	1,676	2,973	4,649	1,162	na[2]	9685.42	9685416666	9685416666
Methadone	59	-	59		na[3]	491.67	491666666.7	491666666.7
Amphetamine	930	276	1,206		22.5	2261.25	2261250000	2261250000
Cannabis – herbal	2,789	18,595	21,384		11.5	20493.00	20493000000	
Cannabis – resin	21,675	40,387	62,062		13	67233.83	67233833333	87726833333

1) Quantities for LSD and ecstasy-type drugs are in thousands of doses
2) Purity factor not relevant since dose per kg data is corrected for purity
3) Purity factor not relevant as the methadone total is based on active ingredient in the liquid seized.

7 Estimating Concentrations of Pharmaceuticals in Drinking Water

7.1 Previous Approaches

7.1.1 Evaluation of potential for pharmaceuticals and illegal drugs to reach raw and treated waters

There are very many approaches that could be used to calculate pharmaceutical PECs in surface water from their use data. These include the use of detailed environmental models such as EUSES (EC, 2003), GREAT-ER (http://www.great-er.org/pages/home.cfm), and SimpleBox (Den Hollander et al., 2003), but these all require large amounts of information on each substance and scenario that is to be modelled. For the pharmaceuticals and scenarios that are of interest for this project the required data are not available and default values would have to be used. In view of this and because the available data and understanding of the fate and behaviour of pharmaceuticals in the environment involves such high uncertainties, use of complex models is not justified for the current study.

A simpler and more appropriate approach that can be used for calculating PECs in wastewaters is based on a model proposed by the European Medicines Evaluation Agency (EMEA, 2005b) for risk assessment of pharmaceuticals in the environment. The calculation uses a simple equation based on usage, population and wastewater production and can be modified to generate the PEC_{dw} which provides a likely concentration for the pharmaceuticals in drinking waters (Equation 7.1). The extent of removal, R, during sewage treatment can be adjusted as required, as can the dilution factor (D) for STW effluent in receiving waters and the extent of removal, W, in drinking water treatment.

Equation 7.1

$$PECdw = \frac{A \times (100-R) \times (100-M) \times (100-W)}{365 \times P \times V \times D \times 100 \times 100 \times 100}$$

Where:

PEC_{dw} is the predicted concentration in drinking water ($mg.l^{-1}$);
M is the percentage metabolised in humans
A is the amount of active ingredient used per year in the catchment ($mg\ yr^{-1}$);
R is the removal rate in sewage treatment (set as a percentage, see below);
P is the population under consideration (i.e. for the UK; 59600000 or the population equivalent [PE] for each catchment scenario);
V is the volume of waste water produced per capita per day (assumed to be 200L)
W is the removal rate in the appropriate DWTW scenario and
D is the dilution factor in the environment (derived from the 5%ile flow rate)

The modified approach takes account of the findings from the literature review, in particular the percentage of the dose which is excreted unchanged and the chemical form in which different types of pharmaceuticals are excreted. However, it has been noted that previous studies suggest that only a very small percentage of the dose taken is metabolised for many substances and that pharmaceuticals excreted as conjugates (e.g., glucoronides and sulphates) can be converted back to the active ingredient in sewers and sewage treatment works (Andersen et al., 2003). Consequently for the worst case modelling it was assumed that there was no metabolism.

This simple approach has been used previously for environmental risk assessment of human pharmaceuticals and has been used for studies prioritising the risk of pharmaceuticals in UK surface waters (Watts et al., 2005). It lends itself readily to investigating, consistently, many pharmaceuticals with a range of different scenarios for fate and behaviour in the environment and treatment processes.

Ternes et al. (2005) concluded that a rough prediction of the pharmaceutical concentration in raw wastewater can be made using the quantity of pharmaceuticals sold.

Bendz et al. (2005) used the principles given in the EU environmental risk assessment for new human pharmaceuticals to calculate theoretical concentrations of a number of pharmaceuticals in the influent to a selected STW, which they then compared to actual concentrations measured. The results are given in Table 7.1. They found that lower concentrations of gemfibrozil, trimethoprim and atenolol and higher concentrations of carbamazepine were measured compared to the theoretical values. For diclofenac, naproxen and metoprolol the measured and theoretical concentrations were very similar. Possible reasons for the discrepancies were seasonal variations in annual consumption rates and variations in excretion rates.

Table 7.1 Comparison between the theoretical and measured concentrations of pharmaceuticals in the influent to a STW (Bendz et al., 2005)

Pharmaceutical	Excretion	Theoretical concentration µg l^{-1}	Measured concentration µg l^{-1}
Gemfibrozil	50% (as glucorinide)	3.25	0.71
Diclofenac	15% unchanged, < 1% as conjugates	0.32	0.16
Ibuprofen	1-8% unchanged, 14% as glucuronide	0.46-3.6	3.59
Naproxen	65% as acyl-glucoronide	5.72	3.65
Propranolol	< 1% unchanged	0.01	0.05
Metoprolol	3-10% unchanged	0.18-0.59	0.16
Atenolol	90%	3.38	0.03
Trimethoprim	60%	0.37	0.08
Carbamazepine	1 – 2% unchanged	0.11	1.68

7.1.2 Fate and concentrations in STWs

Biodegradation is an important removal process during wastewater treatment. Yu et al. (2006) carried out a series of short-term biodegradation tests using diluted waste activated sludge as the medium and then compared the results against those generated using BIOWIN software which is part of the EPIWIN suite available from the USEPA (http://www.epa.gov/opptintr/exposure/pubs/episuite.htm). Using different statistical approaches BIOWIN calculates the probability of rapid or slow biodegradation for a given chemical, under aerobic conditions with mixed cultures of microorganisms, dependent on its structure. Yu et al. (2006) found that the non-linear BIODEG program produced the best fit with the experimental data. However, some inconsistencies exist between the predicted and experimental biodegradation results. Boethling et al. (2004) found that for pharmaceuticals BIOWIN 5 and 6 were more accurate than Biowin3 in predicting ready biodegradability, with 82.5% (52/63), 87.3% (55/63), and 76.2% (48/63) correctly classified, respectively The BIOWIN data and the physicochemical properties of the drugs were used by the EPIWIN software in a simple Mackay fugacity model to provide estimates of removal in STW.

7.2 Estimates from the current study

7.2.1 Drinking Water Modelling scenarios

Five DWTW scenarios based on real UK situations have been modelled that were based as closely as possible on the following specifications.

A) a DWTW with normal treatment (e.g. coagulation settlement and rapid gravity filtration ;RGF) abstracting from a catchment with high sewage input, i.e. low treatment and poor dilution.

B) a DWTW with more advanced treatment (e.g. ozone and Granular Activated Carbon; GAC)but abstracting from a similar catchment to A.

C) a DWTW with normal treatment (e.g. coagulation settlement and RGF) abstracting from a catchment with low sewage input, i.e. high treatment, high dilution.

D) a DWTW with more advanced treatment (e.g. ozone and GAC) abstracting from a similar catchment to C.

Suitable DWTWs were identified for three of the above scenarios and hence our models accurately reflected number of consumers, typical flows and treatment efficiency over the seasonal cycle, rather than using default values. It was difficult to obtain a catchment that matched Scenario A since catchments with high sewage input tend to have works with significantly more than just basic DWT processes. Consequently two catchments were modelled for Scenario A that came as close to meeting that specification as was possible.

