Occurrence and Fate of Human Pharmaceuticals in the Environment

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Contents

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Reviews of Environmental Contamination and Toxicology 202,
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1 Introduction

Pharmaceuticals from a wide spectrum of therapeutic classes are used in human medicine worldwide. Pharmaceutically active compounds are defined as substances used for prevention, diagnosis or treatment of a disease and for restoring, correcting or modifying organic functions (Daughton and Ternes 1999). Pharmaceuticals include more than 4000 molecules with different physico-chemical and biological properties and distinct modes of biochemical action (Beausse 2004). Most medical substances are administrated orally. After administration, some drugs are metabolised, while others remain intact before being excreted. Therefore, a mixture of pharmaceuticals and their metabolites will enter municipal sewage and sewage treatment plants (STP; Kümmerer 2004). Depending on their polarity, water solubility and persistence, some of these compounds may not be completely eliminated or transformed during sewage treatment and, therefore, pharmaceuticals and their metabolites may enter surface waters through domestic, industrial and hospital effluents. Sorptive pharmaceuticals could also present a risk to the aquatic environment through the disposal of sewage sludge on agricultural soils and eventual runoff to surface waters, or leaching to ground waters after rainfall (Topp et al. 2008a). They may also enter the environment through the disposal of unused and expired drugs and from emissions from manufacturing processes (Stackelberg et al. 2004).

Human-use medicines are designed to have a biological effect and to be bioavailable. However, it has only been in recent years that there has been increasing concern over the trace amounts of pharmaceuticals that are appearing in the environment and the effects they may produce (Daughton and Ternes 1999; Halling-Sørensen et al. 1998). Although pharmaceuticals have long been released to the environment, recent concern derives partly from the fact that new analytical methods are now capable of detecting pharmaceuticals at levels that occur in the environment (Erickson 2002). In addition, it is only recently that the potential adverse environmental effects of pharmaceuticals have been recognised (Brooks et al. 2005; Harries et al. 1997); this has triggered significant new research. Because of the polarity and emissions of pharmaceuticals to the sewerage system, most new research has been carried out in the aquatic environment (Ternes 1998).

In recent decades, more than 100 different drugs have been detected in the aquatic environment at concentrations from the nanogram (ng) to the ug/L range (Daughton and Ternes 1999; Jørgensen and Halling-Sørensen 2000; Kümmerer 2001). Even though these concentrations are low, these chemicals may pose a risk because they are developed to trigger specific biological effects at low doses in humans. Furthermore, as pharmaceuticals are continuously released into the environment, organisms will be exposed to many of these substances for their entire lifetime. Therefore, it is possible that pharmaceuticals may cause effects on non-target organisms in the aquatic and terrestrial environment (Boxall 2004; Daughton and Ternes 1999). Ecotoxicity studies in the laboratory have demonstrated effects of pharmaceuticals on end points such as reproduction, growth,

behaviour and feeding for fish and invertebrates (Martinovic et al. 2007; Parrot and Blunt 2005; Pascoe et al. 2003; Quinn et al. 2008; Stanley et al. 2007). In the real environment, pharmaceuticals have been detected in fish tissues (Brooks et al. 2005), and oestrogenic effects on male fish have been reported in rivers (Harries et al. 1997; Kirby et al. 2003). In the terrestrial environment, the catastrophic decline of vulture populations has been found to result from exposure to the human anti-inflammatory drug diclofenac (Oaks et al. 2004). Potential bioaccumulation and persistence of released pharmaceuticals is also of concern. Moreover, pharmaceuticals released into the environment as mixtures also raise concerns, because the combined environmental effects of pharmaceuticals are largely unknown (Stackelberg et al. 2004; Tixier et al. 2003). Another major concern is that environmental release of antibiotic compounds has potential to spread drug resistance (Golet et al. 2001).

In addition to ecological risk effects, human health may be at risk through long-term consumption of drinking water containing trace levels of pharmaceuticals. Although these compounds exist at doses far below the ones used in therapy, drinking water standards have not yet been established for most of pharmaceuticals; hence, the potential health risk is not known (Kümmerer 2004). However, there are some studies that defend the view that there is no risk to human health (Schwab et al. 2005; Webb et al. 2003).

Large volumes of data have been generated in the last decade on the fate and occurrence of pharmaceuticals in the environment; therefore, it is timely to review the existing knowledge. This chapter focuses on exposure and constitutes a synthesis of the existing knowledge on properties, usage and consumption, occurrence, treatability in sewage treatment plants and fate of human-use pharmaceuticals in the environment; we also attempt to identify gaps in knowledge and recommend priorities for future research in the area. Pharmaceuticals mentioned in this chapter, including usage and chemical abstract service (CAS) numbers, are listed in the Appendix.

2 Usage, Consumption and Properties

Large amounts of pharmaceuticals, representing a wide spectrum of therapeutic classes, are used and prescribed in human medicine worldwide (Díaz-Cruz and Barceló 2004). In most cases, only a rough estimation of pharmaceutical consumption is available, because they are often sold as over-the-counter drugs (Díaz-Cruz and Barceló 2004; Stackelberg et al. 2004). Usage data for active compounds sold in three different European countries are summarised in Table 1. These data indicate that, in general, the analgesic acetaminophen and the analgesic and anti-inflammatory drugs acetylsalicylic acid and ibuprofen are the pharmaceuticals sold in highest quantities, followed by the antibiotics, and the antiepileptic carbamazepine. Usage and properties of these different groups are discussed below, and chemical structures and properties of selected pharmaceuticals are presented in Table 2.

Table 1 Volume of pharmaceutically active compounds sold in different countries (kg/yr)

Therapeutic class	Compound	France (2004)[a]	UK (2004)[b]	Spain (2003)[c]
Antibiotics				
Macrolides	Azithromycin	4073	756	–
	Clarithromycin	15,105	8807	–
	Erythromycin	–	48,654	8100
Penicillins	Penicillin V	–	32,472	–
	Amoxicillin	333,223	149,764	–
Sulfonamides	Sulfamethoxazole	16,730	3113	12,700
	Sulfadiazine	–	362	–
Quinolones	Ciprofloxacin	12,186	16,445	–
Tetracyclines	Tetracycline	–	2101	–
Other	Trimethoprim	3346	11,184	3700
Analgesics and anti-inflammatories	Acetaminophen	3,303,077	3,534,737	–
	Acetylsalicylic acid	396,212	177,623	–
	Diclofenac	9896	35,361	32,300
	Ibuprofen	240,024	330,292	276,100
	Naproxen	37,332	33,580	42,600
Beta-blockers	Acebutolol	–	943	–
	Atenolol	18,337	49,547	–
	Metoprolol	8786	3907	2300
	Propranolol	12,487	9986	–
Hormones	Progesterone	–	751	–
	Testosterone	–	–	–
Lipid regulators				
Fibrates	Gemfibrozil	–	1418	–
	Fenofibrate	85,670	2815	–
Statins	Atorvastatin	7924	–	–
	Simvastatin	6943	14,596	–
	Lovastatin	–	–	–
Selective serotonin reuptake inhibitors	Fluoxetine	3740	4826	4200
	Paroxetine	5515	2663	–
	Citalopram	3487	4799	1600
Other classes				
Antiepileptic	Carbamazepine	33,514	52,245	20,000
Iodinated X-ray contrast media	Iopromide	–	–	20,000

[a]Besse et al. (2007)
[b]Environment Agency (2008)
[c]Carballa et al. (2008)

Table 2 Chemical structures and properties for selected pharmaceuticals

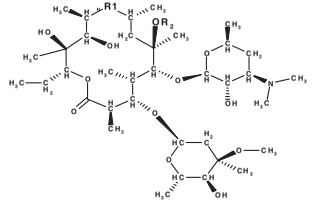
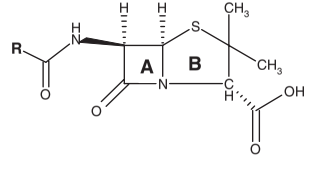
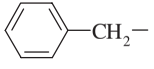
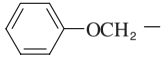
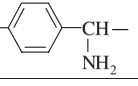
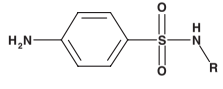
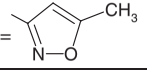
Therapeutic class/compound chemical structure	Compound/chemical structure or side chains	Log K_{ow}[a]	p*K*a	Water solubility (mg /L)
Antibiotics				
Macrolides 	Azithromycin R1=N–CH_3 R2=H	4.02	8.74	7.09 (est)
	Clarithromycin R1==O R2=CH_3	3.16	8.99	0.34 (est)
	Erythromycin R1==O R2 = H	3.06	8.88	1.44 (est)
Penicillins 	Penicillin G R= 	1.83	2.74	210 (est)
	Penicillin V R= 	2.09	2.79	101 (est)
	Amoxicillin R= 	0.87	–	3430 (est)
Sulfonamides 	Sulfonylamide R=H	–0.62	10.58	7500
	Sulfamethoxazole R= 	0.89	–	610

Table 2 (continued)

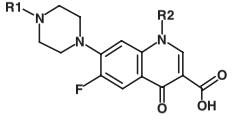
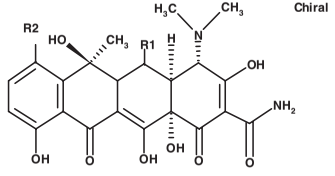
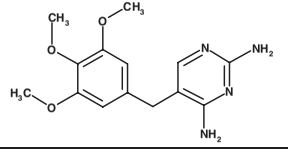
Therapeutic class/compound chemical structure	Compound/chemical structure or side chains	Log K_{ow}	p*Ka*	Water solubility (mg/L)
Antibiotics				
Quinolones 	Ciprofloxacin R1=  R2=H	0.28	6.09	3.00 E +4
	Norfloxacin R1=–C_2H_5 R2=H	−1.03	–	1.78 E +5 (est)
Tetracyclines 	Tetracycline R1=H R2=H	−1.30	3.3	231
	Chlortetracycline R1=H R2=Cl	–0.62	3.3	630
	Oxytetracycline R1=OH R2=H	–0.90	3.27	313
Trimethoprim		0.91	7.12	400

Table 2 (continued)

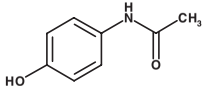
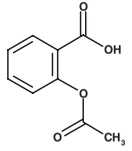
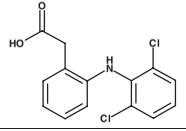
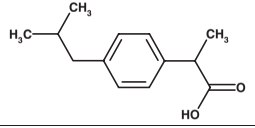
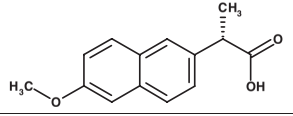
Therapeutic class/compound chemical structure	Compound/chemical structure or side chains	Log K_{aw}	pK	Water solubility (mg/L)
Analgesics and anti-inflammatories				
Acetaminophen		0.46	9.38	1.40 E +4
Acetylsalicylic acid		1.19	3.49	4600
Diclofenac		4.51	4.15	2.37
Ibuprofen		3.97	4.91	21
Naproxen		3.18	4.15	15.90

Table 2 (continued)

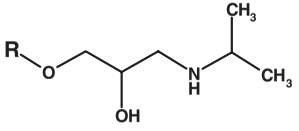
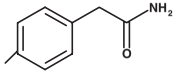
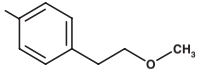
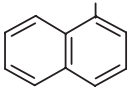
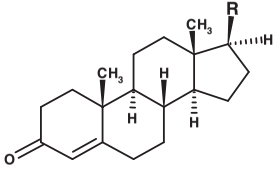
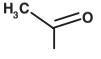
Therapeutic class/compound chemical structure	Compound/chemical structure or side chains	Log K_{ow}	pKa	Water solubility (mg/L)
Beta-blockers				
	Atenolol R = 	0.16	–	1.33 E +4
	Metoprolol R= 	1.88	–	1.69 E +4
	Propanolol R = 	3.48	9.42	61.70
Hormones				
Steroids 	Progesterone R = 	3.87	–	8.81
	Testosterone R = OH	3.32	–	23.40

Table 2 (continued)

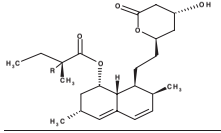
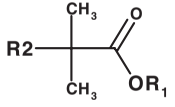
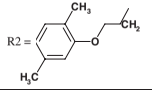
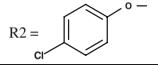
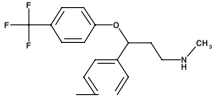
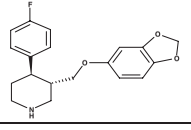
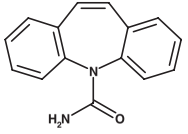
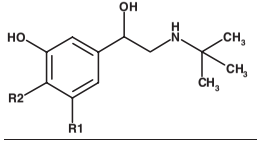
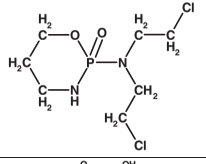
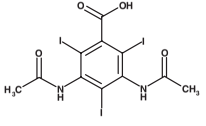
Therapeutic class/compound chemical structure	Compound/chemical structure or side chains	Log K_{ow}	p*K*a	Water solubility (mg/L)
Lipid regulators				
Statins 	Lovastatin R=H	4.26	–	2.14 (est)
	Simvastatin R=CH_3	4.68	–	0.76 (est)
Fibrates 	Gemfibrozil R1=H 	4.77 (est)	–	–
	Clofibrate R1=C_2H_5 	3.62	–	–
Selective serotonin reuptake inhibitors (SSRIs)				
Fluoxetine		4.05	–	60.3 (est)
Paroxetine		3.95	–	–

Table 2 (continued)

Therapeutic class/compound chemical structure	Compound/chemical structure or side chains	Log K_{ow}	p*K*a	Water solubility (mg/L)
Others				
Antiepileptic Carbamazepine		2.45	–	17.70 (est)
B2-Sympathomimetics	Terbutaline R1=OH R2=H	0.90	–	2.13 E +5 (est)
	Albuterol R1=CH_2OH R2=OH	0.64 (est)	–	1.43 E +4
Antineoplastic Agents Cyclophosphamide		0.63	–	4 E +4
Iodinated X-ray Contrast Media Diatrizoate		–	–	–

Syracuse Research Corporation (2004) – all data. est – estimated

[a]Log K_{ow}, octanol–water partition coefficient

2.1 Analgesics and Anti-inflammatories

Major analgesics, including aspirin, are drugs used to relieve pain. Analgesic drugs include the opioid analgesics, also known as narcotic analgesics, such as codeine and the more potent morphine (Analgesics 2000). Analgesic drugs also include the nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen (paracetamol). NSAIDs are used to relieve pain, and also to suppress inflammation in a way similar to steroids, but without their side effects; acetaminophen, however, lacks anti-inflammatory properties. The anti-inflammatory, analgesic and antipyretic drugs are not chemically related, but nevertheless share certain therapeutic actions. NSAIDs act by inhibiting the enzyme cyclooxygenase, an enzyme responsible for the biosynthesis of the prostaglandins, which are lipid compounds derived enzymatically from fatty acids and are secreted into the bloodstream, causing fever, inflammation, muscle contraction and other bodily processes (Analgesics 2000). NSAIDs are acidic compounds with variable hydrophobicity. As analgesics, NSAIDs are effective against low-intensity or moderate-intensity pain. Their antipyretic activity reduces the body temperature in febrile states, but their main clinical application is as anti-inflammatory agents in the treatment of musculoskeletal disorders, such as rheumatoid arthritis and osteoarthritis (Roberts and Morrow 2001). The active substance sold in highest amounts is by far acetaminophen, with more than 3 million kg sold in the United Kingdom and in France, in 2004. Acetylsalicylic acid (aspirin) and ibuprofen are also sold in very high amounts. Other substances from these therapeutic classes are naproxen, ketoprofen, diclofenac, fenoprofen and indomethacin.

2.2 Antibiotics

The term antibiotic is used to denote any drug, natural or synthetic, that has a selective toxic action on bacteria or other single-celled microorganisms (Chambers 2001). Antibiotics are classified according to the type of organism against which they are active. Most are used to treat bacterial infections (antibacterial drugs) and include substances from the penicillin, tetracycline, macrolide, quinolone and sulfonamide classes (Aronson 2001). Penicillins, macrolides and sulfonamides tend to be used in the largest amounts with major active ingredients comprising amoxicillin, sulfamethoxazole and erythromycin.