In view of the parameter variability associated with this aspect of the project a probabilistic analysis using Crystal Ball software was used for the drugs that showed the lowest exposure ratios (see below) for the worst case scenario. This allowed for

the examination of the worst case results in more detail and assessment of the effect of variability of model input parameters

7.2.2 Fate and concentrations in receiving STWs

The PEC_{dw} equation enables the losses during sewage treatment to be estimated by using a removal percentage, and for different scenarios to be studied. The removal percentages for different treatment types and substance types have been estimated from the available literature data, data in the report of the POSEIDON project (Ternes et al., 2005), and other relevant papers identified in the preceding sections. Where data were not available for the substances of interest a conservative approach was used that assumed no removal in STW for the worst case (deterministic) model estimates. For the probabilistic modelling a QSAR-based approach was used to estimate removal in STWs as described in the following paragraph.

The modelling of likely losses from degradation and sorption during sewage treatment was assessed either by using the data collected from the scientific literature and presented in previous sections of this report or by the estimates from simple Mackay fugacity model (Mackay, 1991 & 1996) incorporated in the SRC EPIWIN software. All calculations were based on the structural type of the pharmaceutical and the way in which that influenced its behaviour in the STW. The estimated removal rates were applied to all of the scenarios described above.

7.2.3 Fate and concentrations in DWTWs and final potable water

The modelling of likely losses from degradation, sorption and advanced treatment options was estimated for different structural types of pharmaceuticals either by using relevant data presented in the preceding sections or default values. The estimated removal rates were applied as appropriate to all of the scenarios described above.

Concentrations of priority substances in drinking water were predicted using a simple mass balance spreadsheet modelling approach. The PEC_{dw} equation enables the losses during drinking water treatment to be estimated by using a removal percentage for the different scenarios studied. The removal percentages for different treatment types and substance types have been estimated from the available literature data identified in the preceding sections. Where data were not available for the substances of interest a conservative approach was used that assumed no removal in DWTW for the worst case model estimates. In the probabilistic model, a range of removal was used for the DWTWs with advanced treatment processes, i.e. GAC and ozonation, as most pharmaceuticals that have been examined are significantly removed by these processes in combination.

7.2.4 Estimated Potential Worst Case Concentrations in Drinking Waters

The initial deterministic modelling approach was to use a worst case situation where the following assumptions were made in the simple mass balance model shown in Equation 7.1:

1. The total UK usage per year [A] for each of the medically used pharmaceuticals was set at twice the value estimated from the IMS data to allow for uncertainties in the data (see section 3.1). For most pharmaceuticals this will amount to a large overestimate of annual usage

2. There was no metabolism [M = 0%] after taking the drug, i.e. all of the amount of pharmaceutical and illegal drug used was excreted unchanged. Many pharmaceuticals are significantly metabolised and for those this will result in an overestimate.

3. There was no loss in STWs [R = 0% as a default] unless there was published data providing information on losses in which case the minimum percentage removal value was used. Since the losses in STW processes of most of the pharmaceuticals have not been assessed this will result in an overestimate for those that have not been examined experimentally but which would be removed significantly.

4. The river flow rate used to estimate the dilution factor [D] was the 5%ile value from the data supplied covering several years of flow measurements. This represents very low flow conditions experienced for only a short period in most years and hence will result in an underestimate of the dilution factor for most situations.

5. There was no loss or further dilution during transport in rivers between STW discharge points and DWTW intakes.

6. There was no loss in DWTWs [W = 0% as a default] unless there was published data providing information on losses, in which case the minimum percentage removal value was used. Since the losses in DWTW processes of most of the pharmaceuticals have not been assessed this will result in an overestimate for those that that have not been examined experimentally and are removed significantly.

As a consequence of the assumptions made, this is a very worst case assessment and the concentrations estimated will be the highest that could be expected under the most extreme of conditions. The model shown in equation 7.1 and with the assumptions made above was used to estimate the possible concentrations in drinking water in five typical UK catchments for all of the 394 pharmaceuticals, nine illegal drugs, two combined groups of pharmaceuticals with similar modes of action (NSAIDS and Statins) and one pharmaceutical used in a pandemic situation (Tamiflu). For all of the drugs, the worst case (i.e. highest concentrations) was observed for scenario B (see table 7.4) as a consequence of the high catchment population and sewage input. Hence data are only presented for that scenario, but the full results for all of the drugs and scenarios are available in a spreadsheet.

7.3 Assessment of the Significance of the Estimated Concentrations in Potable Water

Pharmaceuticals provide a significant benefit to individuals and society. They have played a vital part in improving public health over the past 50 years when there have been remarkable developments in the range of pharmaceuticals available and the

diseases and conditions that they are used to treat. However, pharmaceuticals are required to be licensed and in order to achieve a license they have to undergo rigorous safety testing. Once on the market there is a system for reporting adverse side effects. By definition pharmaceuticals are administered at doses that will have an effect in the body, either in destroying infections or on physiological processes. There will also be some individuals that show side effects and there is usually a balance between the risks and the benefits. Some pharmaceuticals, such as the anti-asthma drug cromoglycate (also known as Cromolyn or Intal, CAS RN 16110-51-3) have very few adverse reactions while others such as the powerful anti-cancer drugs invariably show adverse reactions. However, this means that there is significant experience and data on the effects of pharmaceuticals in humans at a range of doses.

Pharmaceuticals are usually metabolised to some extent in the body and may be excreted as both the parent compound and as metabolites, which generally do not show the same level of activity. However, there are some compounds that are metabolised from a physiologically inactive form to an active form before being further metabolised. Pharmaceuticals are administered in several ways, orally, by injection, as suppositories, in drops, by inhalation and in creams, ointments and lotions. Those used topically will also enter the sewage system as a consequence of being washed from the skin and clothing.

7.3.1 Approach for assessing the risks of pharmaceuticals in relation to drinking water

It would not be appropriate to carry out a risk assessment of pharmaceuticals by determining concentrations and assessing these against health-based values determined using traditional toxicological approaches such as those used by the World Health Organisation in their Guidelines for Drinking Water Quality. The numbers of pharmaceuticals in use are much greater and the data on toxicology are confidential and have not been reviewed in such a way as to expedite the development of health-based values. In addition pharmaceuticals are required to produce a beneficial effect at doses below those that cause significant toxicity. It is therefore more appropriate to determine an appropriate dose and calculate the margin of exposure (MOE) between the concentration in drinking water and that dose. There is some difficulty in determining a suitable dose since a range of doses are usually used for each substance and some pharmaceuticals are not recommended for some sectors of the population. In particular there are few data on infants and small children, a fact which is exercising those in paediatric medicine when determining the suitability and dose of medicines in this field.

Approaches that have been used previously in assessing the potential risks associated with pharmaceuticals in drinking water is to use either the median dose or the lowest clinically effective dose, also referred to as the minimum therapeutic dose (MTD). Either approach is potentially valid. For example, the Australian draft guidelines on reuse of wastewater use the median dose (NWQMS, 2007). The approach used in the Australian guidelines was to calculate surrogate TDIs (S-TDIs) for pharmaceuticals by dividing the lowest recommended therapeutic dose (as mg kg^{-1} day^{-1}) by safety factors, as follows:

- *all pharmaceuticals*— a safety factor of 100 is applied, comprising 10 for differences in response between humans (intraspecies variation) and 10 for the lowest therapeutic dose not being a no-effect level.
- *cytotoxic drugs* — an additional safety factor of 10 is applied due to the higher level of toxicity associated with these compounds.
- *hormonally active steroids* —an additional safety factor of 10 is applied on the grounds that their potential effects on hormonal function and fertility is unwanted in those not being treated.

For the purposes of the current evaluation a margin of 1000 has been used for all substances in order to take a more precautionary approach in determining the priority substances for further examination by probabilistic modelling. This additional factor has been used previously in assessing the risks of individual pharmaceuticals in drinking water in the UK and has been accepted as being precautionary by the medical profession. It also provides an additional reassurance with regard to infants and young children.

In this current evaluation, 396 pharmaceuticals and 11 illegal drugs have been considered. It was not possible to determine the dose for all of these pharmaceuticals as a small number are topically applied and the dose is uncertain. For these an assumed minimum therapeutic dose of 10 mg was used, which is highly conservative but provides a basis for the initial comparison with the modelled concentrations in drinking water. In some other cases it was not possible to determine the dose because the required information was not readily available and a very precautionary MTD value of 1 mg was used, e.g. this was the case with all of the illegal drugs. A number of sources were used both to determine the lowest dose on a daily basis and to provide assurance by comparing several sources. These sources included the internet database RxList (http://www.rxlist.com/script/main/hp.asp), the British Medical Association New Guide to Medicines and Drugs (BMA, Dorling and Kindersley, 2001) and the WHO Model Formulary (WHO, 2004). It was not possible to gain access to the prescribing manual, MIMS on line, although this is the most comprehensive source of information. The minimum single therapeutic dose was compared against the worst case from the modelled concentrations. No allowance was made for the consumption of more than 1 litre of drinking water per day or for consumption by infants or children because this approach was used to determine the 20 highest risk substances for closer examination, i.e. those with the smallest margin between dose and modelled exposure and these are shown in Table 7.4. The reason for this was that for the majority of the pharmaceuticals, at least two (minimum) therapeutic doses will be taken per day and for some, for example the NSAIDS, more than two doses will be taken in a day.

Combinations of pharmaceuticals: Some groups of similar substances do occur and it is appropriate to consider them both individually and as a group since the structure and mechanism of action is similar. These groups include the non-steroidal anti-inflammatory compounds or NSAIDS that include such compounds as ibuprofen, and the statins that are widely, and increasingly, used as lipid lowering drugs. Additionally the most common opioid compounds such as codeine, dihydrocodeine and methadone would also potentially have similar activity, although this would be much more dependent on the individual compound because, unlike the statins and NSAIDS they are of substantially different potency and a simple comparison would

not be appropriate. In order to consider the implications of these similar mode of action compounds, modelling of mixtures of the NSAIDS and statins shown in Tables 7.2 and 7.3 was carried out.

Table 7.2 NSAIDs combined for the Total in the Modelling

NSAIDs	Minimum Therapeutic Dose (mg)	UK Medicines Act*
Aceclofenac	200	PO
Acemetacin	30	PO
Benzydamine	Topical application	PM
Choline	3000	GS
Diclofenac	75	PO, PM & GS
Difunisal	500	PO
Etodolac	600	PO
Felbinac	1000	PO & PM
Fenbufen	600	PO
Fenoprofen	400	PO
Ibuprofen	200	GS
Indometacin	75	PO
Ketoprofen	100	PO
Mefenamic acid	500	PO
Meloxicam	7.5	PO
Nabumetone	1000	PO
Naproxen	500	PO
Piroxicam	20	PO & PM
Tiaprofenic acid	600	PO

Table 7.3 Statins combined for the Total in the Modelling

Statins	Minimum Therapeutic Dose (mg)	UK Medicines Act*
Fluvastatin	20	PO
Pravastatin	10	PO
Rosuvastatin	5	PO
Simvastatin	5	PM

*The UK Medicines Act, 1968 lists 3 types of medicines viz:
- general sales list medicines (GSL),
- pharmacy medicines (P), and
- prescription only medicines (POM).

The status of the drugs in 2004 is given here.

The exposure ratio (or margin of exposure – MOE) was determined by dividing the minimum therapeutic dose by the theoretical maximum (worst case of the five scenarios) intake from drinking water. Only ten substances showed a potential worst case intake from drinking water that was above an intake 1000 fold less than the minimum therapeutic dose. Only four more would be below the 1000 margin if allowance was made for 2 litres consumption. The substances with a factor of less than 1000 are considered in more detail below.

The *NSAIDS total* combines the amounts of 19 anti-inflammatory drugs on the list of 394 pharmaceuticals that were modelled deterministically and is the only

'pharmaceutical' that has an exposure ratio (MOE) below 100. All of the NSAIDs were assumed to have the same mode of action and the minimum therapeutic dose (7.5mg) of the most active NSAID (meloxicam) was used to derive the exposure ratio. Most of the NSAIDs, and especially the ones used in greatest quantities, have minimum therapeutic doses of 100 mg or greater and the use of a median value for the MTD would put the ratio well above 1000. It should be noted that individually, all of the NSAIDs had MOE that were in excess of 5000. Most of the 19 NSAIDS comprising this group (see Table 7.2) were prescription only in 2004, only three were available from a pharmacist, one of which was also available on general sale. Only one NSAID was available solely as a general sale list pharmaceutical, namely ibuprofen which is the one sold in the greatest quantities in the UK.

Cannabis is an illegal drug generally taken mostly by smoking and hence only a fraction of the total amount of the active substances present in the plant material will be inhaled and pass into the blood stream. Since there are no minimum therapeutic dose data available for Tetrahydrocannabinol (THC; one of the major active substances) a default value of only 1 mg was used. The typical THC content of herbal cannabis and cannabis resin varies from 1-25% and a typical 'joint' will also vary in both concentration and weight. Using the average weight of machine-made cigarettes sold commercially, which is between 1 and 1.2 gm, and assuming a weight of 1.1 gm, the THC content would be equivalent to between 11 and 275 mg per cigarette. The content of cannabis in hand-rolled, commercial cigarettes in India is a little less at 250 mg, so the THC content of these would be 2.5 to 62.5 mg per cigarette. THC is also extensively metabolised in humans and will be substantially removed by STW processes. The influence of these removal processes can be seen in the MOE values for the probabilistic modelling below.

Oseltamivir Phosphate (Tamiflu) The low MOE for this pharmaceutical is found only in a very special situation where the drug is being used under pandemic conditions to control or prevent the spread of an outbreak. In this situation some 90% of the population in the catchment area will be receiving the drug and it is unlikely that the presence of about 1/350th of a therapeutic dose ingested from drinking water in these circumstances would be of significance. Tamiflu was authorised for use in the European Union in 2002.

LSD is an illegal drug and as such the accuracy of the estimates of usage are unknown. A very precautionary MTD of only 1 mg was used for the calculation of the exposure (MOE) ratio and the typical 'dose' in the UK is about 100mg from Home Office figures. This drug is extensively metabolised in humans and the amount excreted unchanged is very low. The influence of these removal processes can be seen in the MOE values for the probabilistic modelling below.

Cocaine is also an illegal drug and as such the accuracy of the estimates of usage are unknown. A very precautionary MTD of only 1 mg was used for the calculation of the exposure (MOE) ratio, whereas a 'line' of coke is about 25 mg and four lines may be taken in a day and the content of the active drug can be up to 83%. This drug is extensively metabolised in humans and the amount excreted unchanged is very low. The influence of these removal processes can be seen in the MOE values for the probabilistic modelling below.

Aminophylline is a mixture of theophylline and ethylenediamine which is used as a smooth muscle relaxant. The drug is extensively metabolised in humans and the

amount excreted unchanged is only about 10%. The influence of these removal processes can be seen in the MOE values for the probabilistic modelling below. It was available only on prescription or from a pharmacy in 2004..

Beclometasone is a corticosteroid that is administered by inhalation and acts at the point of contact in the airways. This will not be the route of administration if it is ingested in drinking water and so a simple examination of the exposure would be misleading. The drug is extensively metabolised in humans and the amount excreted unchanged is only about 12%. The influence of these removal processes can be seen in the MOE values for the probabilistic modelling below. It was available on general sale in some formulations and prescription only for others in 2004

Zidovudine is an anti-viral drug. The drug is extensively metabolised in humans and the amount excreted unchanged is only about 12%. The influence of these removal processes can be seen in the MOE values for the probabilistic modelling below. It was prescription only in 2004.