Macrolides are bacteriostatic drugs, so called because they prevent bacteria from multiplying rather than killing them. Their activity spectrum is similar to the penicillins, and thus they are used for treating infections in patients that are allergic to the latter (Macrolide antibiotics 2000). Macrolides contain a 14-, 15- or 16-membered lactone ring, to which one or more deoxy sugars are attached; this ring is responsible for their pharmacological activity (Chambers 2001). They are bases and have medium hydrophobicity (Rogers 1996). Macrolide

antibiotics are typically used for the treatment of respiratory tract infections such as pneumoniae and chlamydia, diphtheria, and tetanus. The major macrolides used include erythromycin and clarithromycin. Other examples of pharmaceuticals belonging to this class are lincomycin, roxithromycin and spyramycin.

The penicillins belong to a wider group, the β-lactam antibiotics that share a common mechanism of action, i.e. the inhibition of the synthesis of the bacterial peptidoglycan cell wall. Penicillin antibiotics cause death of bacteria when they try to divide. Structurally, they consist of a thiazolidinine ring (A) bonded to a β-lactam ring (B), to which a side chain (R) is attached. The requisite for biological activity is in the penicillin nucleus itself. Penicillins G and V are among the more important of penicillins and are effective against susceptible gram-positive cocci. Penicillin G (benzylpenicillin) is the only natural penicillin clinically used and is the congener with greatest antimicrobial activity (Petri 2001a). Within the penicillin class, amoxicillin is the most used antibiotic, followed by penicillin V. Other examples of the class are cloxacillin, nafcillin, oxacillin and dicloxacillin.

The quinolones are synthetic antibacterial drugs that have been of minor importance because of their limited therapeutic use and the development of bacterial resistance. The more recently introduced fluorinated 4-quinolones (also known as fluoroquinolones) constitute an important therapeutic advance as a result of their broader spectrum of antimicrobial activity and effectiveness against a wide variety of infectious diseases (Petri 2001b). The fluoroquinolones are mainly used to treat penicillin-resistant infections; they act by inhibiting the enzymes that maintain the structure of bacterial DNA, which are important in nucleic acid synthesis (Quinolones 2000; Stumpf et al. 1999). The substances of this class contain a carboxylic acid moiety in position 3 of the basic ring structure, are hydrophobic zwitterionic compounds and are used for treatment of urinary tract infections. The most widely used fluoroquinolone is ciprofloxacin, which is the medicine of choice for treating anthrax infections (Golet et al. 2002a). Other fluoroquinolones include enoxacin, lomefloxacin, norfloxacin and ofloxacin.

The sulfonamides were the first clinically effective anti-infective drugs employed for the prevention and cure of bacterial infections in humans (Aronson 2001). The term sulfonamide is used as a generic name for derivatives of para-aminobenzenesulfonamide (sulfanilamide). The prerequisite for antibacterial action is that the sulfur is directly linked to the benzene ring. Sulfonamides are hydrophilic and amphoteric compounds. These substances act by inhibiting a metabolic pathway that is necessary for DNA synthesis and are bacteriostatic drugs. They have a broad range of antimicrobial activity against both gram-positive and gram-negative bacteria. They are used primarily to treat urinary tract infections and are used in combination with trimethoprim for the treatment of otitis, bronchitis sinusitis and pneumonia (Petri 2001b). Common sulfa drugs include sulfamethoxazole and sulfasalazine. Other examples are sulfadiazine, sulfapyridine, sulfathiazole and

sulfamethazine. Trimethoprim is an antibacterial agent, commonly used in combination with sulfonamide antibacterial drugs. Although the activity spectrum of trimethoprim is very similar to that of sulfamethoxazole, it is 20–100 times more powerful against most gram-positive and gram-negative microorganisms. Trimethoprim is a diaminopyrimidine with low hydrophobicity (Petri 2001b). Initially, trimethoprim exhibited significant antimalarial activity, but resistance can develop when the drug is used alone. In combination with sulfamethoxazole, trimethoprim is widely used in the treatment of respiratory tract infections, severe urinary tract infections and enteric infections (Petri 2001b). Trimethoprim has been sold in the United Kingdom at quantities exceeding 10,000 kg/yr.

Tetracycline antimicrobial activity and effectiveness in controlling infections was established in vitro, and since their introduction, tetracyclines have become widely used in therapy. Tetracyclines are congeners of polycyclic naphthacenecarboxamide and they differ by substitutions at the fifth, sixth and seventh backbone ring positions (Chambers 2001). They are zwitterionic compounds and have low hydrophobicity. Tetracyclines are effective against a wide range of aerobic and anaerobic gram-positive and gram-negative bacteria, and hence became known as a "broad-spectrum" group of antibiotics; they act by inhibiting protein synthesis in sensitive organisms (Tetracyclines 2000). Many infective organisms have developed resistance to tetracyclines. As a result, their usage has decreased, although they are still the first choice for treatment of chlamydia bacteria, which causes a variety of diseases including sexually transmitted infections, parrot disease and eye infections, among a wide range of other infections. Tetracyclines are also used to treat brucellosis, acne, gum disease, Lyme disease and exacerbations of chronic bronchitis (Tetracyclines 2000). Tetracycline is the most used and sold pharmaceutical from this class. Oxytetracycline, chlorotetracycline, democlocycline and doxycycline are also routinely used.

Other classes of antibacterial drugs are the aminoglycosides and the cephalosporins. The latter are mainly used for the treatment of severe infections in hospitals. Chloramphenicol is the first choice treatment for meningitis and acute typhoid fever and is commonly used for the treatment of eye infections (Aronson 2001). Other categories of antibiotic drugs used in the treatment of infections are antiviral (e.g., acyclovir), antiprotozoal (e.g., pyrimethamine), antinematodal (e.g., levamisole) and antifungal drugs (e.g., miconazole).

2.3 Beta-Blockers

β-Blockers, or β-adrenergic receptor antagonists, are drugs that act on blood vessels, preventing vasodilatation and reducing the speed and force of heart contractions. These substances block the stimulation of β-adrenergic

receptors by noradrenaline in the sympathetic nervous system, hence lowering the blood pressure and heart rate (Beta-blockers 2000). There are two types of beta-receptors, the β1 receptors, which are located primarily in the heart muscle, and the β2 receptors, which are found in the blood vessels. While selective β-adrenergic antagonists only act on the β1 receptors, non-selective β-adrenergic antagonists interact with both types of receptors (Beta-blockers 2000). Propanolol is an example of a non-selective β-adrenergic antagonist that has equal affinity for β1 and β2 receptors. Substances such as metoprolol and atenolol are examples of selective β1 antagonists as a result of their greater affinity for β1 receptors (Hoffman 2001). Most beta-blockers are basic compounds with variable hydrophobicity. β-Blockers are used in the treatment of hypertension, ischemic heart disease, congestive heart failure, certain arrhythmias and can also be taken to prevent migraine headaches. In the form of eye drops, they can be used to reduce fluid pressure inside the eyes of people afflicted with glaucoma (Beta-blockers 2000; Hoffman 2001). The active substances sold in higher quantities in the United Kingdom and in France are atenolol (with almost 50,000 kg sold in the United Kingdom in 2004) and propranolol. Other class examples include betaxolol, bisoprolol, carazolol and celiprolol.

2.4 Hormones and Steroids

Most hormones belong to one of the following groups: proteins and peptides, steroids or derivatives of the amino acid tyrosine. Protein and peptide hormones are mainly produced by certain cells of the thyroid, the pancreas, the parathyroids and the pituitary gland (Forsling 2001). The synthesis of these hormones is the same as of any other protein, involving transcription of the gene and translation of a messenger RNA (ribonucleic acid). Steroid hormones, such as cortisol and sex hormones, are released by the ovaries or paired testes and by the cortex or the adrenal gland, and they are synthesized from cholesterol (Forsling 2001). The tyrosine derivatives are the thyroid hormones and the catecholamines that include adrenaline, noradrenaline and dopamine, which are produced by the adrenal glands. Hormones can be synthesised for use as medication and tend to be hydrophobic compounds. The peptide hormone insulin is widely used to treat diabetes. Oestrogens and progestagens such as norethindrone, progesterone and ethinyloestradiol are used for contraception. Progesterone is the hormone sold in higher amounts, with approximately 700 kg sold in the United Kingdom in 2004. However, natural hormones, such as testosterone and 17-beta-oestradiol, have also been reported in the aquatic environment (Kolpin et al. 2002). Other examples of steroid hormones include oestradiol and mestranol.

2.5 Lipid Regulators

Lipid regulating agents are substances used to lower levels of triglycerides and low-density lipoproteins (LDL) and increase levels of high-density lipoproteins (HDL) in the blood (Mahley and Bersot 2001). These substances are used among people at risk of heart attack. There are three kinds of lipid regulators, fibric acid derivatives (or fibrates), statins [or 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors] and niacin (or nicotinic acid). Fibrates are used to lower concentrations of triglycerides and increase levels of the beneficial HDL. However, they are less effective than statins in the decrease of LDL from blood (Mahley and Bersot 2001). Lipid regulators are hydrophobic compounds. Fibrates are usually the drugs of choice for the treatment of hypertriglyceridemia or high levels of triglycerides in blood. Examples of fibrates are bezafibrate, gemfibrozil and fenofibrate. Statins are one of the most effective substances to treat dyslipidemia, or disruption of the amount of lipids in blood. These drugs inhibit HMG-CoA reductase, which catalyzes a rate-limiting step in cholesterol biosynthesis. Statins are used to decrease levels of LDL, but have less effect than fibrates and niacin in reducing triglycerides and raising HDL in the blood (Mahley and Bersot 2001). Examples of statins are atorvastatin, simvastatin and lovastatin. Niacin is also used in the treatment of dyslipidemia and it favourably affects all lipid parameters, increasing HDL level and decreasing LDL. It also decreases triglycerides levels in blood. The lipid regulator most sold in the United Kingdom is simvastatin.

2.6 Selective Serotonin Reuptake Inhibitors

Since the 1950s, antidepressants have been developed for the treatment of clinical depression. Tricyclic antidepressants were the first agents successfully used; however, they exhibit neuro-pharmacological effects in addition to their original action. Currently, the selective serotonin reuptake inhibitors (SSRIs) have emerged as a major therapeutic advance in psychopharmacology (Baldessarini 2001). Low levels of the neurotransmitter serotonin have been associated with clinical depression, among other disorders, and SSRIs act by blocking the reuptake of the neurotransmitter serotonin by the nerves in the brain, thus extending its action (Selective serotonin reuptake inhibitor 2006). They are hydrophobic and generally basic compounds. Fluoxetine, the active ingredient of Prozac, is the one of the most widely used SSRIs in the United Kingdom for the treatment of depression, obsessive–compulsive disorder and social phobia among other disorders (Sanders-Bush and Mayer 2001). Most of the SSRIs are aryl or aryloxyalkylamines and several of them, including fluoxetine, are racemates; both enantiomers of fluoxetine are active against serotonin transport, and the (*S*)-enantiomer of fluoxetine may also have antimigraine effects, which are not found in the (*R*)-enantiomer (Sanders-Bush and Mayer 2001). In addition to fluoxetine, citalopram and paroxetine are the

active substances used in higher quantities. Paroxetine is more often used in France, whereas in the United Kingdom, almost 5000 kg each of fluoxetine and citalopram were sold in 2004.

2.7 Other Pharmaceuticals

A very important group of compounds used in cancer treatment are the antineoplastic agents, also known as cytotoxic drugs. This major group is divided in different classes, such as the alkylating agents and the antimetabolites (Chabner et al. 2001). The main pharmacological action of the alkylating agents is to disturb DNA synthesis and prevent cell replication (Chabner et al. 2001). Cyclophosphamide is an example of an alkylating agent. Other examples are ifosfamide, methotrexate and tamoxifen. Epilepsy is the term used for a brain function disorder that is characterized by periodic and unpredictable occurrence of seizures, which are defined as a temporary abnormal activity of brain neurons. The antiepileptics or antiseizure drugs are used in the treatment of epilepsy. These compounds act by inhibiting the propensity of seizures. Carbamazepine is the primary drug used for the treatment of partial seizures (McNamara 2001). In the United Kingdom, more than 50,000 kg of carbamazepines were sold in 2004. β2-Sympathomimetics (or β2-selective adrenergetic agonists) are substances prescribed mainly for the treatment of asthma; they are bronchodilators. However, they also stimulate β1-receptors located in the heart and, thereby, increase heart rate, hence putting patients with cardiovascular diseases at risk. Administration of these substances by inhalation in the form of aerosols enhances their effective activation of β2-receptors in the bronchi, with less potential to activate cardiac β1-receptors. Albuterol, terbutaline and fenoterol are examples of β2-sympathomimetics (Hoffman 2001).

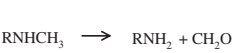
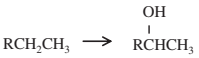
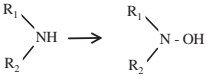
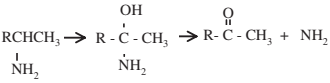
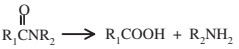
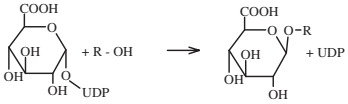
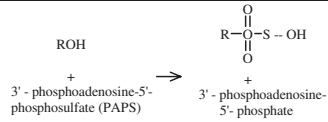
Iodinated X-ray contrast media are used in hospitals to intensify the contrast of structures during imaging (Contrast medium 2002). Examples of this class are iopromide, iomeprol, diatrizoate and iopadimol.

3 Metabolism

After administration of a medicine, absorption must occur before the drug reaches the interior of the body. With the majority of pharmaceuticals, absorption occurs by simple diffusion (Galbraith et al. 2004). However, absorption is affected by some chemical–physical characteristics of medicines such as molecular size and shape, degree of ionization and relative lipid solubility (Wilkinson 2001). Cell membranes retain lipid constituents that allow lipophilic substances to cross membranes rapidly and easily. After absorption, the medicine enters the circulation. After performing its action, the drug may be metabolised to a more hydrophilic substance for excretion. If a medicine remains lipophilic, it will be again reabsorbed and stay in the body for a longer period (Galbraith et al. 2004). In

general, metabolism of pharmaceuticals will generate more polar metabolites with lower activity, and these are more easily excreted from the body. In some cases, biological active or toxic metabolites are generated (Halling-Sørensen et al. 1998). Metabolism of pharmaceuticals involves two successive pathways: phase I and phase II metabolism. Phase I consists of oxidative (e.g. hydroxylation, N-oxidation, deamination) or hydrolysis reactions, whereas phase II involves conjugation (e.g. addition of a glucuronic acid, sulfate, acetate or amino acids; Table 3; Wilkinson 2001).

Table 3 Reactions involved in pharmaceuticals metabolism (adapted from Wilkinson 2001)

Phase I	Reaction	Examples
1. Oxidative reactions		
N-Dealkylation		Diazepam, codeine, erythromycin, tamoxifen, caffeine
Aliphatic hydroxylation		Ibuprofen, meprobamate
N-Oxidation		Quinidine, acetaminophen
Deamination		Diazepam
2. *Hydrolysis reactions*		Aspirin, clofibrate, enalapril, cocaine
		Lidocaine, indomethacin
Phase II		
3. Conjugation reactions		
Glucuronation	 UDP - glucuronic acid	Acetaminophen, oxazepam, morphine
Sulfation		Sulfonamides

Therefore, following administration and uptake, pharmaceuticals may be excreted unchanged, as conjugates, or as major metabolites or metabolite mixtures (Table 4). Data indicate that tetracyclines, penicillins, fluoroquinolones and β-blockers (with the exception of propranolol and betaxolol) are excreted unchanged, whereas analgesics and anti-inflammatory drugs are extensively metabolised, although percent excretion rates for most metabolites are unknown.