Ecstasy is an illegal drug and as such the accuracy of the estimates of usage are unknown. A very precautionary MTD of only 1 mg was used for the calculation of the exposure (MOE) ratio wheras the typical amount in a tablet is about 65mg based on analysis of seized tablets in the UK. It is only slightly metabolised and up to 90% is excreted unchanged by humans.

Acamprosate is used for treating alcoholism and is only poorly metabolised in humans with more than 99% excreted unchanged. It was prescription only in 2004.

Table 7.4 Top 24 Drugs from Worst Case Deterministic Modelling

Name	Worst Case [Scenario B] PECdw (mg.l^{-1})	Minimum Therapeutic Dose (mg)	Exposure Ratio (MOE) for Worst Case	Comments
Total for NSAIDS	0.0975	7.5	77	Combination of 19 anti-inflammatory
Cannabis (tetrahydrocannabinol)	0.00974	1	103	Illegal drug
LSD	0.00335	1	298	Illegal drug
Oseltamivir Phosphate (Tamiflu)	0.214	52	350	Used under pandemic conditions
Cocaine (methylbenzoylecgonine)	0.00253	1	395	Illegal drug
Aminophylline	0.00231	1	432	Smooth muscle relaxant
Beclometasone	0.000728	0.05	687	Antiasthmatic
Zidovudine	0.000648	0.5	771	Anti-viral
Ecstasy	0.0010754	1	930	Illegal drug
Acamprosate	0.000648	1	963	Alcoholism treatment
Total for Statins	0.00447	5	1118	Lipid lowerers
Nitroglycerin	0.00104	0.15	1154	Vasodilator
Heroin (diamorphine)	0.000130	1	1326	Illegal drug

Name	Worst Case [Scenario B] PECdw (mg.l^{-1})	Minimum Therapeutic Dose (mg)	Exposure Ratio (MOE) for Worst Case	Comments
Simvastatin	0.000754	5	1543	Lipid lowerer
Codeine	0.00324	20	2134	Narcotic analgesic
Ramipril	0.00937	1.25	2172	Diuretic
Lisinopril	0.00224	2.5	2647	Angiotensin converting enzyme inhibitor
Methadone	0.000944	1	2916	Opioid agonist
Furosemide	0.000343	20	3793	Diuretic
Amphetamine	0.00527	1	3983	Illegal drug
Norethisterone	0.000251	0.35	3990	Progesterone derivative
Doxazosin	8.77E-05	1	4455	?-blocker
Bendroflumethiazide	0.000224	2.5	4547	Diuretic
Ciclosporin	0.000550	2	5748	Immunosuppression

The overall picture is reassuring as even in this worst case deterministic model only one exposure ratio is less than 100 and only 10 exposure ratios are less than 1000. A quarter of the substances in the top 24 are illegal drugs and it should be stressed that the accuracy of the estimates of usage for those substances cannot be assessed as it is not possible to obtain accurate information on usage of illegal drugs. Nearly half of the substances in the top 24 substances show exposure ratios in excess of 2000. As might be expected most of the pharmaceuticals in the top 24 are widely used, for example furosemide is a diuretic used to treat oedema that is very widely prescribed in older people.

In view of the large uncertainty associated with the estimated amounts of illegal drugs it is of interest to compare the estimated worst case concentrations in UK drinking waters with measured concentrations in rivers. This can be done using data for cocaine where the concentration in the river Po was reported to be about 1 ng.l^{-1} and that of its major metabolite, benzoylecgonine was about 25 ng.l^{-1} (Zuccato 2005). This compares to the estimated worst case concentration in UK drinking water for Scenario B of about 2500 ng.l^{-1} for cocaine, a factor of 2500 higher than the reported concentration for the river Po. Assuming similar usage of cocaine in the UK and Italy, which is not unreasonable, the large difference in predicted and estimated concentration will reflect differences in the specific catchments and the worst case nature of the UK estimate. Although no specific concentration for cocaine in the river Thames was given in the Sunday Telegraph article (see 6.1 for reference) the calculation suggested that the concentration was equivalent to a daily intake of 2 kg cocaine in the whole London area and this was about half of the quantity associated with the river Po study.

The top 24 pharmaceuticals from the deterministic modelling (shown in Table 7.4) were used for more detailed probabilistic modelling of scenario B that takes into account metabolism in the drug users, losses during sewage treatment and losses during drinking water treatment.

The deterministic MOE values for all of the substances included in this study are tabulated in Annex 2 of this report.

7.3.2 Probabilistic modelling

The initial deterministic modelling assumptions were refined for the probabilistic modelling to provide a more realistic view of the worst case situation. The following revised assumptions were made in the probabilistic modelling, which was still based on the simple model shown in Equation 7.1:

1. The total UK usage per year [A] for each of the medically used pharmaceuticals was the value estimated from the IMS data. For the illegal drugs, where there is no real measure of the accuracy of the estimates, the usage estimate was kept at a fixed value. For Tamiflu, the usage estimate was kept at the single value used in the deterministic model.

2. There was metabolism [M ? 0%] after taking the drug and the range of values used was set as a range from 0% to the value obtained from literature searches.

3. There was loss in STWs [R ? 0%] and the range of values used was set based on the literature reported range, or the QSAR estimated (EPIWIN) removal percentage.

4. The river flow rate used to estimate the dilution factor [D] was the 5%ile value from the data supplied covering several years of flow measurements. This represents very low flow conditions experienced for only a short period in most years and hence will result in an underestimate of the dilution factor for most situations.

5. There was no loss or further dilution during transport in rivers between STW discharge points and DWTW intakes.

6. There was loss in DWTWs [W ? 0%] and the range of values used was set based on the literature reported range or a default range of 50-100%.

The probabilistic modelling used the same model equation as the deterministic model, but selected combinations of input values at random from the ranges of values (assuming a uniform distribution) set for each of the variable parameters and estimated the PEC_{dw} for each combination. This was repeated 10000 times, for each of the substances and each of the five DWTW scenarios to produce a realistic view of the range of concentrations that are likely to be produced in a realistic worst case situation for all of the 24 drugs that produced the lowest exposure ratios.

The figures below show example outputs from the probabilistic modelling for the following:

?? All five of the DWTW scenarios for the Total NSAIDs.

?? The worst case DWTW scenario (scenario B) for all of the substances that have an exposure ratio less than 1000.

Figure 7.1 Outputs from Probabilistic Monitoring for the Five DWTWScenarios for Total NSAIDS