Table 4 Metabolism excretion rates for selected pharmaceuticals

Pharmaceutical	Excretion rates (%)[a]Unchanged	Metabolites	Reference
Acebutolol	30–40	NA	1
Acetaminophen	2.0–3	NA	1
	≤5	NA	2
Acetylsalicylic acid	1	NA	1
Albuterol	NA	50	1
Amoxicillin	80–90	10.0–20	3
	≥70	NA	2
Ampicillin	30–60	20–30	3
	6–39	NA	2
Atenolol	85	NA	1
Atorvastatin	<2	>70	1
	≤5	NA	2
Azithromycin	6	NA	1
Betaxolol	15	NA	1
Bezafibrate	40–69	NA	2
Bisoprolol	50	NA	1
Carbamazepine	1.0–2	NA	4
	≤5	NA	2
Chloramphenicol	5.0–10	NA	3
	≤5	NA	2
Chlorotetracycline	>70	NA	3
Cyclophosphamide	6.5 ± 4.3	60	1
Cimetidine	75	NA	1
Ciprofloxacin	45–60	40–55	1
	≥70	NA	2
Codeine	3.0–16	NA	1
Diclofenac	6.0–39	NA	2
Diltiazem	1.0–3	NA	1
Doxycycline	41 ± 19	NA	1
Erythromycin	12.0–15	NA	1
Oestradiol	<1	50–80	1
Oestrogen	NA	70–88	1
Ethinyloestradiol	23–59	30–53	1
Fluoxetine	≤5	NA	2
Gemfibrozil	<2	70	1
Ibuprofen	1.0–8	NA	4
	≤5	NA	2
Indomethacin	15 ± 8	NA	1
Ifosfamide	14–53	NA	5
Lovastatin	10	>70	1
Metoprolol	39	NA	1
Metronidazole	40	NA	6
Nadolol	70	NA	1
Naproxen	<1	NA	1
Nifedipine	traces	NA	1
Norethindrone	<5	90–95	1

Table 4 (continued)

Pharmaceutical	Excretion rates (%)[a]Unchanged	Metabolites	Reference
Norfloxacin	40–69	NA	2
Oxytetracycline	>80	NA	3
Penicillin G	50–70	30–70	3
Penicillin V	80–85	NA	1
Primidone	64	12	1
	6.0–39	NA	2
Progesterone		55–70	1
Propranolol	<0.5	NA	1
Ranitidine	68–79	NA	1
	6.0–39	NA	2
Salicylic acid	≤5	NA	2
Simvastatin	13	>70	1
Sotalol	80–90	NA	1
Sulfamethoxazole	10.0–30	55–75	1
	6–39	NA	2
Tetracycline	80–90	NA	7
	≥70	NA	2
Timolol	20	NA	1
Trimethoprim	50–60	NA	1
	30–69	NA	2

References: 1 – Anderson et al. (2002); 2 – Jjemba (2006); 3 – Hirsch et al. (1999); 4 – Ternes (1998); 5 – Steger-Hartmann et al. (1996); 6 – Kümmerer et al. (2000); 7 – Kühne et al. (2000).
NA – not available
[a]Maximum excretion rates

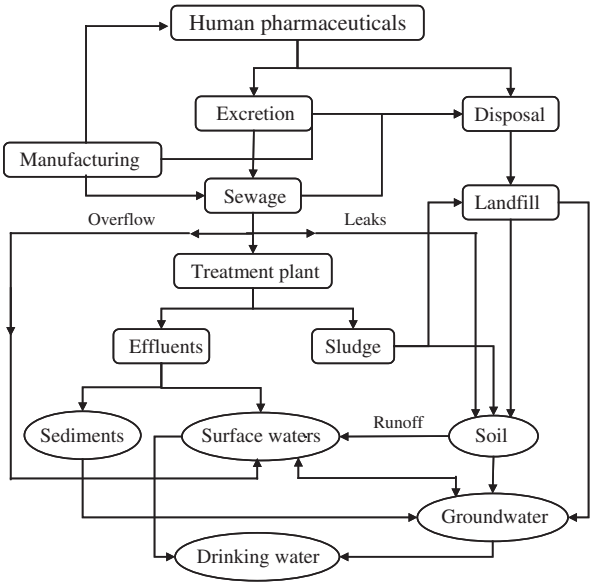


Fig. 1 Major pathways by which human-use pharmaceuticals reach the environment

4 Release of Pharmaceuticals to the Environment

The main sources for the occurrence of pharmaceuticals in the environment are the discharge of waste effluents from manufacturing processes, sewage treatment plants, the inappropriate disposal of unused or expired drugs and accidental spills during production or distribution (Díaz-Cruz and Barceló 2004; Williams 2005; Fig. 1). Furthermore, the common application of sewage sludge to agricultural soils as a fertilizer constitutes an additional pathway for introducing human-use medicines to the environment (Oppel et al. 2004; Topp et al. 2008a; Xia et al. 2005). In the following sections we discuss these input routes in more detail.

4.1 Emissions from Manufacturing

The manufacturing of pharmaceuticals has two major stages: the production of the active pharmaceutical ingredient (API) and the manufacture of the finished drug (e.g., tablets, capsules; Velagaleti et al. 2002). In pharmaceutical manufacturing facilities, synthesis and purification of APIs are usually achieved with organic solvents that are often reused in the synthesis process and are then treated or disposed of by incineration. In pharmaceutical product manufacturing, most generated waste is solid, and this material is commonly incinerated (Williams 2005). Therefore, discharges of pharmaceuticals from manufacturing processes are probably small and do not explain the widespread distribution of human-use pharmaceuticals in the environment (Williams 2005). Releases from pharmaceutical manufacturing are generally well regulated. However, this might not be the case in developing countries. For example, in one study concentrations as high as 31 000 μg/L were reported for the fluoroquinolone ciprofloxacin in effluent from a wastewater treatment plant in India; this plant received wastewater from 90 bulk drug manufacturers (Larsson et al. 2007).

4.2 Sewage Treatment Plants (STPs)

The main source of human-use medicines in the environment is from discharge of treated wastewater effluents to the aquatic environment (Alder et al. 2001; Daughton and Ternes 1999; Richardson and Bowron 1985). After usage, pharmaceuticals and their metabolites are excreted and discharged into STPs, where they will be exposed to treatment processes before being released. The removal success of pharmaceutical compounds during sewage treatment depends on their physical and chemical properties, and this is discussed in more detail later. Sewage treatment may also pollute soil from use of recycled sewage sludge as a fertilizer in agricultural fields (Oppel et al. 2004). Pollution may also result from disposal of incinerated-pharmaceutical waste being

disposed of in landfills or dumped at sea (Díaz-Cruz and Barceló 2004). Today, dumping of solid waste in landfills is the most common disposal method (Ahel and Jeličić 2001). However, this is changing as a result of stricter regulations such as the EU Landfill Directive (2003) (DEFRA, UK).

4.3 Sludge Land-Use and Wastewater Irrigation

The application of sewage sludge as fertilizer to agricultural land, although controversial (La Guardia et al. 2004), is still used in several countries (Langenkamp and Part 2001). Therefore, human-use pharmaceuticals may pollute soil primarily through the application of sewage sludge as fertilizer to agricultural land, or irrigation of crops with treated wastewater (Oppel et al. 2004; Ternes et al. 2007). Moreover these deposited pharmaceutical compounds may run off from soil into surface waters after rainfall events (Pedersen et al. 2005; Topp et al. 2008a). Leakages from STPs and sewer drains may also occur, and as with soils, rainfall events may wash these compounds into nearby surface waters (Pedersen et al. 2005; Topp et al. 2008a).

4.4 Emissions from Medical Units

Human-use pharmaceuticals may also be discharged from hospitals in wastewater. A number of pharmaceuticals are only used in hospitals (e.g., anaesthetics and iodinated X-ray contrast media); the environmental occurrence of such agents can, therefore, be primarily attributed to effluent discharges from hospitals (Kümmerer 2001, 2004).

4.5 Disposal of Unwanted Drugs

Proper disposal of expired or unused medicines is a challenge, because little information is available on safe and proper disposal methods. Landfill, medium and high-temperature incineration, return to donor or manufacturer, waste encapsulation and inertization are some of the methods that can be used to dispose of unwanted drugs (Grayling 1999). However, many users still empty unused medicines directly into wastewater systems.

5 Occurrence in the Environment

Over the last decade, more than 100 different drugs have been found as environmental contaminants in effluents of sewage treatment plants, surface water, sediments, sludge, soils, groundwater and even drinking water sources (Braga

et al. 2005; Golet et al. 2002b; Hilton and Thomas 2003; Hirsch et al. 1999; Metcalfe et al. 2003; Stackelberg et al. 2004; Ternes 1998). We provide an overview of data on such contamination in the following sections.

5.1 Aquatic Environment

Pharmaceuticals and their transformation products have been detected worldwide in the effluents of sewage treatment plants (Table 5), surface water (Table 6), groundwater (Table 7), drinking water (Table 8) and sorbed to sediments (Table 9); it is probable that, with the improvement of analytical methods, further pharmaceuticals will be detected in the future at even lower concentrations. The results of pharmaceutical contamination events are somewhat variable, because, in most studies, only single environmental samples were taken.

Table 5 Concentrations of pharmaceutical compounds detected in effluents from sewage treatment plants

Compound	Country	Concentration reported in effluent (min:max) (μg/L)	Reference
Analgesics and anti-inflammatories			
Acetaminophen	GER, UK, USA	nd–6.0 (GER)	1, 2, 3
Acetylsalicylic acid	GER	0.22–1.5	1, 4
Dextropropoxyphene	UK	0.110–0.585	2, 5
Diclofenac	CAN, CH, FRA, GER, GRE, ITA, NOR, SP, SWE, UK	nd–5.45 (ITA)	1, 2, 5, 6, 7, 8, 9,10, 11, 12, 13, 14, 15
Dimethylaminophenazone (aminopyrine)	FRA, GER, GRE, ITA, SWE	nd–1.0 (GER)	1, 7
Fenoprofen	BRA, CAN, FRA, GER, GRE, ITA, SWE	nd–0.405[a] (CAN)	1, 6, 7, 12, 16
Flurbiprofen	FRA, GRE, ITA, SWE	nd–0.34 (ITA)	7, 12
Ibuprofen	CAN, CH, FRA, GER, GRE, ITA, NOR, SP, SWE, UK, USA	nd–7.11 (SWE); 85 (SP)	1, 2, 5, 6, 7, 8, 9, 11, 12, 13, 17, 18, 19, 20
Indomethacin	CAN, GER, SWE	nd–0.60 (GER)	1, 6, 8, 12
Ketoprofen	CAN, CH, FRA, GER, GRE, ITA, SP, SWE	nd–0.871 (SP)	1, 6, 7, 11, 12, 13, 14
Meclofenamic acid	BRA, GER	nd	1, 16
Mefenamic acid	UK	0.133[b]–1.440	2, 5

Table 5 (continued)

Compound	Country	Concentration reported in effluent (min:max) (μg/L)	Reference
Naproxen	CAN, CH, FRA, GER, GRE, ITA, SP, SWE, USA	nd–5.22 (ITA)	1, 6, 7, 8, 11, 12, 13, 14, 18, 20
Phenazone (antipyrine)	FRA, GER, GRE, ITA, SWE	nd–0.41 (GER)	1, 7
Phenylbutazone	GER	nd	21
Propyphenazone	GER	0.095[b]–0.48	21
Tolfenamic acid	BRA, GER	nd–1.6 (BRA)	1, 16
Metabolites – analgesics and anti-inflammatories			
4-Aminoantipyrine	GER	nd[b] – 0.36	21
Carboxi-ibuprofen	GER, NOR, SWE	nd–1.27 (NOR)	9, 12
Gentisic acid	GER	nd[b]–0.59	1
Hydroxi-ibuprofen	GER, NOR, SWE	0.05–1.13 (NOR)	9, 12
o-Hydroxyhippuric acid	GER	nd	1
Oxyphenbutazone	GER	nd	21
Salicylic acid	GER, SP, UK	nd–13.000 (SP)	1, 4, 11, 22
Fluoroquinolone antibiotics			
Ciprofloxacin	CAN, CH, FRA, GRE, ITA, SWE, USA	<0.020–0.2510 (ITA)	7, 17, 23, 24, 25, 26
Enoxacin	FRA, GRE, ITA, SWE	0.01–0.03 ((FRA, GRE, ITA)	7
Lomefloxacin	FRA, GRE, ITA, SWE	0.13–0.32 (ITA)	7
Norfloxacin	CAN, CH, FRA, GRE, ITA, SWE	0.03–0.112 (CAN)	7, 23, 24
Ofloxacin	CAN, FRA, GRE, ITA, SWE, USA	0.045[b]–0.600 (ITA)	7, 23, 17, 26
Macrolide antibiotics			
Azithromycin	CH	0.085[a]–0.255	27
Clarithromycin	CAN, CH, GER, ITA	<0.050–0.536 (CAN)	8, 17, 23, 27, 28
Erythromycin[c]	CAN, CH, GER, ITA, UK, USA	<0.010–6.00 (GER)	2, 5, 8), 17, 23, 25, 27, 28, 29
Roxithromycin	CAN, CH, GER, USA	nd–1.0 (GER)	8, 23, 27, 28, 29
Spyramycin	ITA	0.0750[b]	17
Penicillin antibiotics			
Amoxicillin	ITA	0.0047[b]	17
Cloxacillin	GER	nd	28
Dicloxacillin	GER	nd	28
Methicillin	GER	nd	28
Nafcillin	GER	nd	28

Table 5 (continued)

Compound	Country	Concentration reported in effluent (min:max) (μg/L)	Reference
Oxacillin	GER	nd	28
Penicillin G	GER	nd	28
Penicillin V	GER	nd	28
Sulfonamide antibiotics			
Sulfacetamide	CAN	0.064[b]–0.151	23
Sulfadiazine	CAN, CH	nd–0.019[b]	23, 27
Sulfamethazine	CAN, CH, GER, USA	nd–0.363[b] (CAN)	23, 25, 27, 28, 30
Sulfamethoxazole	CAN, CH, FRA, GER, GRE, ITA, SP, SWE, UK, USA	nd–2.140 (USA)	2, 3, 5, 7, 8, 12, 17, 18, 23, 25, 26, 27, 28, 30
Sulfapyridine	CAN, CH	0.081[b]–0.228 (CAN)	23, 27
Sulfisoxazole	CH, USA	nd	27, 30
Metabolite – sulfonamide antibiotic			
N^4-Acetylsulfamethoxazole	CH, UK	<0.050[b]–2.235 (UK)	2, 5, 27
Tetracycline antibiotics			
Chlorotetracycline	GER, USA	nd	25, 28, 30
Democlocycline	USA	0.09	30
Doxycycline	CAN, GER, USA	0.038[b]–0.09 (USA)	23, 28, 30
Oxytetracycline	GER, USA	nd	28, 30
Tetracycline	CAN, GER, USA	nd–1.00 (USA)	23, 25, 28, 30
Other antibiotics			
Chloramphenicol	GER	0.56	28
Lincomycin	ITA	0.0305[b]	17
Trimethoprim	CAN,CH, FRA, GER, GRE, ITA, SWE, UK, USA	0.009–1.760 (USA)	2, 3, 5, 6, 7, 8, 12, 25, 26, 27, 28
Antidepressants			
Fluoxetine	CAN, USA	nd–0.099	6, 20
Lofepramine	UK	<0.010	2
Metabolite – antidepressant			
Norfluoxetine	CAN	nd	6
Antiepileptic			
Carbamazepine	CAN, CH, FRA, GER, GRE, ITA, SWE, USA	0.0325[a]–6.3 (GER)	1, 3, 6, 7, 8, 12, 13, 14, 17, 31
Carbamazepine metabolites			
CBZ – EP	CAN	0.0191[a]	31

Table 5 (continued)