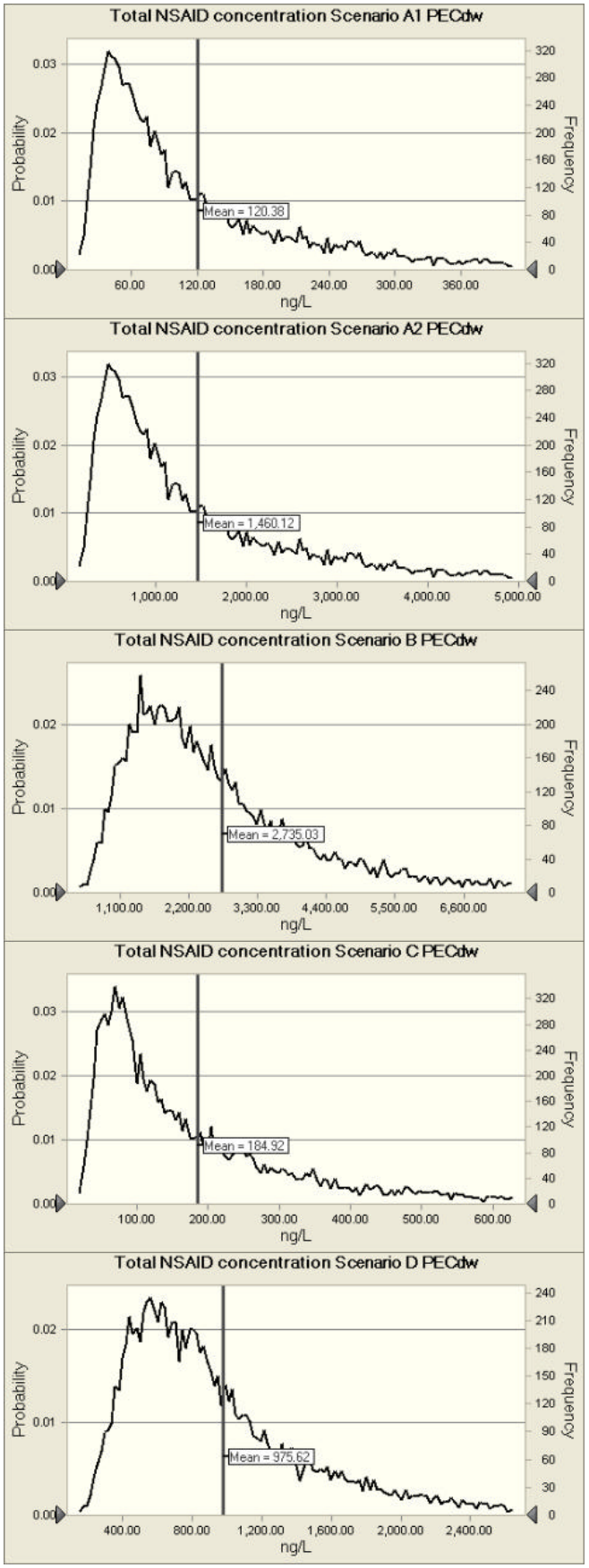
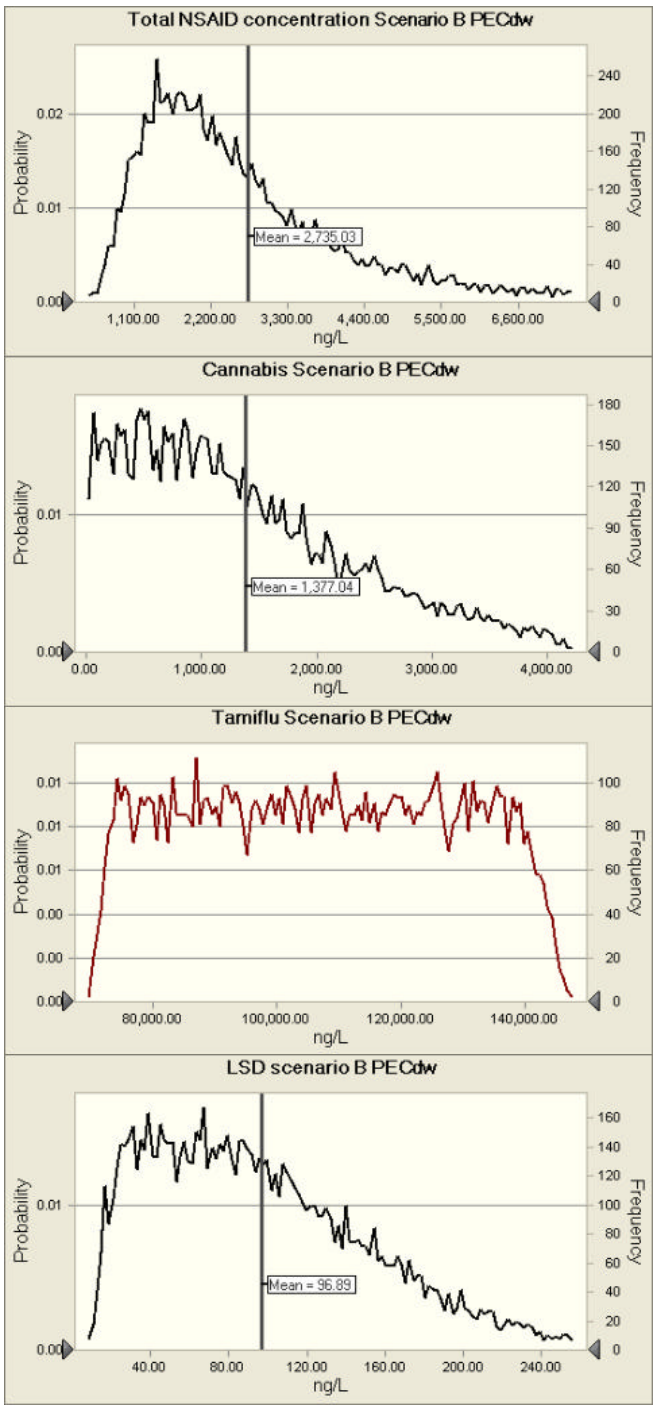
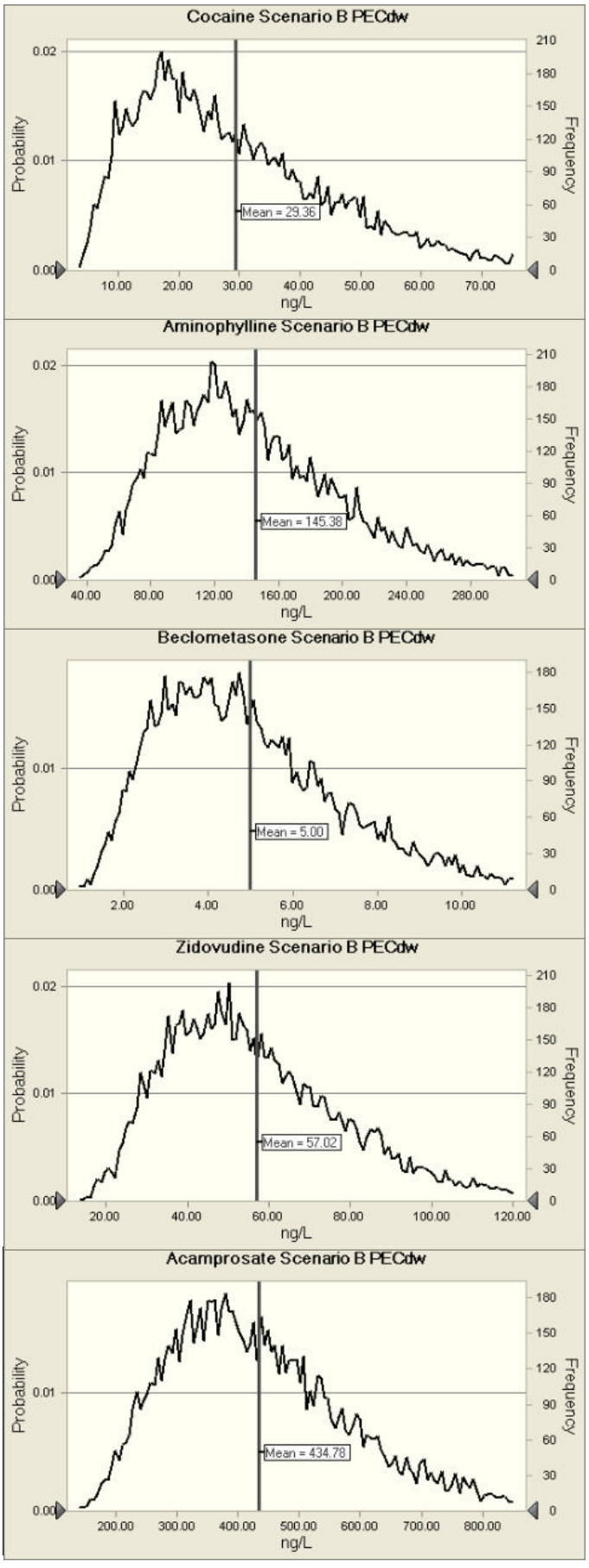


Figure 7.2 Outputs from Probabilistic Monitoring for Scenario B for the Ten Substances with the Lowest Exposure Ratios




Cocaine Scenario B PECdw
Probability
Frequency
Mean = 29.36
ng/L
Aminophylline Scenario B PECdw
Probability
Frequency
Mean = 145.38
ng/L
Beclometasone Scenario B PECdw
Probability
Frequency
Mean = 5.00
ng/L
Zidovudine Scenario B PECdw
Probability
Frequency
Mean = 57.02
ng/L
Acamprosate Scenario B PECdw
Probability
Frequency
Mean = 434.78
ng/L

The results from probabilistic modelling show that for all of the pharmaceuticals identified as having the top 24 MOE values by worst case deterministic modelling the estimated mean concentrations are lower (table 7.5) than are obtained using the deterministic model, reflecting the fact that metabolism, removal in STW and removal in DWTW is taken into account, albeit in a conservative manner. For all except two substances the exposure ratio using the mean concentration estimated from probabilistic modelling is greater than 2000 for the worst case scenario. Those substances are oseltamivir, which is the epidemic/pandemic scenario, and cannabis (tetrahydrocannabinol) which has a ratio of 769.

Table 7.5 Probabilistic Modelling data for the Top 24 Drugs from the Worst Case Deterministic modelling

Name	Worst Case [Scenario B] Mean PECdw ($\mu g.l^{-1}$)	Minimum Therapeutic Dose (mg)	Exposure Ratio (MOE) for Worst Case	Comments
Total for NSAIDS	2.74	7.5	2737	Combination of 19 anti-inflammatory
Cannabis (tetrahydrocannabinol)	1.377	1	726	Illegal drug
Oseltamivir Carboxylate (Tamiflu active metabolite)	107	52	486	Used under pandemic conditions
LSD	0.097	1	10309	Illegal drug
Cocaine (methylbenzoylecgonine)	0.029	1	34483	Illegal drug
Aminophylline	0.15	1	6667	Smooth muscle relaxant
Beclometasone	0.005	0.05	10000	Antiasthmatic
Zidovudine	0.057	0.5	8772	Anti-viral
Ecstasy	0.487	1	2053	Illegal drug
Acamprosate	0.435	1	2299	Alcoholism treatment
Total for Statins	1.27	5	3937	Lipid lowerers
Nitroglycerin	0.0354	0.15	4234	Vasodilator
Heroin (diamorphine)	0.00449	1	222717	Illegal drug
Simvastatin	1.18	5	4227	Lipid lowerer
Codeine	0.0157	20	1277139	Narcotic analgesic
Ramipril	0.153	1.25	8177	Diuretic
Lisinopril	0.396	2.5	6316	Angiotensin converting enzyme inhibitor
Methadone	0.0822	1	12173	Opioid agonist
Furosemide	1.74	20	11507	Diuretic
Amphetamine	0.0174	1	57405	Illegal drug
Norethisterone	0.0236	0.35	14824	Progesterone derivative
Doxazosin	0.00681	1	146843	?-blocker
Bendroflumethiazide	0.275	2.5	9094	Diuretic
Ciclosporin	0.0008	2	2500000	Immunosuppression

8 Conclusions

The literature survey has shown that there are only very limited measured data for the concentrations of pharmaceuticals in UK drinking waters. Data from the rest of Europe and the USA, which mainly report removal of pharmaceuticals during drinking water treatment, have shown that concentrations in finished drinking water at treatment works are generally =100 ng.l^{-1} even for the most widely used pharmaceuticals. No data were available for illegal drugs in drinking water, but the concentrations in rivers and sewage effluent for the most commonly used drugs has been reported as =100 ng.l^{-1} in Switzerland and Italy. Data for UK rivers and streams have shown that median concentrations of pharmaceuticals are almost always =100 ng.l^{-1} with the exceptions being the major use NSAID, ibuprofen, found at median concentrations of 48, 297 and 826 ng.l^{-1}.

Removal of pharmaceuticals by DWTW processes is substantial for almost all of the pharmaceuticals studied when the treatment includes ozonation and activated carbon. This combination, together with the more conventional DWTW processes, can result in removal rates of >90% for a wide variety of pharmaceuticals.

The worst case modelling showed that even in the scenario with the highest estimated concentrations, the exposure ratios (comparison of intake to minimum therapeutic dose) for most of the major used pharmaceuticals and illegal drugs were significantly greater than 1000 and provided a high safety margin. Only 10 substances showed exposure ratios less than 1000 and four of these were illegal drugs. In only one case was the exposure ratio less than 100 and this was a special case since a combined total for all NSAIDs was used, but with the lowest minimum therapeutic dose. It therefore appears that even in this worst case situation there is no significant risk to health from intake of pharmaceuticals via drinking water.

The use of probabilistic modelling, provided a more realistic estimate of likely concentrations in drinking water and showed that, as expected, the estimated concentrations for all except one substance were significantly lower than the estimated concentrations from the worst case (deterministic) model. Using the mean concentrations from the probabilistic model, all of the substances have exposure ratios significantly greater than 100 and only oseltamivir and cannabis have exposure ratios less than 1000. It therefore appears that with this more realistic worst case modelling there is no significant risk to health from pharmaceutical intake via drinking water.

9 Recommendations

The accuracy of the estimates of usage for the illegal drugs is unknown and since many of them showed some of the lowest exposure ratios it would be appropriate to revisit the estimates of usage. This would require close cooperation with illicit drug enforcement agencies who have more precise data but would still entail the use of estimates. In addition, since they were assigned nominal, very low, minimum therapeutic doses it would also be appropriate to search further for data to provide more realistic estimates. In addition, it would be useful to collate data on the percentage of active ingredients in cannabis that are absorbed during use in order to revise the estimates of amounts used.

Some pharmaceuticals produce significant quantities of metabolites which are excreted and enter the environment via sewage treatment. In order to provide answers to questions as to the significance of these substances, worst case modelling of these metabolites for major use pharmaceuticals would be worthwhile to determine their exposure ratios.

In view of the dearth of measured data on the concentrations of pharmaceuticals and illegal drugs in UK drinking waters it would be prudent to carry out a small scale survey. This survey could be guided by the findings from this report and address those substances that have the lowest exposure ratios, the highest concentrations and which are potentially of heightened public perception of a hazard, such as cytotoxic drugs. However, the capabilities of the available analytical methods, particularly their limits of detection, would also be an important consideration in selecting the substances for the survey. In addition, the monitoring could be carried out in the catchments that provided the scenarios with the highest estimated concentrations.