Compound	Country	Concentration reported in effluent (min:max) (μg/L)	Reference
CBZ – 2OH	CAN	0.0704[a]	31
CBZ – 3OH	CAN	0.0692[a]	31
CBZ – 10OH	CAN	0.0325[a]	31
CBZ – DiOH	CAN	1.0812[a]	31
Antineoplastic agents			
Cyclophosphamide	CAN, GER, ITA	nd–0.146 (GER)	1, 6, 17, 32
Ifosfamide	GER	nd–2.9	1, 32
Methotextrate	ITA	0.0	17
Tamoxifen	UK	<0.010–0.042	2, 5
β-Blockers			
Acebutolol	FRA, GRE, ITA, SWE	<0.01–0.13 (FRA)	7
Atenolol	GER, ITA, SWE	<0.050–0.4660	8, 12, 17
Betaxolol	FRA, GER, GRE, ITA, SWE	nd–0.19 (GER)	1, 7
Bisoprolol	GER	0.057[b]–0.37	1
Carazolol	GER	nd[b]–0.12	1
Celiprolol	GER	<0.050–0.28[a]	8
Metoprolol	FRA, GER, GRE, ITA, SWE	0.01–2.2 (GER)	1, 7, 8, 12
Nadolol	GER	0.025[b]–0.06	1
Oxprenolol	FRA, GRE, ITA, SWE	nd–0.05 (FRA)	7
Propranolol	FRA, GER, GRE, ITA, SWE, UK	0.01–0.284 (UK)	1, 2, 5, 7, 8, 12
Sotalol	GER	<0.050–1.32[a]	8
Timolol	GER	nd–0.07	1
β2-Sympathomimetics			
Clenbuterol	GER	nd–0.08	1
Fenoterol	GER	nd–0.060	1
Salbutamol	GER, ITA	nd–0.17	1, 17
Terbutaline	GER	nd–0.12	1
Hormones			
17α-Oestradiol	NL	<0.0001	33
17α-Ethinyloestradiol	CAN, GER, ITA, NL, USA	<0.0001–0.42 (CAN)	17, 33, 34, 35
17β-Oestradiol	CAN, GER, NL, SP, USA	nd–0.064 (CAN)	18, 20, 33, 34, 35, 36
17β-Oestradiol-17-valerate	CAN, GER	nd–0.004 (GER)	34
Oestrone	CAN, GER, NL, SP, USA	nd–0.096 (CAN)	18, 20, 33, 34, 36
16α-Hydroxyoestrone	GER	0.001[b]–0.005	34
Mestranol	CAN, GER	nd–0.004 (GER)	34

Table 5 (continued)

Compound	Country	Concentration reported in effluent (min:max) (μg/L)	Reference
Iodinated X-ray contrast media			
Diatrizoate	GER	0.25[b]–8.7	8, 37
Iomeprol	GER	0.37[b]–3.8	8, 37
Iopamidol	GER	0.66[b]–15	8, 37
Iopromide	GER, SP	0.75[b]–11	8, 18, 37
Iothalamic acid	GER	<0.050[b]–0.64	37
Ioxithalamic acid	GER	<0.050[b]–0.21	37
Metabolites – iodinated X-ray contrast media			
ATI	GER	<0.050	37
ATH	GER	<0.050	37
DAMI	GER	<0.050	37
Lipid regulators			
Atorvastatin	CAN	nd–0.044[a] ± 0.002	6
Bezafibrate	BRA, CAN, FRA, GER, GRE, ITA, SWE	nd–4.6 (GER)	1, 6, 7, 16, 17
Clofibrate	FRA, GER, GRE, ITA, SWE	nd–0.8 (GRE)	1, 7
Etofibrate	GER	nd	1
Fenofibrate	FRA, GER, GRE, ITA, SWE	nd–0.16 (GRE; ITA)	1, 7
Gemfibrozil	CAN, FRA, GER, GRE, ITA, SP, SWE	0.005[a]–4.76 (ITA)	1, 6, 7, 11, 12
Metabolites – lipid regulators			
Clofibric acid	CAN, CH, FRA, GER, GRE, ITA, NOR, SWE, UK, USA	nd–0.68 (ITA)	1, 2, 6, 7, 8, 9, 10, 12, 13, 14, 20
Fenofibric acid	GER	<0.050–1.2	1, 8
Other pharmaceuticals			
Benzoylecgonine	ITA	0.390–0.750	38
Caffeine	CAN, GER, NOR, SWE, UK, USA	<0.050–126 (NOR)	3, 6, 8, 9, 12, 21, 22
Cocaine	ITA	0.042–0.120	38
Cotinine	CAN	nd–0.058 ± 0.003	6
Diazepam	GER, ITA, UK	nd–0.053 (GER)	1, 17, 21, 22
Enalapril	ITA	0.0	17
Furosemide	ITA	0.5850[b]	17
Glibenclamide	GER	nd	21
Hydrochlorothiazide	ITA	0.4391[b]	17

Table 5 (continued)

Compound	Country	Concentration reported in effluent (min:max) (μg/L)	Reference
Nifedipine	GER	nd–0.089	21
Omeprazole	GER, ITA	nd	17, 21
Pentoxifylline	CAN	(0.005[b]–0.011[b]) ± 0.001	6
Ranitidine	ITA	[b]0.2882	17

nd – not detected; ATI – 5-amino-2,4,6-triiodoisophthalic acid – potential metabolite of iopromide, iopadimol and iomeprol; ATH – (2,3-dihydroxypropyl)amide – potential metabolite of iopromide; DAMI – Desmethoxyacetyl iopromide – potential metabolite of iopromide; CBZ-EP – 10,11-dihydro-10,11-epoxycarbamazepine; CBZ-2OH – 2-hydroxycarbamazepine; CBZ-3OH – 3-hydroxycarbamazepine; CBZ-10OH – 10,11-dihydro-10-hydroxycarbamazepine; CBZ-DiOH – 10,11-dihydro-10,11-dihydroxycarbamazepine; GER – Germany; BRA – Brazil; CAN – Canada; CH – Switzerland; FRA – France; GRE – Greece; ITA – Italy; NL – The Netherlands; NOR – Norway; SWE – Sweden; SP – Spain; UK – United Kingdom; USA – United States of America.

References: 1 – Ternes (1998); 2 – Hilton and Thomas (2003); 3 – Skadsen et al. (2004); 4 – Ternes et al. (2004a); 5 – Ashton et al. (2004); 6 – Metcalfe et al. (2003); 7 – Andreozzi et al. (2003); 8 – Ternes et al. (2003); 9 – Weigel et al. (2004); 10 – Koutsouba et al. (2003); 11 – Farré et al. (2001); 12 – Bendz et al. (2005); 13 – Tixier et al. (2003); 14 – Öllers et al. (2001); 15 – Buser et al. (1998a); 16 – Stumpf et al. (1999); 17 – Zuccato et al. (2005a); 18 – Carballa et al. (2004); 19 – Buser et al. (1999); 20 – Boyd et al. (2003); 21 – Ternes et al. (2001b); 22 – Richardson and Bowron (1985); 23 – Miao et al. (2004); 24 – Golet et al. (2002a); 25 – Karthikeyan and Bleam (2003); 26 – Renew and Huang (2004); 27 – Göbel et al. (2004); 28 – Hirsch et al. (1999); 29 – Yang and Carlson (2004a); 30 – Yang and Carlson (2004b); 31 – Miao et al. (2005); 32 – Steger-Hartmann et al. (1996); 33 – Belfroid et al. (1999); 34 – Ternes et al. (1999); 35 – Huang and Sedlak (2001); 36 – Servos et al. (2005); 37 – Ternes and Hirsch (2000); 38 – Zuccato et al. (2005b)

[a]Mean value

[b]Median value

[c]Erythromycin is not detected in environmental samples in its original form but appears as dehydrated Erythromycin, with the loss of one molecule of water (Hirsh et al. 1999)

Table 6 Concentration of pharmaceutical compounds detected in surface waters near discharges of sewage effluents

Compound	Country	Concentration reported in surface water (min:max) (μg/L)	Reference
Analgesics and anti-inflammatories			
Acetaminophen	GER, CZE, UK, USA	nd–10 (USA)	1, 2, 3, 4
Acetylsalicylic acid	GER	nd[a]–0.34	1
Codeine	USA	0.2–1.0	4
Dextropropoxyphene	UK	<0.008–0.682	3, 5, 6

Table 6 (continued)

Compound	Country	Concentration reported in surface water (min:max) (μg/L)	Reference
Diclofenac	AUS, BRA, CAN, CH, CZE, GER, SP, SWE, UK	nd–1.20 (GER)	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15
Dimethylaminophenazone (aminopyrine)	CZE, GER	nd[b]–0.506	1, 2
Fenoprofen	CAN, CZE, GER	nd–0.142[b] ± 0.008	1, 2, 9
Ibuprofen	BRA, CAN, CH, CZE, GER, ITA, NOR, Nsea, SP, SWE, UK, USA	<0.0002–5.044 (UK)	1, 2, 3, 4, 5, 6,8, 9, 10, 12, 13, 15, 16, 17, 18, 19, 20, 21
Indomethacin	CAN, CZE, GER	nd–0.20 (GER)	1, 2,9
Ketoprofen	CAN, CH, GER, SP, SWE	nd–0.300 (SP)	1, 9, 12, 13, 15, 22
Meclofenamic acid	GER	nd	1
Mefenamic acid	AUS, UK	<0.0004–0.366 (UK)	3, 5, 6, 7
Naproxen	AUS, BRA, CAN, CH, CZE, GER, SP, SWE, USA	nd–2.0 (SP)	1, 2, 9, 12, 13, 15, 20, 21
Phenazone (antipyrine)	CZE, GER	<0.010–0.95 (GER)	1, 2
Phenylbutazone	GER	nd	23
Propyphenazone	CZE, GER	<0.002–0.280 (GER)	2, 11, 23
Tolfenamic acid	GER	nd	1
Metabolites – analgesics and anti-inflammatories			
AAA (metamizole metabolite)	CZE, GER	<0.050–0.939	2
4-Aminoantipyrine (metamizole metabolite)	GER	nd–0.63	23
Carboxy-ibuprofen	NOR, SWE	nd–0.68 (SWE)	13, 19
FAA (metamizole metabolite)	CZE, GER	<0.050–0.803	2
Gentisic acid	GER	nd[a]–1.2	1
Hydroxy-ibuprofen	NOR, SWE	nd–0.06 (SWE)	2, 13
o-Hydroxyhippuric acid	GER	nd	1
MAA (metamizole metabolite)	CZE, GER	<0.010–0.368	2
Oxyphenbutazone (phenylbutazone metabolite)	GER	nd	23
Salicylic acid	GER, SP	0.018–8.800 (SP)	1, 12

Table 6 (continued)

Compound	Country	Concentration reported in surface water (min:max) (μg/L)	Reference
Fluoroquinolone antibiotics			
Ciprofloxacin	ITA, USA	nd[a]–0.03 (USA)	4, 17, 18
Enrofloxacin	USA	nd	4
Norfloxacin	USA	0.12[a]	4
Ofloxacin	ITA	0.0331[a]–0.3061	18
Ciprofloxacin + norfloxacin	CH	nd–0.015[a] ± 0.003	24
Macrolide antibiotics			
Clarithromycin	CZE, GER, ITA	nd[a]–0.26 (GER)	2, 17, 18, 25
Erythromycin[c]	CZE, GER, ITA, UK, USA	0.0032[a]–1.70 (GER; USA)	2, 3), , 5, 17, 18, 25, 26
Lincomycin	ITA, USA	<0.0010–0.73 (USA)	4, 17, 18, 27
Roxithromycin	CZE, GER, USA	nd[a]–0.56 (GER)	2, 4, 25, 26
Spyramycin	ITA	0.0098[a]–0.07420	17, 18
Penicillin antibiotics			
Amoxicillin	ITA	nd	17
Cloxacillin	GER	nd	25
Dicloxacillin	GER	nd	25
Methicillin	GER	nd	25
Nafcillin	GER	nd	25
Oxacillin	GER	nd	25
Penicillin G	GER	Nd	25
Penicillin V	GER	nd	25
Sulfonamide antibiotics			
Sulfamerazine	USA	nd–0.19	28
Sulfamethazine	GER, USA	<0.001–0.22 (USA)	4, 25, 27, 28
Sulfamethoxazole	CZE, GER, ITA, SWE, UK, USA	nd–1.9 (USA)	2, 3, 4, 5, 11, 13, 18, 25, 27, 28
Sulfathiazole	USA	<0.0010	27, 28
Metabolite – sulfonamide antibiotic			
N^4-Acetyl-sulfamethoxazole	UK	<0.050[a]–0.240	3, 5
Tetracycline antibiotics			
Chlorotetracycline	GER, USA	nd–0.69 (USA)	4, 25, 28
Democlocycline	USA	nd–0.44	28
Doxycycline	GER, USA	nd–0.08 (USA)	4, 25, 28
Oxytetracycline	GER, ITA, USA	nd–0.34 (USA)	4, 17, 25, 28
Tetracycline	GER, USA	nd–0.14 (USA)	4, 25, 28

Table 6 (continued)

Compound	Country	Concentration reported in surface water (min:max) (μg/L)	Reference
Other antibiotics			
Chloramphenicol	GER	nd[a]–0.06	25
Trimethoprim	CAN, CZE, GER, SWE, UK, USA	nd–0.71 (USA)	2, 3, 4, 5, 6, 9,13, 25, 27
Anti-depressants			
Fluoxetine	CAN, USA	nd–0.046[b] ± 0.004 (CAN)	4, 9, 20
Lofepramine	UK	<0.010	3
Metabolite – anti-depressant			
Norfluoxetine	CAN	nd	9
Paroxetine metabolite	USA	nd	4
Antiepileptic			
Carbamazepine	AUS, CAN, CH, CZE, GEDR, ITA, SWE, USA	<0.001–7.1 (GER)	1, 2, 7, 9, 11, 13, 15, 17, 27
Primidone	GER	0.105	11
Antineoplastic agents			
Cyclophosphamide	CAN, GER, ITA	nd–0.005[b] ± 0.001 (CAN)	1, 9, 17
Ifosfamide	GER	nd	1
Methotextrate			
Tamoxifen	UK	<0.004–0.071	3, 5, 6
Beta-blockers			
Atenolol	ITA, SWE	0.01–0.24100	13, 17, 18
Betaxolol	GER	nd[a]–0.028	1
Bisoprolol	GER	nd[a]–2.9	1
Carazolol	GER	nd[a]–0.11	1
Metoprolol	GER, SWE	0.03–2.2 (GER)	1, 13
Nadolol	GER	nd	1
Propranolol	GER, SWE, UK	<0.001–0.59 (GER)	1, 3, 5, 6, 13
Timolol	GER	nd[a]–0.01	1
β2-Sympathomimetics			
Clenbuterol	GER	nd[a]–0.050	1
Fenoterol	GER	nd[a]–0.061	1
Salbutamol	GER, ITA, USA	nd[a]–0.035 (GER)	1, 4, 17, 18
Terbutalin	GER	nd	1
Hormones			
17α-Oestradiol	AUS, NL, USA	<0.0001[a]–0.074 (USA)	29, 30
17α-Ethinyloestradiol	AUS, GER, ITA, NL, USA	<0.0001[a]–0.831 (USA)	4, 18, 29, 30, 31

Table 6 (continued)

Compound	Country	Concentration reported in surface water (min:max) (μg/L)	Reference
17*β*-Oestradiol	AUS, GER, NL, USA	<0.0003[a]–0.2 (USA)	4, 29, 30, 31, 32
17*β*-Oestradiol-17-valerate	GER	nd	31
19-Norethisterone	USA	0.048[a]–0.872	4
Cis-androsterone	USA	0.017[a]–0.214	4
Equilenin	USA	0.14[a]–0.278	4
Equilin	USA	0.147[a]	4
Hormones			
Oestriol	AUS, USA	0.019[a]–0.051 (USA)	4, 29
Oestrone	AUS, GER, NL, USA	0.0003[a]–1.6 (GER)	4, 20, 29, 30, 31
Mestranol	GER, USA	nd–0.407	4, 31
Progesterone	USA	0.11[a]–0.199	4
Testosterone	USA	0.116[a]–0.214	4
Iodinated X-ray contrast media			
Diatrizoate	GER	0.10–100	33
Iomeprol	GER	0.010–0.89	33
Iopromide	GER	0.017–0.91	33
Iothalamic acid	GER	<0.020[a]–0.19	33
Ioxithalamic acid	GER	<0.030[a]–0.08	33
Metabolites – iodinated X-ray contrast media			
ATI	GER	<0.020	33
ATH	GER	<0.020	33
DAMI	GER	<0.020	33
Lipid regulators			
Atorvastatin	CAN	nd–0.015[b] ± 0.001	9
Bezafibrate	AUS, BRA, CAN, CZE, GER, ITA	nd–3.1 (GER)	1, 2, 7, 8, 9, 11, 17, 18
Clofibrate	GER, UK	nd–0.040 (UK)	1, 34
Etofibrate	GER	nd	1
Fenofibrate	GER	nd	1
Gemfibrozil	CAN, CZE, GER, SP, SWE, USA	nd–1.550 (SP)	1, 2, 4, 9, 12, 13
Metabolites – lipid regulators			
Clofibric acid	AUS, BRA, CAN, CH, CZE, GER, ITA, UK, USA	nd–0.55 (GER)	1, 2, 3, 6, 7, 8, 9, 10, 11, 15, 17, 20, 22, 35
Fenofibric acid	GER	0.045[a]–0.28	1

Table 6 (continued)

Compound	Country	Concentration reported in surface water (min:max) (μg/L)	Reference
Other pharmaceuticals			
1,7-Dimethylxanthine	USA	0.0058–3.1	4, 11
Benzoylecgonine	ITA	0.025[b] ± 0.005	36
Caffeine	CAN, GER, NOR, Nsea, SWE, USA	0.0049–0.88 (GER)	4, 9, 10, 11, 13, 19, 27, 37
Cimetidine	USA	0.074[a]–0.58	4
Clotrimazole	UK	<0.001–0.022	6
Cocaine	ITA	0.0012[b] ± 0.0002	36
Cotinine	CAN, USA	nd–0.90 (USA)	4, 9
Dehydronifedipine	USA	0.012[a]–0.03	4
Diazepam	GER, ITA, UK	0.00029–0.033 (GER)	1, 17, 23, 34
Digoxin	USA	nd	4
Digoxigenin	USA	nd	4
Diltiazem	USA	0.021[a]–0.049	4
Enalapril	ITA	0.0001[a]–0.00054	17, 18
Enalaprilat	USA	0.046[a]	4
Furosemide	ITA	0.0035[a]–0.25470	17, 18
Glibenclamide	GER	nd–0.012	22
Hydrochlorothiazide	ITA	0.0046[a]–0.25580	17, 18
Metformin	USA	0.11[a]–0.15	4
Nifedipine	GER	nd	37
Omeprazole	GER, ITA	nd	17, 18, 37
Pentoxifylline	CAN	nd–0.009 ± 0.001	9
Ranitidine	ITA, USA	0.0013[a]–0.03850	4, 17, 18

nd – not detected; AAA – *N*-acetyl-4-aminoantipyrine; FAA – *N*-formyl-4-aminoantipyrine; MAA – *N*-methyl-4-aminoantipyrine; CZ – Czech Republic; AUS – Austria; Nsea – North Sea. References: 1 – Ternes (1998); 2 – Wiegel et al. (2004); 3 – Hilton and Thomas (2003) ; 4 – Kolpin et al. (2002) ; 5 – Ashton et al. (2004) ; 6 – Thomas and Hilton (2004); 7 – Ahrer et al. (2001); 8 – Metcalfe et al. (2003); 9 – Weigel et al. (2002); 10 – Heberer et al. (2001b); 11 – Farré et al. (2001); 12 – Bendz et al. (2005); 13 – Buser et al. (1998a); 14 – Öllers et al. (2001); 15 – Buser et al. (1999); 16 – Calamari et al. (2003); 17 – Zuccato et al. (2005a); 18 – Weigel et al. (2004); 19 – Boyd et al. (2003); 20 – Boyd et al. (2004); 21 – Tixier et al. (2003); 22 – Ternes et al. (2001b); 23 – Golet et al. (2002a); 24 – Hirsch et al. (1999); 25 – Yang and Carlson (2004a); 26 – Skadsen et al. (2004); 27 – Yang and Carlson (2004b); 28 – Hohenblum et al. (2004); 29 – Belfroid et al. (1999); 30 – Ternes et al. (1999); 31 – Huang and Sedlak (2001); 32 – Ternes and Hirsch (2000); 33 – Richardson and Bowron (1985); 34 – Buser et al. (1998a); 35 – Zuccato et al. (2005b)

[a]Median value

[b]Mean ± standard deviation

[c]Erythromycin is not detected in environmental samples in its original form but as dehydrated Erythromycin, with the loss of one molecule of water (Hirsch et al. 1999)

Table 7 Occurrence of pharmaceuticals in groundwater

Compound	Country	Groundwater sampling location	Concentration (μg /L)	LOD (Q) (μg /L)	Reference
Analgesics and anti-inflammatories					
Diclofenac	Germany	Baden–Wurttemberg[a] $n = 4$ samples	0.590[b]	0.0087 (0.029)	1
	Germany	Lake Wansee transect – 4 shallow wells	nd[c]–0.040	0.001–0.0010	2
	Germany	Lake Wansee transect – 3 deep wells	nd	0.001–0.0010	2
	Germany	Lake Wansee transect – water supply well	nd	0.001–0.0010	2
	Germany		0.93[b]		3
	Germany		3.5[b,d]		3
Dimethylaminophenazone	Croatia	Jakuševec landfill leachate	0.06[c]–16	0.050	4
	Croatia	Zagreb	<0.050[e]–36	0.050	4
	Germany	Berlin	0.4[f]	0.050 (LOQ)	5
Phenazone	Germany	Baden-Wurttemberg[a] $n = 5$ samples	0.025[b]	0.0034 (0.012)	1
	Germany	Berlin	3[f]	0.050 (LOQ)	5
Propyphenazone	Croatia	Jakuševec landfill leachate	3.7[c]–60	0.050	4
	Croatia	Zagreb	5[e] –50	0.050	4
	Denmark	Grinsted landfill – distance 0 m	300[g] –4000	20	6
	Denmark	Grinsted landfill – distance 50 m	30[g] –300	20	6
	Denmark	Grinsted landfill – distance 115 m	70	20	6
	Denmark	Grinsted landfill – distance 150 m	<10	20	6
	Germany	Lake Wansee transect – 4 shallow wells	0.010[c] –0.170	0.001–0.0010	2
	Germany	Lake Wansee transect – 3 deep wells	nd	0.001–0.0010	2
	Germany	Lake Wansee transect – water supply well	0.050	0.001–0.0010	2
	Germany	Berlin	1[f]	0.005 (LOQ)	5
Macrolide antibiotics					
Clarithromycin	Germany		nd	0.02 (LOQ)	7
Erythromycin	Germany	Baden–Wurttemberg[a] $n = 10$ samples	0.049[b]	0.0042 (0.014)	1
Roxythromycin	Germany		nd	0.02 (LOQ)	7
Penicillin antibiotics					

Table 7 (continued)

Compound	Country	Groundwater sampling location	Concentration (μg /L)	LOD (Q) (μg /L)	Reference
Cloxacillin	Germany		nd	0.02 (LOQ)	7
Dicloxacillin	Germany		nd	0.02 (LOQ)	7
Methicillin	Germany		nd	0.02 (LOQ)	7
Nafcillin	Germany		nd	0.02 (LOQ)	7
Oxacillin	Germany		nd	0.02 (LOQ)	7
Penicillin G	Germany		nd	0.02 (LOQ)	7
Penicillin V	Germany		nd	0.02 (LOQ)	7
Sulfonamide antibiotics					
Sulfadiazine	Denmark	Grinsted landfill – distance 0 m	100[g]–480	20	6
	Denmark	Grinsted landfill – distance 15 m	720[g]–1160	20	6
	Denmark	Grinsted landfill – distance 37 m	170[g]–440	20	6
	Denmark	Grinsted landfill – distance 50 m	<20[g]–80	20	6
	Denmark	Grinsted landfill – distance 82 m	<20	20	6
Sulfaguanidine	Denmark	Grinsted landfill – distance 0 m	110[g]–1600	20	6
	Denmark	Grinsted landfill – distance 15 m	280[g]–900	20	6
	Denmark	Grinsted landfill – distance 37 m	110[g]–480	20	6
	Denmark	Grinsted landfill – distance 50 m	<20[g]–540	20	6
	Denmark	Grinsted landfill – distance 82 m	<20	20	6
Sulfamethazine	Denmark	Grinsted landfill – distance 0 m	100[g]–900	20	6
	Denmark	Grinsted landfill – distance 15 m	540[g]–900	20	6
	Denmark	Grinsted landfill – distance 37 m	50[g]–310	20	6
	Denmark	Grinsted landfill – distance 50 m	<20[g]–140	20	6
	Denmark	Grinsted landfill – distance 82 m	<20	20	6
	Germany		0.16[b]	0.02 (LOQ)	7
Sulfamethizole	Denmark	Grinsted landfill – distance 0 m	60[g]–310	20	6
	Denmark	Grinsted landfill – distance 15 m	190[g]–330	20	6
	Denmark	Grinsted landfill – distance 37 m	<20[g]–190	20	6
	Denmark	Grinsted landfill – distance 50 m	<20[g]–70	20	6
	Denmark	Grinsted landfill – distance 82 m	<20	20	6

Table 7 (continued)

Compound	Country	Groundwater sampling location	Concentration (μg /L)	LOD (Q) (μg /L)	Reference
Sulfamethoxazole	Germany	Baden–Wurttemberg[a] $n = 11$ samples	0.410[b]	0.0018 (0.0062)	1
	Germany		0.47[b]	0.02	7
	Germany	Braunschweig – 6 wells in irrigation area	LOQ[C] – 0.11 ± 0.07	0.025	8
	USA	Wisconsin – Lake Geneva	0.01 and 0.08	0.05 (LOQ)	9
	USA	Nebraska wells	0.002	0.023	2
Sulfanylamide	Denmark	Grinsted landfill – distance 0 m	40[g]–170	20	6
	Denmark	Grinsted landfill – distance 15 m	210[g]–300	20	6
	Denmark	Grinsted landfill – distance 37 m	30[g]–170	20	6
	Denmark	Grinsted landfill – distance 50 m	<20[g]–40	20	6
	Denmark	Grinsted landfill – distance 82 m	<20	20	6
Sulfanilic acid	Denmark	Grinsted landfill – distance 0 m	930[g]–6470	20	6
	Denmark	Grinsted landfill – distance 15 m	6280[g]–10440	20	6
	Denmark	Grinsted landfill – distance 37 m	1000[g]–5530	20	6
	Denmark	Grinsted landfill – distance 50 m	70[g]–1610	20	6
	Denmark	Grinsted landfill – distance 82 m	50	20	6
	Denmark	Grinsted landfill – distance 115 m	<20[g]–45	20	6
Tetracycline antibiotics					
Chlorotetracycline	Germany		nd	0.02 (LOQ)	7
Doxycycline	Germany		nd	0.02 (LOQ)	7
Oxytetracycline	Germany		nd	0.02 (LOQ)	7
Tetracycline	Germany		nd	0.02 (LOQ)	7
	USA	Wisconsin – Lake Geneva	0.5	0.05 (LOQ)	9
	USA	Wisconsin – Spooner	0.34	0.05 (LOQ)	9
Other antibiotics					
Chloramphenicol	Germany		nd	0.02 (LOQ)	7
Trimethoprim	Germany		nd	0.02 (LOQ)	7
Antiepileptics					
Carbamazepine	Germany	Baden–Wurttemberg[a] $n = 13$ samples	0.900[b]	0.0096 (0.032)	1

Table 7 (continued)

Compound	Country	Groundwater sampling location	Concentration (μg /L)	LOD (Q) (μg /L)	Reference
	Germany	Lake Wansee transect – 4 shallow wells	0.160[c]–0.360	0.001–0.0010	2
	Germany	Lake Wansee transect – 3 deep wells	nd	0.001–0.0010	2
	Germany	Lake Wansee transect – water supply well	0.020	0.001–0.0010	2
	Germany		1.1[b]		3
	Germany	Braunschweig – 6 wells in irrigation area	3.2[c] ± 1.9 – 9.6 ± 6.3	0.025	8
Primidone	Germany	Lake Wansee transect – 4 shallow wells	0.195[c]–0.535	0.001–0.0010	2
	Germany	Lake Wansee transect – 3 deep wells	nd	0.001–0.0010	2
	Germany	Lake Wansee transect – water supply well	0.015	0.001–0.0010	2
β-Blocker					
Sotalol	Germany	Baden–Wurttemberg[a] $n = 3$ samples	0.560[b]	0.0023 (0.0080)	1
Hormones and steroids					
17α-Oestradiol	Austria	$n = 59$ groundwater sites	0.00021[b]	0.001 (LOQ)	10
17α-Ethinylstradiol	Austria	$n = 59$ groundwater sites	0.00094[b]	0.0001 (LOQ)	10
17β-Oestradiol	Austria	$n = 59$ groundwater sites	0.00079[b]	0.001 (LOQ)	10
Oestriol	Austria	$n = 59$ groundwater sites	0.00016[b]	0.003 (LOQ)	10
Oestrone	Austria	$n = 59$ groundwater sites	0.0016[b]	0.001 (LOQ)	10
Iodinated X-ray contrast media					
Amidotrizoic acid	Germany	Baden–Wurttemberg[a] $n = 21$ samples	1.100[b]	00036 (0.012)	1
Diatrizoate	Germany	Hessian Ried	0.03[b]–0.17	0.010 (LOQ)	11
Iopamidol	Germany	Baden–Wurttemberg[a] $n = 5$ samples	0.300[b]	0.0045 (0.014)	1
	Germany	Hessian Ried	0.16[h]–2.4	0.010 (LOQ)	11
	Germany	Braunschweig – 6 wells in irrigation area	<LOQ[c] – 0.07	0.025	8
Iopromide	Germany	Hessian Ried	<0.010[h]–0.21	0.010 (LOQ)	11
Iothalamic acid	Germany	Hessian Ried	<0.010[h]–0.049	0.010 (LOQ)	11
Ioxithalamic acid	Germany	Hessian Ried	<0.010[h]–0.010	0.010 (LOQ)	11
Lipid regulator					
Bezafibrate	Germany	Lake Wansee transect – 4 shallow wells	nd[c]–0.020	0.001–0.0010	2
	Germany	Lake Wansee transect – 3 deep wells	nd	0.001–0.0010	2

Table 7 (continued)

Compound	Country	Groundwater sampling location	Concentration (μg /L)	LOD (Q) (μg /L)	Reference
	Germany	Lake Wansee transect – water supply well	nd	0.001–0.0010	2
	Germany		0.19[b]		3
Lipid regulators – metabolite					
Clofibric acid	Germany	Lake Wansee transect – 4 shallow wells	nd[c]–0.060	0.001–0.0010	2
	Germany	Lake Wansee transect – 3 deep wells	nd	0.001–0.0010	2
	Germany	Lake Wansee transect – water supply well	0.070	0.001–0.0010	2
	Germany		11[b,e]		3
	Germany		4.2[b,d]	0.001	12
Other pharmaceuticals					
1,7-Dimethylxanthine	USA	Nebraska wells	nd	0.019	2
Caffeine	USA	Nebraska wells	nd	0.500 (LOQ)	2

LOD – limit of detection; LOQ – limit of quantification; nd – not detected. References: 1 – Sacher et al. (2001); 2 – Heberer et al. (2001c); 3 – Ternes (2001a); 4 – Ahel and Jeličić (2001); 5 – Reddersen et al. (2002); 6 – Holm et al. (1995); 7 – Hirsch et al. (2004); 8 – Ternes et al. (2007); 9 – Karthikeyan and Bleam (2003); 10 – Hohenblum et al. (2004); 11 – Ternes and Hirsch (2000); 12 – Scheytt et al. (2001)

[a]n = number of positive results in 105 samples

[b]Maximum concentration

[c]Minimum and maximum concentrations detected

[d]Groundwater influenced by STP (sewage treatment plant) effluent irrigation

[e]Groundwater influenced by a landfill site

[f]Mean

[g]Minimum and maximum concentration from a depth of 5.5 m at 10 m

[h]Median and maximum concentrations

Table 8 Occurrence of pharmaceuticals in drinking water

Compound	Country	Sampling location	Concentration (μg/L)	LOD (Q) (μg/L)	Reference
Analgesics and anti-inflammatories					
Acetaminophen	USA		nd	0.009	1
	USA	Ann Arbor	<0.0020	0.002	2
Acetylsalicylic acid	Germany		<0.010	0.010 (LOQ)	3
Codeine	USA		nd	0.24	1
Diclofenac	Germany		<0.001[a] –0.006	0.001 (LOQ)	3
Dimethylaminophenazone	Germany	Berlin	nd	0.050 (LOQ)	4
	Germany		<0.020	0.020 (LOQ)	3
Fenoprofen	Germany		<0.005	0.005 (LOQ)	3
Ibuprofen	Canada	Ontario	nd	0.0026	5
	Germany		<0.001[a]–0.003	0.001 (LOQ)	3
	USA		nd	0.018	1
	USA	Louisiana	nd	0.0026	5
	USA	Ann Arbor	0.0018 + 0.001	0.002	2
Indomethacin	Germany		<0.005	0.005 (LOQ)	3
Ketoprofen	Germany		<0.005	0.005 (LOQ)	3
Naproxen	USA	Louisiana	nd	0.0004	5
	Canada	Ontario	nd	0.0004	5
Phenazone	Germany	Berlin	0.400[b]	0.050 (LOQ)	4
	Germany		<0.010[a]–0.050	0.010 (LOQ)	3
Propyphenazone	Germany	Berlin	0.120[b]	0.005 (LOQ)	4
Metabolites – analgesics and anti-inflammatories					
AMDOPH	Germany	Berlin	0.900[b]	0.010 (LOQ)	4
AMPH	Germany	Berlin	0.030[b] (estimated)	0.020 (LOQ)	4
DMOAS	Germany	Berlin	Traces	0.010 (LOQ)	4
Salicylic acid	Germany		<0.010	0.010 (LOQ)	3