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GLOSSARY

ACE inhibitor	Angiotensin converting enzyme (acetylcholinesterase) inhibitor used in the treatment of hypertension
ADI	Annual Daily Intake
Anti-epileptic/anti-convulsant	A drug used to control seizures
Anti-neoplastic	A drug used in cancer treatment
Analgesic	A drug used as pain killer
Anti-inflammatory	A drug used to treat inflammation with pain relieving properties
Beta-blocker	A drug which blocks the effects of adrenalin and noradrenalin in the body. Important in the treatment of hypertension, angina, cardiac problems and glaucoma
Diuretic	A drug which acts on the kidney to increase urine flow and fluid loss
DOC	Dissolved Organic Carbon
DWTW	Drinking Water Treatment Works
GAC	Granular Activated Carbon
GSL	General sales list medicine
K_d	The soil-porewater distribution coefficient
K_{ow}	The octanol-water partition coefficient
Lipid regulator	A drug which lowers the level of cholesterol in the blood
MOE	Margin of Exposure – the ratio of the worst case concentration to MTD
MTD	Minimum Therapeutic Dose
OC	Oseltamivir carboxylate – the active form of Tamiflu
OTC	Medicines sold over the counter without prescription which are mostly GSL
PEC	Predicted Environmental Concentration
P	Pharmacy medicines
POM	Prescription only medicines
pKa	The acid dissociation constant
RGF	Rapid Gravity Filtration
RO	Reverse Osmosis
STW	Sewage Treatment Works

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ANNEXES

Annex 1 Milestones

Target	Description of milestone
1.	Identify relevant studies
2.	Assess study quality
3.	Summarise Findings and relevance of studies
4.	Evaluate potential to reach raw and treated water
5.	Group compounds based on mode of action or chemical functionality
6.	Obtain relevant usage data and estimate degradation during different stages
7.	Evaluate Scenarios
8.	Consider high inputs
9.	Conclude on likely levels and their health significance
10.	Recommend further research
11.	Draft Final Report

* The start date of the project was 14th July 2006 (with a revised finish date of 31st December 2007). An additional milestone was added in July 2007 to estimate concentrations of Tamiflu in UK drinking waters.

Annex 2 Deterministic PEC and Margin of Exposure (MOE) Values for all Pharmaceuticals Assessed

The following table shows the PEC and MOE values for the worst case scenario for all of the substances that were considered in this study and for which it was appropriate to calculate an MOE value.

Name	PEC for Worst Case Scenario ($\mu g.l^{-1}$)	MOE for Worst Case Scenario
Total For NSAIDS	97.5090	77
Cannabis (Tetrahydrocannabinol)	9.7408	103
LSD	3.3519	298
Oseltamivir Carboxylate [Tamiflu Active Metabolite]	148.4000	350
Cocaine (Methylbenzoylecgonine)	2.5304	395
Aminophylline	2.3130	432
Beclometasone	0.0728	687
Zidovudine	0.6483	771
Ecstasy/MDMA (N-Methyl-3,4-Methylenedioxyamphetamine)	1.0754	930
Acamprosate	1.0380	963
Total For Statins	4.4718	1118
Nitroglycerin	0.1300	1154
Heroin (Diamorphine)	0.7539	1326
Simvastatin	3.2413	1543
Codeine	9.3708	2134
Ramipril	0.5755	2172
Lisinopril	0.9443	2647
Methadone	0.3430	2916
Furosemide	5.2728	3793
Amphetamine	0.2511	3983
Norethisterone	0.0877	3990
Doxazosin	0.2244	4455
Bendroflumethiazide	0.5498	4547
Ciclosporin	0.3480	5748
Atenolol	8.3622	5979
Lansoprazole	2.3086	6497
Chlorphenamine	0.1324	7554
Metformin	110.4695	7694
Amlodipine	0.6214	8047
Omeprazole	1.1904	8400
Warfarin	0.2110	9477
Enalapril	0.5121	9763
Ibuprofen	18.9238	10569
Dexamethasone	0.0910	10987
Pravastatin	0.8269	12093
Dihydrocodeine	2.3930	12537
Gliclazide	6.2240	12853
Losartan	1.8505	13510
Candesartan (Cilexetil)	0.1474	13565

Name	PEC for Worst Case Scenario ($\mu g.l^{-1}$)	MOE for Worst Case Scenario
Hydrocortisone	0.7224	13843
Felodipine	0.1773	14097
Diclofenac	5.0022	14993
Allopurinol	6.6597	15016
Valproic Acid	16.2007	15431
Diltiazem	7.0274	17076
Lidocaine	0.5635	17745
Medroxyprogesterone	0.1365	18314
Methadone (From Seizures)	0.0546	18318
Nicorandil	0.4981	20075
Dantron	0.1959	20415
Temazepam	0.4595	21761
Nicotine	1.3683	21926
Venlafaxine	3.1145	24081
Perindopril	0.1626	24597
Hydrochlorothiazide	0.4782	26140
Dextropropoxyphene	7.2883	27441
Meprobamate	0.1086	27635
Pyridoxine	0.1799	27792
Ranitidine	10.6787	28093
Diphenhydramine	0.6658	30039
Salicylic Acid	1.6244	30781
Amiloride	0.1604	31176
Diazepam	0.1259	31761
Morphine	0.6283	31834
Escitalopram	0.1548	32308
Baclofen	0.1535	32573
Citalopram	0.6053	33042
Salbutamol	0.2405	33258
Acetylsalicylic Acid (Asprin)	14.9890	33358
Pholcodine	0.1413	35397
Rosuvastatin	0.1411	35440
Levodopa	3.5106	35606
Zopiclone	0.2069	36244
Azathioprine	0.5484	36468
Cetirizine	0.2709	36918
Alendronic Acid	0.2656	37656
Clopidogrel	1.9795	37888
Imipramine	0.1307	38266
Isosorbide Mononitrate	2.6074	38352
Nifedipine	1.5301	39214
Propranolol	1.5080	39787
Paracetamol	15.6992	41403
Quinine	7.1938	41703
Cinnarizine	0.1764	42522
Dosulepin	1.7165	43694
Fexofenadine	1.3620	44053
Paroxetine	0.4422	45225

Name	PEC for Worst Case Scenario ($\mu g.l^{-1}$)	MOE for Worst Case Scenario
Glibenclamide	0.0411	48631
Mirtazapine	0.3053	49129
Benserazide	0.3897	51324
Esomeprazole	0.3863	51778
Phenylephrine	0.0939	53273
Domperidone	0.1806	55364
Rofecoxib	0.3607	55447
Verapamil	2.0807	57674
Metoclopramide	0.1725	57978
Amiodarone	1.6979	58898
Minoxidil	0.0848	58929
Betahistine	0.4010	59858
Nitrazepam	0.0835	59896
Quetiapine	0.8145	61388
Clotrimazole	1.5106	66200
Bisoprolol	0.0742	67422
Bisacodyl	0.0741	67463
Penicillin V	7.2110	69338
Meloxicam	0.1066	70371
Tramadol	5.4802	72990
Cyclizine	0.3403	73457
Oxytetracycline	6.6795	74856
Lamotrigine	1.3307	75150
Fluvastatin	0.2625	76178
Fenofibrate	0.5876	76587
Oxybutynin	0.0653	76591
Spironolactone	0.6500	76919
Orlistat	1.5381	78017
Loratadine	0.1278	78243
Flucloxacillin	12.7804	78245
Mebeverine	5.0956	78500
Naproxen	6.3386	78882
Trimethoprim	1.2666	78950
Telmisartan	0.2500	79994
Ciprofloxacin	2.4472	81726
Amitriptyline	1.8195	82441
Gabapentin	10.7633	83617
Clavulanic Acid	2.3650	84568
Sotalol	0.9076	88141
Rabeprazole	0.2257	88627
Dipyridamole	3.3690	89047
Sertraline	0.5455	91653
Fosinopril	0.0543	92129
Prednisolone	0.4173	95863
Tamoxifen	0.2080	96175
Oxcarbazepine	0.2578	96989
Alverine	0.5946	100913
Lopinavir	0.2960	101339