Table 8 (continued)

Compound	Country	Sampling location	Concentration (μg/L)	LOD (Q) (μg/L)	Reference
Fluoroquinolone antibiotics					
Ciprofloxacin	USA		nd	0.02	1
Enrofloxacin	USA		nd	0.02	1
Norfloxacin	USA		nd	0.02	1
Macrolide antibiotics					
Clarithromycin	Germany		<0.020	0.020 (LOQ)	3
Erythromycin[c]	Germany		<0.020	0.020 (LOQ)	3
	USA		nd	0.05	1
Lincomycin	USA		nd	0.05	1
	USA	Ann Arbor	<0.0010	0.001	2
Roxithromycin	Germany		<0.020	0.020 (LOQ)	3
	USA		nd	0.03	1
Penicillin antibiotics					
Cloxacillin	Germany		<0.050	0.050 (LOQ)	3
Dicloxacillin	Germany		<0.050	0.050 (LOQ)	3
Methicillin	Germany		<0.050	0.050 (LOQ)	3
Nafcillin	Germany		<0.050	0.050 (LOQ)	3
Oxacillin	Germany		<0.050	0.050 (LOQ)	3
Penicillin G	Germany		<0.050	0.050 (LOQ)	3
Penicillin V	Germany		<0.050	0.050 (LOQ)	3
Sulfonamide antibiotics					
Sulfamethazine	Germany		<0.020	0.020 (LOQ)	3
	USA		nd	0.05	1
	USA	Ann Arbor	<0.0010	0.001	2
Sulfamethizole	USA		nd	0.05	1
Sulfonamide antibiotics					
Sulfamethoxazole	Germany		<0.020	0.020 (LOQ)	3

Table 8 (continued)

Compound	Country	Sampling location	Concentration (μg/L)	LOD (Q) (μg/L)	Reference
	USA		nd	0.05	1
	USA	Nebraska – bank filtration sites	0.006[d]	0.023	6
	USA	Ann Arbor	<0.0010	0.001	2
Sulfathiazole	USA		nd	0.10	1
	USA	Ann Arbor	<0.0010	0.00	2
Tetracycline antibiotics					
Chlorotetracycline	Germany		<0.020	0.020 (LOQ)	3
	USA		nd	0.05	1
Democlocycline	USA		nd	0.05	1
Doxycycline	Germany		<0.020	0.020 (LOQ)	3
	USA		nd	0.1	1
Oxytetracycline	Germany		<0.020	0.020 (LOQ)	3
	USA		nd	0.1	1
Tetracycline	Germany		<0.020	0.020 (LOQ)	3
	USA		nd	0.05	1
Other antibiotics					
Chloramphenicol	Germany		<0.020	0.020 (LOQ)	3
Trimethoprim	Germany		<0.020	0.020 (LOQ)	3
	USA		nd	0.03	1
	USA	Ann Arbor	<0.0010	0.001	2
Antidepressant					
Fluoxetine	Canada	Ontario	nd	0.0254	5
	USA		nd	0.018	1
	USA	Louisiana	nd	0.0254	5
Antiepileptics					
Carbamazepine	USA		−0.258[d]	0.011	1
	USA	Ann Arbor	<0.0010	0.001	2
	Germany		<0.010[a]–0.030	0.010 (LOQ)	3

Table 8 (continued)

Compound	Country	Sampling location	Concentration (μg/L)	LOD (Q) (μg/L)	Reference
Antineoplastic agents					
Cyclophosphamide	Germany		<0.010	0.010 (LOQ)	3
Ifosfamide	Germany		<0.010	0.010 (LOQ)	3
β-Blockers					
Atenolol	Germany		<0.005	0.005 (LOQ)	3
Betaxolol	Germany		<0.005	0.005 (LOQ)	3
Bisoprolol	Germany		<0.005	0.005 (LOQ)	3
Carazolol	Germany		<0.005	0.005 (LOQ)	3
Celiprolol	Germany		<0.005	0.005 (LOQ)	3
Metoprolol	Germany		<0.005	0.005 (LOQ)	3
Nadolol	Germany		<0.005	0.005 (LOQ)	3
Propanolol	Germany		<0.005	0.005 (LOQ)	3
Sotalol	Germany		<0.005	0.005 (LOQ)	3
Timolol	Germany		<0.005	0.005 (LOQ)	3
β2-Sympathomimetics					
Clenbuterol	Germany		<0.010	0.010 (LOQ)	3
Fenoterol	Germany		<0.005	0.005 (LOQ)	3
Salbutamol	Germany		<0.005	0.005 (LOQ)	3
	USA		nd	0.029	1
Terbutalin	Germany		<0.010	0.010 (LOQ)	3
Hormones and steroids					
17α-Ethinyloestradiol	Germany		<0.005	0.005 (LOQ)	3
17β-Oestradiol	Canada	Ontario	nd	0.0001	5
Oestrone	USA	Louisiana	nd	0.0003	5
	Canada	Ontario	nd	0.0003	5
Iodinated X-ray contrast media					
Diatrizoate	Germany		0.021[a]–0.085	0.010 (LOQ)	3
Iopamidol	Germany		<0.010[a]–0.079	0.010 (LOQ)	3

Table 8 (continued)

Compound	Country	Sampling location	Concentration (μg/L)	LOD (Q) (μg/L)	Reference
Iopromide	Germany		<0.010[a]–0.086	0.010 (LOQ)	3
Iothalamic acid	Germany		<0.010	0.010 (LOQ)	3
Ioxithalamic acid	Germany		<0.010	0.010 (LOQ)	3
Lipid regulators					
Bezafibrate	Germany		<0.025[a]–0.027	0.025 (LOQ)	3
Clofibrate	Germany		<0.020	0.020 (LOQ)	3
Etofibrate	Germany		<0.020	0.020 (LOQ)	3
Fenofibrate	Germany		<0.020	0.020 (LOQ)	3
Gemfibrozil	Germany		<0.005	0.005 (LOQ)	3
	USA		nd	0.015	1
Metabolites – lipid regulators					
Clofibric acid	Canada	Ontario	nd	0.0008	5
	Germany		0.001[a]–0.070	0.001 (LOQ)	3
	USA	Louisiana	nd	0.0008	5
Fenofibric acid	Germany		<0.005[a]–0.042	0.005 (LOQ)	3
Other pharmaceuticals					
Caffeine	USA		0.119[d]	0.014	1
(psychomotor stimulant)	USA	Nebraska – bank filtration sites	0.043[d]	0.500 (LOQ)	6
Cimetidine	USA		nd	0.007	1
Cotinine	USA		0.025[d]	0.023	1
Dehydronifedipine	USA		0.004[d]	0.01	1
Diazepam	Germany		<0.020	0.020 (LOQ)	3
Digoxigenin	USA		nd	0.008	1
Diltiazem	USA		nd	0.012	1
Diphenhydramine	USA		nd	0.0148	1
1,7-Dimethylxanthine	USA		nd	0.018	1
	USA	Nebraska – bank filtration sites	nd	0.023	6
Pentoxifylline	Germany		<0.010	0.010 (LOQ)	3

Table 8 (continued)

Compound	Country	Sampling location	Concentration (μg/L)	LOD (Q) (μg/L)	Reference
Ranitidine	USA		nd	0.01	1

AMDOPH – phenazone-type metabolite – 1-acetyl-1-methyl-2-dimethyl-oxamoyl-2-phenylhydrazide; AMPH – phenazone-type metabolite – 1-acetyl-1-methyl–2-phenylhydrazide; DMOAS – phenazone-type metabolite – dimethyloxamide acid-(*N*'-methyl-*N*-phenyl)-hydrazide. References: 1 – Stackelberg et al. (2004); 2 – Skadsen et al. (2004); 3 – Ternes (2001a); 4 – Reddersen et al. (2002); 5 – Boyd et al. (20032003); 6 – Heberer et al. (2001a)

[a]Median and maximum concentration

[b]Mean

[c]Erythromycin is not detected in environmental samples in its original form but as dehydrated Erythromycin, with the loss of one molecule of water (Hirsch et al. 1999)

[d]Highest concentration

Table 9 Occurrence of pharmaceuticals in sediments

Compound	Country	Sample	Location	Concentration (μg/kg)	LOD (Q) (μg/kg)	Reference
Analgesic						
Diclofenac	Switzerland	Lake sediments	Lake Greifensee	nd	<10	1
Fluoroquinolone antibiotic						
Flumequine	Italy		Trout and sea bass farms	578.8[a]	0.012	2
Tetracycline antibiotic						
Oxytetracycline	Italy		Trout and sea bass farms	246.3[a]	0.061	2
Hormones and seroids						
17α-Ethinyloestradiol	Australia	Ocean sediments	Malabar, Sidney	<0.05[b]–0.5	0.05 (LOQ)	3
	Germany	Eight river sediments		<LOQ[c]–0.9	0.4 (LOQ)	4
	Spain	Rver sediments	Anoia River	nd[b]–22.8	1.00	5
	Spain	River sediments	Cardener River	nd[b]–4.16	1.00	5
17β-Oestradiol	Australia	Ocean sediments	Malabar, Sidney	0.22[b]–2.48	0.05 (LOQ)	3
	Germany	Eight river sediments		<LOQ[c]–1.5	0.2 (LOQ)	4
Diethylstilbestrol	Spain	River sediments	Anoia River	nd[b]–2.01	0.10	5
	Spain	River sediments	Cardener River	nd[b]	0.10	5
Oestradiol	Spain	River sediments	Anoia River	nd[b]	1.00	5
	Spain	River sediments	Cardener River	nd[b]	1.00	5
Oestriol	Spain	River sediments	Anoia River	nd[b]–3.37	0.05	5
	Spain	River sediments	Cardener River	nd[b]–2.92	0.05	5
Oestrone	Australia	Ocean sediments	Malabar, Sidney	0.16[b]–1.17	0.05 (LOQ)	3
	Germany	Eight river sediments		<LOQ[c]–2	0.2 (LOQ)	4
	Spain	River sediments	Anoia River	nd[b]–3.55	0.50	5
	Spain	River sediments	Cardener River	nd[b]–11.9	0.50	5
Levonorgestrel	Spain	River sediments	Anoia River	nd[b]–1.20	0.04	5

Table 9 (continued)

Compound	Country	Sample	Location	Concentration (μg/kg)	LOD (Q) (μg/kg)	Reference
	Spain	River sediments	Cardener River	nd[b]–2.18	0.04	5
Mestranol	Germany	Eight river sediments		<LOQ	0.4 (LOQ)	4
Norethindrone	Spain	River sediments	Anoia River	nd[b]–0.79	0.04	5
	Spain	River sediments	Cardener River	nd[b]–1.08	0.04	5
Progesterone	Spain	River sediments	Anoia River	nd[b]–2.00	0.04	5
	Spain	River sediments	Cardener River	nd[b]–6.82	0.04	5
Antihistimine						
Diphenhydramine	USA	River sediments	Five locations within USA	<LOD–48.6	5	6

nd – not detected. References: 1 – Buser et al. (1998b); 2 – Lalumera et al. (2004); 3 – Braga et al. (2005); 4 – Ternes et al. (2002a); 5 – López de Alda et al. (2002); 6 – Ferrer et al. (2004)

[a]From aquaculture

[b]Minimum and maximum concentrations detected

[c]Median and maximum concentrations detected

5.1.1 Analgesics and Anti-inflammatories

Pharmaceuticals belonging to this therapeutic class have been widely reported in sewage treatment effluents and surface waters in Europe, the United States and Canada. With the exception of acetylsalicylic acid, compounds that are sold in higher quantities, such as ibuprofen, diclofenac, acetaminophen and naproxen, are the ones more often detected in effluents at the highest concentrations. Salicylic acid is the degradation product from a number of compounds, including acetylsalicylic acid. Acetylsalicylic acid has been detected in the aquatic environment at low levels, but salicylic acid has been detected at much higher concentrations (Farré et al. 2001; Ternes 1998). Other analgesics and anti-inflammatories detected in both sewage effluent samples and surface waters include fenoprofen, indomethacin, ketoprofen and phenazone (Andreozzi et al. 2003; Bendz et al. 2005; Metcalfe et al. 2003; Ternes 1998; Wiegel et al. 2004). In groundwater samples, diclofenac, dimethylaminophenazone, phenazone and propyphenazone were detected (Ahel and Jeličić 2001; Heberer et al. 2001a; Holm et al. 1995; Reddersen et al. 2002; Sacher et al. 2001; Ternes 2001a). In drinking water samples, most analgesic and anti-inflammatory pharmaceuticals, for which analyses was conducted, were not detected above limits of detection (Boyd et al. 2003; Skadsen et al. 2004; Stackelberg et al. 2004). The exceptions were phenazone, propyphenazone and phenazone-type metabolites, diclofenac and ibuprofen (Reddersen et al. 2002; Ternes 2001a).

5.1.2 Antibiotics

Macrolides, sulfonamides, tetracyclines, fluoroquinolones, chloramphenicol and trimethoprim have been identified in sewage effluents and surface waters from Europe and the United States. Although members of the penicillin class are sold in the highest amounts, they have not generally been detected in any of the analysed samples from sewage effluents or surface waters in Germany (Hirsch et al. 1999). The reason may be the chemical instability of the β-lactam ring of the penicillins, which is rapidly hydrolysed and degraded (Hirsch et al. 1999). However, Zuccato et al. (2005a) reported a median value of 4.7 ng/L for amoxicillin in Italian sewage effluents, although surface water concentrations were below detection limits.

The most frequent detected antibiotic in environmental samples is the degradation product of the macrolide erythromycin. Erythromycin is excreted with an apparent loss of one molecule of water, thus the degradation product, dehydrated erythromycin, is detected in environmental samples (Hirsch et al. 1999). The highest concentration (median value of 2.5 μg/L) was observed in effluents from STPs in Germany (Hirsch et al. 1999); much lower concentrations were detected in other countries.

The fluoroquinolone antibiotics ciprofloxacin, norfloxacin, ofloxacin, enoxacin and lomefloxacin have been detected in all sewage effluents samples

collected in France, Italy, Greece and Sweden (Andreozzi et al. 2003). The occurrence of the fluoroquinolone antibiotic flumequine has also been reported in sediments from trout and sea bass farms in Italy (Lalumera et al. 2004).

Sulfonamide antibiotics, particularly sulfamethoxazole, have been reported in sewage effluent samples in Europe, Canada and the United States. In Canada, sulfamethoxazole and sulfapyridine were identified in all effluent samples (Miao et al. 2004). Sulfamethoxazole was identified in surface waters from the United States (Kolpin et al. 2002; Skadsen et al. 2004; Yang and Carlson 2004a), although it has not been detected in the United Kingdom, or in Italy (Ashton et al. 2004; Hilton and Thomas 2003; Zuccato et al. 2005a). However, in the United Kingdom, its major metabolite, acetylsulfamethoxazole, has been detected in sewage effluents (Ashton et al. 2004) and in rivers downstream of STP discharges (Ashton et al. 2004; Hilton and Thomas 2003).

Miao et al. (2004) reported the occurrence of doxycycline and tetracycline in final effluents from STPs in Canada. Democlocycline was found in sewage effluents and in surface waters in the United States (Yang and Carlson 2004a). Oxytetracycline was detected in sediments collected from trout and sea bass farms (Lalumera et al. 2004).

Other antibiotics such as trimethoprim were very frequently detected in both final effluents and surface waters in Europe, Canada and the United States (Andreozzi et al. 2003; Metcalfe et al. 2003; Renew and Huang 2004). In Germany, Hirsch et al. (1999) detected another antibiotic, chloramphenicol, in sewage effluents and in surface waters at levels up to 0.56 and 0.06 μg/L, respectively.

In groundwater samples, with the exception of tetracycline itself, the following antibiotics have not been detected: the tetracyclines, the penicillins, chloramphenicol and trimethoprim (Hirsch et al. 1999; Karthikeyan and Bleam 2003). Sulfonamides have been detected in high concentrations in groundwater below a landfill site in Denmark (Holm et al. 1995).

Drinking water samples were analysed for fluoroquinolones, sulfonamides, macrolides, penicillins, tetracyclines, chloramphenicol and trimethoprim, but no antibiotics were detected (Stackelberg et al. 2004; Skadsen et al. 2004).

5.1.3 Beta-Blockers

The β-blockers metoprolol, propranolol, betaxolol, bisoprolol and carazolol were detected in German sewage effluents and surface waters (Ternes 1998). In contrast, betaxolol was not detected in any sewage effluent sample from Greece, France, Italy and Sweden, and atenolol and oxprenolol were also detected (Andreozzi et al. 2003).

In groundwater samples, sotalol was the only compound from this class to be investigated and was detected as a contaminant (Sacher et al. 2001). Drinking water samples were investigated for β-blockers, but none were found above limits of detection (Ternes 2001a).

5.1.4 Hormones and Steroids

The reproductive hormones 17β-oestradiol, oestrone, 16α-hydroxyoestrone and the contraceptive 17α-ethinyloestradiol were detected at low concentrations in sewage effluents from Canada and Germany, whereas mestranol was only detected in Germany (Servos et al. 2005; Ternes et al. 1999). In Spain and The Netherlands, oestrone was identified in final effluents at approximately the same concentration (Belfroid et al. 1999; Carballa et al. 2004). Although 17α-oestradiol was not detected in effluents from STPs, it was found in The Netherlands in coastal waters and also in Austrian rivers (Belfroid et al. 1999; Hohenblum et al. 2004).

Kolpin et al. (2002) reported the occurrence of the reproductive hormones 17α-oestradiol, 17β-oestradiol, oestriol, oestrone, progesterone, testosterone, the oestrogen replacements, equilenin and equilin, as well as the ovulation inhibitors 17α-ethinyloestradiol, 19-norethisterone and mestranol, and the steroid *cis*-androsterone in US streams. Oestrone and ethinyloestradiol have been detected in both ocean and river sediments (Braga et al. 2005; López de Alda et al. 2002). In Australia, near a deep ocean sewage outfall, steroid hormones were detected in all samples of ocean sediments at the nanogram per gram level (Braga et al. 2005). López de Alda et al. (2002) also detected oestrogens and progestogens in river sediments in Spain, recording maximum concentrations of ethinyloestradiol and oestrone at 22.8 and 11.9 ng/g, respectively. In Austrian groundwater samples, hormones were detected (Hohenblum et al. 2004), but were below limits of detection in drinking water samples (Boyd et al. 2003).

5.1.5 Lipid Regulators

Several lipid regulators and their metabolites have been found in sewage effluents and surface waters in Europe, Brazil, Canada and the United States (Bendz et al. 2005; Boyd et al. 2003; Farré et al. 2001; Metcalfe et al. 2003; Stumpf et al. 1999; Ternes 1998). Metcalfe et al. (2003) reported the occurrence of atorvastatin, bezafibrate and gemfibrozil in final effluent and surface water samples from Canada. In Germany, Ternes (1998) detected bezafibrate and gemfibrozil in sewage effluents and in rivers and streams, whereas etofibrate and clofibrate were not detected in any of the matrices, and fenofibrate was only found in two effluents. However, Andreozzi et al. (2003) reported clofibrate in an effluent in Greece, and fenofibrate in Italy, France and Greece sewage effluents. Clofibric acid and fenofibric acid, the polar metabolites of etofibrate, clofibrate and fenofibrate were frequently detected in sewage effluents at the nanogram per litre level in German surface waters (Ternes 1998; Ternes et al. 2003). On the other hand, Andreozzi et al. (2003) only found clofibric acid in half of the STPs studied, and according to this author, other drugs, like gemfibrozil and fenofibrate might have replaced the corresponding parent compounds. In surface waters, clofibric acid was also found in Austria, Brazil, Italy, Switzerland, the United Kingdom and the United States (Ahrer et al. 2001; Boyd et al. 2003;

Calamari et al. 2003; Öllers et al. 2001; Stumpf et al. 1999; Thomas and Hilton 2004; Tixier et al. 2003). This metabolite (clofibric acid) was also detected in the North Sea off the coasts of Germany, The Netherlands, Norway and the inner German Bight with concentrations that ranged from 0.28 to 1.35 ng/L (Weigel et al. 2002).

Bezafibrate and clofibric acid were investigated and detected in ground and drinking water samples (Boyd et al. 2003; Heberer et al. 2001b; Scheytt et al. 2001; Ternes 2001a). Other lipid regulators were not detected in drinking water samples (Boyd et al. 2003; Stackelberg et al. 2004).

5.1.6 Antidepressants

Fluoxetine was the only antidepressant detected in sewage effluents (Metcalfe et al. 2003) and in surface waters from Canada and the United States (Metcalfe et al. 2003; Kolpin et al. 2002). Norfluoxetine, lofepramine and a paroxetine metabolite were not identified in surface waters in the United Kingdom, Canada or the United States (Hilton and Thomas 2003; Kolpin et al. 2002; Metcalfe et al. 2003).

Antidepressants have not been investigated in groundwaters, and fluoxetine was not detected in drinking water samples from Canada or the United States (Boyd et al. 2003; Stackelberg et al. 2004).

5.1.7 Antiepileptics

Carbamazepine is the most often used antiepileptic, and it has been frequently detected in final sewage effluents and surface waters (Bendz et al. 2005; Metcalfe et al. 2003; Öllers et al. 2001; Ternes 1998; Zuccato et al. 2005a). In sewage effluents, concentrations above 1 μg/L were detected in France, Germany, Greece and Sweden (Andreozzi et al. 2003; Bendz et al. 2005; Ternes 1998; Ternes et al. 2003). In German surface waters, carbamazepine was detected at median values of 0.25 μg/L (Ternes 1998; Wiegel et al. 2004). In Canada, Miao et al. (2005) reported the occurrence of carbamazepine metabolites in final sewage effluents, and one of its metabolites (10,11-dihydro-10,11-dihydroxy-carbamazepine) was identified. Another antiepileptic drug, primidone, has also been reported in the Lake Wannsee, in Germany (Heberer et al. 2001a).

In groundwater samples from Germany, carbamazepine and primidone have been detected (Sacher et al. 2001; Heberer et al. 2001b; Ternes 2001a; Ternes et al. 2007). Carbamazepine has also been reported in drinking water samples in the United States and Germany (Stackelberg et al. 2004; Ternes 2001a).

5.1.8 Antineoplastic Agents

Cyclophosphamide and ifosfamide were detected in an effluent from a hospital in Germany (Steger-Hartmann et al. 1996). They were also detected in sewage effluents and some river water samples in Canada, Italy and Germany

(Metcalfe et al. 2003; Zuccato et al. 2005a; Ternes 1998). Two antineoplastic agents, methotrexate and tamoxifen, were not detected in sewage effluents or surface waters in Italy (Zuccato et al. 2005a), but tamoxifen was present in United Kingdom sewage effluents and in river estuaries at levels up to 71 ng/L (Ashton et al. 2004; Thomas and Hilton 2004).

Antineoplastic agents were not investigated in groundwater samples and were below limits of detection in drinking water samples (Ternes 2001a).

5.1.9 β_2-Sympathomimetics

In sewage effluents and rivers in Germany, salbutamol, terbutaline, clenbuterol and fenoterol were only sporadically detected, all with median concentrations below detection limits (Ternes 1998). Salbutamol was not found in US streams, and in Italy it was detected, but at very low concentrations (Kolpin et al. 2002; Calamari et al. 2003; Zuccato et al. 2005a). β_2-Sympathomimetics were not investigated in ground water samples, and salbutamol was not detected in drinking water samples (Stackelberg et al. 2004).

5.1.10 Iodinated X-ray Contrast Media

In Germany, Ternes and Hirsch (2000) reported the occurrence of X-ray contrast media in effluents from STPs and receiving waters. The loading of these compounds increased on weekdays because their application mainly takes place in hospitals and radiological practices during the regular workweek. Iopadimol, iopromide, iothalamic acid, ioxitalamic acid and diatrizoate were found (Ternes and Hirsch 2000; Ternes et al. 2003). In the same study, levels of these compounds were reported in rivers and creeks that received effluent discharge from STPs. Iodinated X-ray contrast media metabolites were not found in final effluents or surface waters in Germany (Ternes and Hirsch 2000).

Diatrizoate, iopadimol and iopromide have been detected in both ground and drinking water samples (Sacher et al. 2001; Ternes et al. 2007; Ternes and Hirsch 2000; Ternes 2001a). Amidotrizoic, iothalamic and ioxithalamic acids were also identified in groundwater, but were below limits of detection in drinking water samples (Sacher et al. 2001; Ternes and Hirsch 2000; Ternes 2001a).

5.1.11 Other Pharmaceuticals

Other pharmaceuticals, including antacids, diuretics, anxyolitic, antihypertensives, antidiabetics, and even an illicit drug, have been reported in sewage effluents and surface waters in Europe, Canada and the United States.

Caffeine, a psychomotor stimulant, was detected in effluents from sewage treatment plants and surface waters (Bendz et al. 2005; Kolpin et al. 2002; Metcalfe et al. 2003; Ternes et al. 2001b, 2003; Weigel et al. 2004). The highest concentration (up to 126 μg/L) was detected from an STP in Norway. However,

these high concentrations were detected in October when the volume flow was one-third of what it is in spring, and the contribution of the melting snow to the sewage flow has to be taken into account. In the same study, caffeine was even detected in the open North Sea/Artic Ocean (Weigel et al. 2004). The caffeine metabolite, 1,7-dimethylxanthine, was only studied in the United States and was found at a median concentration of 0.11 μg/L (Kolpin et al. 2002; Heberer et al. 2001a). The illicit drug cocaine and its major urinary metabolite, benzoylecgonine, were found in sewage effluent samples in Italy at concentrations as high as 120 and 750 ng/L, respectively; benzoylecgonine was also found in the Po River (Zuccato et al. 2005b). In Canada, Metcalfe et al. (2003) reported the occurrence of the nicotine metabolite cotinine in final effluents of STPs, which was also found in surface waters in the same country and streams in the United States (Kolpin et al. 2002). Diazepam, an anxyolitic agent, has been identified in final effluents and surface waters in Germany and in the United Kingdom (Ternes 1998; Ternes et al. 2001b; Richardson and Bowron 1985), whereas it was not detected in nine STPs from Italy (Zuccato et al. 2005a). Nevertheless, in Italy it was detected in surface waters (Calamari et al. 2003). The occurrence of antihypertensives in the aquatic environment was also investigated, but in effluents of STPs only enalapril and nifedipine were studied. Enalapril was not found in STPs, but was present in surface waters in Italy (Zuccato et al. 2005a), and nifedipine was found in sewage effluents from Germany, but not in rivers and streams (Ternes et al. 2001b). In US streams, the metabolites of these compounds, enalaprilat and dehydronifedipine, were detected, as was another antihypertensive, diltiazem (Kolpin et al. 2002). Diuretics, such as furosemide and hydrochlorothiazide, were also studied in Italy and were detected in final effluents from STPs (Calamari et al. 2003; Zuccato et al. 2005a). Metformin, another antidiabetic, was reported to be present in US streams (Kolpin et al. 2002). The antacid omeprazole was not identified in effluents of STPs or rivers in Germany or Italy, although ranitidine was detected in both matrices in Italy, and, together with cimetidine in US streams (Kolpin et al. 2002; Ternes et al. 2001b; Zuccato et al. 2005a). Finally, the cardiac stimulant digoxin and its metabolite digoxigenin were investigated in US streams but were not detected (Kolpin et al. 2002). The antihistaminic diphenhydramine has been reported in aquatic sediments samples collected downstream five different wastewater treatment plants in the United States, with a maximum concentration of 48.6 ng g^{-1} (Ferrer et al. 2004).

Groundwater samples were investigated for caffeine and 1,7-dimethylxanthine but they were not detected (Heberer et al. 2001a). However, both cotinine and dehydronifedipine were found above limits of detection in US drinking water (Stackelberg et al. 2004). Other pharmaceuticals were investigated in drinking water samples, but were not detected (Heberer et al. 2001a; Stackelberg et al. 2004).

Table 10 Occurrence of pharmaceuticals in sewage sludge

Compound	Country	Sample	Location	Concentration (mg/kg[a] DW [dry weight])	LOD (Q) (mg/kg [a] (DW)	Reference
Fluoroquinolone antibiotics						
Norfloxacin	Switzerland	Excess sludge[b]	Zurich-Werdholzli	2.6[c] + 0.1	0.12 (0.45)	4
	Switzerland	Raw sludge[b]	Zurich-Werdholzli	2.1[c] + 0.2	0.12 (0.45)	4
	Switzerland	Digested sludge[b]	Zurich-Werdholzli	2.9[c] + 0.4	0.12 (0.45)	4
Ofloxacin	Sweden	Anaerobic digested sludge	Five STPs (2002)	0.975[c]	0.1 (LOQ)	2
	Sweden	Anaerobic digested sludge	Five STPs (2003)	0.475[c]	0.1 (LOQ)	2
Macrolide antibiotics						
Azithromycin	Switzerland	Activated sludge		$(64 + 30)^c \times 10^{-3}$	$(3–30) \times 10^{\times 3}$ (LOQ)	5
	Switzerland	Digested sludge		2.5[c] + 1.0 μg/L	1–220 ng/L	5
Clarithromycin	Switzerland	Activated sludge		$(67 + 28)^c \times 10^{\times 3}$	$(3–30) \times 10^{-3}$ (LOQ)	5
	Switzerland	Digested sludge		0.7[c] + 0.4 μg/L	1–220 ng/L	5
Erythromycin	Switzerland	Sewage sludge		$<6 \times 10^{-3}$	6×10^{-3} (LOQ)	5
Roxithromycin	Switzerland	Sewage sludge		$<3 \times 10^{-3}$	3×10^{-3} (LOQ)	5
Sulfonamide antibiotics						
Sulfamethoxazole	Switzerland	Activated sludge		$(68 + 20)^c \times 10^{\times 3}$	$(3–30) \times 10^{-3}$ (LOQ)	5
	Switzerland	Digested sludge		Nd	1–220 ng/L	5
Sulfapyridine	Switzerland	Activated sludge		$(28 + 3)^c \times 10^{\times 3}$	$(3–30) \times 10^{-3}$ (LOQ)	5
	Switzerland	Digested sludge		1.0[c] + 0.1 μg/L	1–220 ng/L	5

Table 10 (continued)

Compound	Country	Sample	Location	Concentration (mg/kg[a] DW [dry weight])	LOD (Q) (mg/kg [a] (DW)	Reference
Metabolite – sulfonamide antibiotic						
N^4-Acetyl sulfamethoxazole	Switzerland	Activated and digested sludge		nd		5
Other antibiotic						
Trimethoprim	Switzerland	Activated sludge		$(41 + 15)^c \times 10^{-3}$	$(3–30) \times 10^{-3}$ (LOQ)	5
	Switzerland	Digested sludge		0.1 μg/L (estimated)	1–220 ng/L	5
Analgesics						
Dimethylaminophenazone	Germany			nd		1
Phenazone	Germany			nd		1
Propyphenazone	Germany			nd		1
Metabolites – analgesics						
AMDOPH	Germany			0.3		1
AMPH	Germany			nd		1
DMOAS	Germany			nd		1
Fluoroquinolone antibiotics						
Ciprofloxacin	Sweden	Anaerobic digested sludge	Five STPs (2002)	2.80[c]	0.1 (LOQ)	2
	Sweden	Anaerobic digested sludge	Five STPs (2003)	2.28[c]	0.1 (LOQ)	2
	Switzerland	Untreated raw sludge	Dubendorf	1.40 + 0.12	0.12 (0.45)	3
	Switzerland	Untreated raw sludge	Zurich-Werdholzli	2.03 + 0.20	0.12 (0.45)	3
	Switzerland	Digested sludge	Kloten-Opfikon	2.42 + 0.06	0.12 (0.45)	3

Table 10 (continued)