Name	PEC for Worst Case Scenario ($\mu g.l^{-1}$)	MOE for Worst Case Scenario
Atovaquone	0.2449	102094
Acetazolamide	2.3887	104658
Theophylline	2.7830	107798
Etoricoxib	0.5302	113160
Chlortalidone	0.2625	114288
Lofepramine	0.5972	117218
Etidronic Acid	0.4218	118536
Undecylenic Acid	0.4215	118614
Phenytoin	2.4979	120103
Captopril	0.4003	124905
Metronidazole	4.6578	128815
Trazodone	0.7620	131232
Phenobarbital (Phenobarbitone)	0.2285	131273
Mefenamic Acid	3.6475	137081
Doxycycline	0.6986	143146
Quinapril	0.0692	144454
Minocycline	0.6893	145064
Sildenafil	0.1704	146691
Tranexamic Acid	3.2130	155619
Pseudoephedrine	1.5302	156841
Cimetidine	4.8599	164614
Procyclidine	0.0607	164828
Mesalazine	14.4541	166042
Terbinafine	1.3270	188394
Cefalexin	5.1451	194358
Lamivudine	0.4881	204884
Iomeprol	0.9354	213813
Sulfasalazine	13.6383	219969
Fluoxetine	0.0882	226772
Dextromethorphan	0.1707	234321
Amoxicillin	3.1376	239040
Sulpiride	0.8009	249731
Carbidopa	0.4912	254455
Clarithromycin	1.9558	255644
Clomipramine	0.2600	288438
Tolbutamide	1.7238	290062
Carbocisteine	0.6682	299291
Guaifenesin	2.6661	300060
Piroxicam	0.0654	305589
Chlordiazepoxide	0.0478	313730
Indoramin	0.0796	313900
Metoprolol	0.2343	320150
Promethazine	0.1473	339428
Chlorpromazine	0.5714	350015
Thioridazine	0.0557	359313
Labetalol	0.5497	363837
Oxazepam	0.0409	366358
Entacapone	0.5431	368279

Name	PEC for Worst Case Scenario ($\mu g.l^{-1}$)	MOE for Worst Case Scenario
Nicardipine	0.0670	372983
Ketoconazole	0.5285	378453
Ursodeoxycholic Acid	0.7860	381681
Hydroxyzine	0.1279	390809
Fluconazole	0.1262	396177
Etodolac	1.5062	398363
Raloxifene	0.1445	415341
Isosorbide Dinitrate	0.0719	417138
Aciclovir	2.3887	418631
Celiprolol	0.4734	422520
Naftidrofuryl	0.7024	427088
Nitrofurantoin	0.2271	440316
Meptazinol	0.4525	441988
Ketoprofen	0.2249	444674
Methocarbamol	2.2471	445025
Miconazole	0.4493	445141
Dicycloverine	0.0652	460054
Hydralazine	0.0857	466630
Nizatidine	0.6344	472906
Carbimazole	0.0621	483045
Cefuroxime	1.4815	506250
Trimipramine	0.0972	514165
Phenolphthalein	0.0567	529001
Azapropazone	2.2600	530983
Flurbiprofen	0.0935	535029
Promazine	0.0910	549528
Pethidine	0.0875	571258
Acarbose	0.2588	579616
Amisulpride	0.6795	588682
Aceclofenac	0.3361	595141
Cefaclor	0.8293	602902
Hydroxychloroquine	0.7983	626297
Salicylamide	0.4731	634150
Triamterene	0.1560	641071
Oxprenolol	0.2467	648540
Ceftazidime	0.3515	711220
Estradiol	0.0014	713771
Megestrol	0.0555	721245
Indometacin	0.0983	763283
Flecainide	0.3929	763507
Phenylpropanolamine	0.0963	779117
Nabumetone	1.2413	805603
Mycophenolate Mofetil	1.2138	823876
Nevirapine	0.2320	861920
Rifampicin	0.4741	949143
Ephedrine	0.0523	956175
Doxepin	0.0784	956328
Ciprofibrate	0.1043	958645

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Acemetacin	0.0311	964945
Sumatriptan	0.0985	1014977
Lymecycline	1.0736	1117683
Hydroxycarbamide	1.2438	1125559
Disopyramide	0.1738	1150981
Nefopam	0.0824	1213080
Topiramate	0.3150	1269726
Nelfinavir	0.1943	1286554
Cefotaxime	0.3811	1312062
Efavirenz	0.4565	1314215
Chloral Hydrate	0.5600	1339177
Methyldopa	1.4930	1339547
Cefradine	1.0756	1394602
Fluvoxamine	0.0356	1404784
Amobarbital	0.0426	1407003
Clomethiazole	0.3471	1440690
Itraconazole	0.1387	1442369
Cyproterone	0.1346	1485540
Tenofovir Disoproxil	0.1893	1584949
Ofloxacin	0.1248	1602002
Orphenadrine	0.1211	1651957
Pyrazinamide	0.2948	1695870
Primidone	0.4338	1729091
Propylthiouracil	0.0578	1729879
Amantadine	0.1147	1743963
Mebenazole	0.0562	1778973
Isoniazid	0.1655	1812571
Clindamycin	0.3037	1975800
Vigabatrin	0.4993	2002868
Levofloxacin	0.1223	2043619
Proguanil	0.1925	2077461
Fusidic Acid	0.7202	2082783
Acebutolol	0.1887	2119251
Abacavir (Ziagen)	0.2757	2176072
Propafenone	0.1805	2216219
Meropenem	0.2168	2306172
Penicillamine	0.2106	2374406
Ampicillin	0.6242	2402897
Deanol	0.0411	2430150
Terbutaline	0.0202	2474363
Olsalazine	0.3970	2518810
Moclobemide	0.1190	2521059
Fenbufen	0.2330	2575422
Ethosuximide	0.1837	2721865
Tiaprofenic Acid	0.2156	2782698
Griseofulvin	0.2388	2930806
Cefadroxil	0.3363	2973640
Azithromycin	0.1679	2978308

Name	PEC for Worst Case Scenario ($\mu g.l^{-1}$)	MOE for Worst Case Scenario
Sulindac	0.0489	3070571
Balsalazide	2.5991	3078002
Felbinac	0.2888	3462419
Famciclovir	0.1330	3760445
Flavoxate	0.2047	3908260
Chloroquine	0.1234	4052160
Ethambutol	0.2395	4174834
Difunisal	0.1139	4391619
Gemfibrozil	0.2646	4535842
Disulfiram	0.1070	4671293
Clodronic Acid	0.6257	5113882
Inositol Nicotinate	0.5531	5424189
Mefloquine	0.0439	5696061
Valaciclovir	0.1746	5728320
Progesterone	0.0333	5998520
Piracetam	0.3076	6502069
Tetracycline	0.1493	6698174
Cefuroxime Axetil	0.1098	6833356
Methenamine	0.1395	7166171
Flutamide	0.0960	7810793
Erythromycin	0.0605	8263732
Danazol	0.0633	12647995
Acipimox	0.0355	14086206
Mexiletine Hydrochloride	0.0396	15146457
Diatrizoic Acid	3.2018	15616355
Ceftriaxone	0.1874	16010736
Carbamazepine	0.0232	17238413
Betaine	0.1689	17763669
Fenoprofen	0.0204	19616448
Quinidine	0.0606	19803277
Sulfadiazine	0.0805	24855924
Phenyltoloxamine	0.0002	26424655
Nefazadone	0.0072	27788202
Triclofos	0.0340	29431883
Norfloxacin	0.0267	29978831
Prochlorperazine	0.1193	41924873
Choline	0.0682	44017134
Cisapride	0.0008	49170174
Framycetin (Synonym For Neomycin Sulfate)	0.0510	78485020
Nalidixic Acid	0.0397	100833460
Sulfamethoxazole	0.0066	152279659
Pentoxifylline	0.0042	285870401
Bezafibrate	0.0012	338373131
Phentermine	0.0000	353182605
Lactitol	0.0058	521592050
Piperazine	0.0009	2854829725
Chlorpropamide	0.000019	5297738998
Terfenadine	0.000006	8934678713

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Probenecid	0.00000002	10234268591