Compound	Country	Sample	Location	Concentration (mg/kg[a] DW [dry weight])	LOD (Q) (mg/kg [a] (DW)	Reference
	Switzerland	Digested sludge	Zurich-Werdholzli	2.27 + 0.20	0.12 (0.45)	3
	Switzerland	Excess sludge[b]	Zurich-Werdholzli	2.5[c] + 0.1	0.12 (0.45)	4
	Switzerland	Raw sludge[b]	Zurich-Werdholzli	2.2[c] + 0.4	0.12 (0.45)	4
	Switzerland	Digested sludge[b]	Zurich-Werdholzli	3.1[c] + 0.4	0.12 (0.45)	4
Norfloxacin	Sweden	Anaerobic digested sludge	Five STPs (2002)	2.18[c]	0.1 (LOQ)	2
	Sweden	Anaerobic digested sludge	Five STPs (2003)	0.84[c]	0.1 (LOQ)	2
	Switzerland	Untreated raw sludge	Dubendorf	1.54 + 0.03	0.12 (0.45)	3
	Switzerland	Untreated raw sludge	Zurich-Werdholzli	1.96 + 0.15	0.12 (0.45)	3
	Switzerland	Digested sludge	Kloten-Opfikon	2.37 + 0.07	0.12 (0.45)	3
	Switzerland	Digested sludge	Zurich-Werdholzli	2.13 + 0.19	0.12 (0.45)	3
Antidepressant						
Fluoxetine	US	Treated sludge		370[d]		6
Antiepileptic						
Carbamazepine	Canada	Raw sludge	Peterborough (ON)	$(69.6 + 2.2)^{c} \times 10^{-3}$	0.15×10^{-3} (0.50×10^{-3}) WW[e]	7
	Canada	Treated sludge	Peterborough (ON)	$(258.1 + 4.7)^{c} \times 10^{-3}$	0.17×10^{-3} (0.58×10^{-3}) WW	7
	US	Treated sludge		68[c]		6

Table 10 (continued)

Compound	Country	Sample	Location	Concentration (mg/kg[a] DW [dry weight])	LOD (Q) (mg/kg [a] (DW)	Reference
Metabolite – antiepileptic						
CBZ – DiOH	Canada	Raw sludge	Peterborough (ON)	$(7.5 + 0.7)^{c} \times 10^{-3}$	0.11×10^{-3} (0.32×10^{-3})WW	7
	Canada	Treated sludge	Peterborough (ON)	$(15.4 + 1.3)^{c} \times 10^{-3}$	0.10×10^{-3} (0.34×10^{-3})WW	7
CBZ – EP	Canada	Raw sludge	Peterborough (ON)	nd	0.06×10^{-3} (0.22×10^{-3})WW	7
	Canada	Treated sludge	Peterborough (ON)	nd	0.07×10^{-3} (0.23×10^{-3})WW	7
CBZ – 2OH	Canada	Raw sludge	Peterborough (ON)	$(1.9 + 1.1)^{c} \times 10^{-3}$	0.08×10^{-3} (0.26×10^{-3})WW	7
	Canada	Treated sludge	Peterborough (ON)	$(3.4 + 0.9)^{c} \times 10^{-3}$	0.07×10^{-3} (0.22×10^{-3})WW	7
CBZ – 3OH	Canada	Raw sludge	Peterborough (ON)	$(1.6 + 0.8)^{c} \times 10^{-3}$	0.07×10^{-3} (0.22×10^{-3})WW	7
	Canada	Treated sludge	Peterborough (ON)	$(4.3 + 0.9)^{c} \times 10^{-3}$	0.06×10^{-3} (0.20×10^{-3})WW	7
CBZ – 10OH	Canada	Raw sludge	Peterborough (ON)	nd	0.10×10^{-3} (0.34×10^{-3})WW	7
	Canada	Treated sludge	Peterborough (ON)	nd	0.08×10^{-3} (0.28×10^{-3})WW	7
Psychomotor stimulant						
Caffeine	Canada	Raw sludge	Peterborough (ON)	$165.8^{c} \times 10^{-3}$	0.50×10^{-3} (1.70×10^{-3})WW	7
	Canada	Treated sludge	Peterborough (ON)	$7.6^{c} \times 10^{-3}$	0.40×10^{-3} (1.35×10^{-3})WW	7
Hormones and steroids						
17α-Ethinyloestradiol	Germany	Activated sludge	Two municipal STPs	<LOQ and 4×10^{-3}	4×10^{-3} (LOQ)	8

Table 10 (continued)

Compound	Country	Sample	Location	Concentration (mg/kg[a] DW [dry weight])	LOD (Q) (mg/kg [a] (DW)	Reference
	Germany	Digested sludge	Two municipal STPs	2×10^{-3} and 17×10^{-3}	4×10^{-3} (LOQ)	8
Hormones and steroids						
17β-Oestradiol	Germany	Activated sludge	Two municipal STPs	5×10^{-3} and 17×10^{-3}	2×10^{-3} (LOQ)	8
	Germany	Digested sludge	Two municipal STPs	9×10^{-3} and 49×10^{-3}	2×10^{-3} (LOQ)	8
Oestrone	Germany	Activated sludge	Two municipal STPs	<LOQ and 37×10^{-3}	2×10^{-3} (LOQ)	8
	Germany	Digested sludge	Two municipal STPs	16×10^{-3} and <LOQ	2×10^{-3} (LOQ)	8
Mestranol	Germany	Activated sludge	Two municipal STPs	<LOQ	2×10^{-3} (LOQ)	8
	Germany	Digested sludge	Two municipal STPs	<LOQ	2×10^{-3} (LOQ)	8

References: 1 – Reddersen et al. (2002); 2 – Lindberg et al. (2005); 3 – Golet et al. (2002b); 4 – Golet et al. (2003); 5 – Göbel et al. (2005); 6 – Kinney et al. (2006); 7 – Miao et al. (2005); 8 – Ternes et al. (2002a)

[a]Unless otherwise stated

[b]Sampling dates are the 4th–10th October 2000 and the 8th and 15th of July 2002

[c]Average concentration

[d]Median concentration from nine different STPs

[e]Wet weight

Table 11 Occurrence of pharmaceuticals in soil

Compound	Country	Sample	Location	Concentration(mg/kg DW)	LOD (Q)(mg/kg DW)	Reference
Analgesics						
Dimethylaminophenazone	Croatia	Soil below landfill	Jakuševec	0.003–0.007		1
Propyphenazone	Croatia	Soil below landfill	Jakuševec	0.003–2.9		1
Fluoroquinolone antibiotics						
Ciprofloxacin	Switzerland	Sludge-treated soil[a]	Wetzikon	0.35 + 0.04	0.05 (0.18)	2
	Switzerland	Sludge-treated soil[a]	Reckenholz	0.40 + 0.03	0.05 (0.18)	2
	Switzerland	Sludge-treated soil[b]	Wetzikon	0.28 + 0.01	0.05 (0.18)	2
	Switzerland	Sludge-treated soil[b]	Reckenholz	0.27 + 0.04	0.05 (0.18)	2
Norfloxacin	Switzerland	Sludge-treated soil[a]	Wetzikon	0.32 + 0.01	0.05 (0.18)	2
	Switzerland	Sludge-treated soil[a]	Reckenholz	0.29 + 0.01	0.05 (0.18)	2
	Switzerland	Sludge-treated soil[b]	Wetzikon	0.27 + 0.01	0.05 (0.18)	2
	Switzerland	Sludge-treated soil[b]	Reckenholz	0.30 + 0.01	0.05 (0.18)	2
Tetracycline antibiotics						
Tetracycline	Germany	Soil amended with liquid manure	Lower Saxony	$(86.2–198.7)^{c} \times 10^{-3}$	1×10^{-3} (5×10^{-3})	3
Chlortetracycline	Denmark	Loamy sand soil amended with liquid manure		nd[d]–15.5×10^{-3}	0.6×10^{-3} (1.1×10^{-3})	4
	Germany	Soil amended with liquid manure	Lower Saxony	$(4.6–7.3)^{c} \times 10^{-3}$	2×10^{-3} (5×10^{-3})	3

nd – not detected. References: 1 – Ahel and Jeličić (2001); 2 – Golet et al. (2002b); 3 – Hamsher et al. (2002); 4 – Jacobsen et al. (2004)
[a]8 months after application
[b]21 months after application
[c]Average concentrations
[d]Higher concentration – 9 d after application and lower concentration – 155 d of application

5.2 Occurrence in Soil and Sewage Sludge

Pharmaceuticals may be sorbed to sewage sludge during sewage treatment and then end up in the environment through application of sludge to agricultural fields as fertilizer (Golet et al. 2002b; Oppel et al. 2004). When wastewater is used for irrigation pharmaceuticals may also be released to soils (Ternes et al. 2007). Pharmaceutical compounds have also been detected in sludge and soils (Golet et al. 2002b; Hamscher et al. 2002; Miao et al. 2005; Göbel et al. 2005; Tables 10 and 11).

Most methods developed for the analysis of pharmaceuticals in solid media involve accelerated solid extraction (ASE; Reddersen et al. 2002), followed by solid-phase extraction for clean-up of the samples (Golet et al. 2002b; Miao et al. 2005; Göbel et al. 2005; Kinney et al. 2006). Quantification is usually achieved using liquid chromatography tandem mass spectrometry (Miao et al. 2005; Göbel et al. 2005) or liquid-chromatography with fluorescence detection (Golet et al. 2002b).

There are only a few studies in which the occurrence of analgesics in sewage or soil samples is reported (Reddersen et al. 2002; Ahel and Jeličić 2001). Although dimethylaminophenazone and propyphenazone were not detected in sewage sludge samples in Germany (Reddersen et al. 2002), one of their metabolites, AMDOPH (1-acetyl-1-methyl-2-dimethyl-oxamoyl-2-phenylhydrazide), was detected. These phenazone-type analgesics have also been found in soil samples beneath the main landfill in Zagreb, Croatia, with a maximum concentration of 2.9 mg/kg dry wt for propyphenazone (Ahel and Jeličić 2001). Golet et al. (2002b) and Göbel et al. (2005) reported the occurrence of antibiotics in sewage sludge samples from Switzerland. Average concentrations of sulfonamide and macrolide antibiotics and trimethoprim ranged from 28 to 68 μg/kg of dry wt (Göbel et al. 2005). Golet et al. (2002b, 2003) determined concentrations of the fluoroquinolone antibiotics ciprofloxacin and norfloxacin in sewage sludge samples, and also in sludge-treated soil samples. In both studies, it was demonstrated that these compounds persist in soils and are detected in soils several months after application. The antidepressant fluoxetine was detected in treated sludge samples from nine different STPs in the United States (Kinney et al. 2006). In North America, the occurrence of carbamazepine (Kinney et al. 2006) and its major metabolites has been reported in raw and treated sludge samples (Miao et al. 2005).

In Germany, Ternes et al. (2002a) detected oestrone and 17β-oestradiol in activated and digested sludge at levels up to 37 and 49 μg/kg, respectively.

6 Environmental Fate of Human Pharmaceuticals

After excretion, pharmaceuticals enter sewage treatment plants where they will be affected by different treatment processes. During sewage treatment, pharmaceuticals may be removed through microbial degradation or sorption to

solids that are later removed with sludge (Carballa et al. 2004; Daughton and Ternes 1999). The more persistent agents are likely to be released to the environment where they are transported and distributed in various compartments including surface waters, soil and sediments. The potential impact of human-use medicines in the environment is dependent on the persistence and biological activity of their transformation products (Arnold et al. 2003). Distribution and fate of pharmaceuticals are dependent on a range of factors, such as the physico-chemical properties of the drug, and on processes such as partitioning to soil and sediments and degradation in the aquatic and soil environment (Boxall et al. 2004; Daughton and Ternes 1999). Environmental characteristics such as climate and soil type also affect the fate and behaviour of pharmaceuticals (Boxall et al. 2004). In this section we review the main fate processes and the factors affecting them.

6.1 Fate in Wastewater Treatment Plants

In conventional STPs, pharmaceuticals may be removed by microbial degradation or sorption to solids that are later disposed of as sludge (Carballa et al. 2004; Daughton and Ternes 1999). Typically, conventional STPs utilize both primary and secondary treatment stages (Fig. 2). Some plants may utilize tertiary treatments. After sewage treatment, both treated effluent and solid waste streams are produced. The effluent is usually discharged into surface waters and the solid waste, known as sewage sludge, may be incinerated, put into a landfill or recycled by using it as fertilizer on agricultural fields. Removal of pharmaceuticals by different processes is summarized in Table 12.

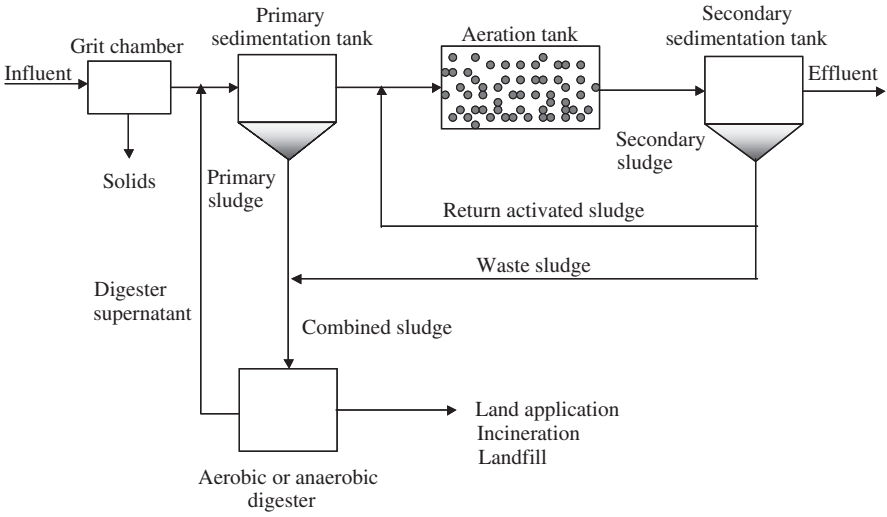


Fig. 2 Schematic of a conventional STP

Table 12 Removal of pharmaceuticals by different processes in wastewater and drinking water treatment plants

Process	High removal (>90%)	Medium removal (50–89%)	Low removal (<40%)	Variable	Reference
Activated sludge	Acetaminophen (92–99) Carboxi-ibuprofen[a] (96) Caffeine (85 ± 4–99.7) Hydroxy-ibuprofen[a] (95) Mefenamic acid (91.54) Salbutamol (94.6) Salicylic acid[a] (>99)	1,7-Dimethylxanthine[a] (77 ± 11) 16α-Hydroxyoestrone (68) Acebutolol (40–80) Acetylsalicylic acid (81) Ciprofloxacin (78 ± 5–> 80) Clarithromycin (54) Codeine (46 ± 19) Fenofibric acid (45–64) Gemfibrozil (46–75) Indomethacin (75–83) Iomeprol (89) Iopromide (83) Ketoprofen (65–77) Norfloxacin (>80) Sotalol (40–80)	Carbamazepine (0–30) Celiprolol (36) Diatrizoate (0) Dimethylaminophenazone(38) Erythromycin[b] (25) Iopamidol (17) Phenazone (33) Roxithromycin (33)	17α-Ethinyloestradiol (67–>90) 17β-Oestradiol (0.6–>98) Atenolol (<0[c]–84) Bezafibrate (50–97) Clofibric acid[a] (26–52) Diclofenac (18–75) Oestrone (61 ± 9–>98) Ibuprofen (75–97) Metoprolol (<0[c]–83) Naproxen (66–93) Propranolol (65–96) Trimethoprim (0–69) Sulfamethoxazole (<0[c]–55)	1, 2, 3, 4 6, 7, 8, 9 11, 12, 15 19, 20, 21 24, 26, 27 28
Activated sludge/UV	Caffeine (99.9)		Carbamazepine (29)		5
Biological filter	17β-Oestradiol (92)	17α-Ethinyloestradiol (64) Oestrone (67) Indomethacin (71) Ketoprofen (48)	Bezafibrate (17) Clofibric acid[a] (15) Diclofenac (9) Fenofibric acid[a] (6) Gemfibrozil (16) Ibuprofen (22) Naproxen (15)		6, 8

Table 12 (continued)

Process	High removal (>90%)	Medium removal (50–89%)	Low removal (<40%)	Variable	Reference
Aeration of groundwater followed by filtration (iron and Mn)	Dimethylaminophenazone (> 95) Phenazone (90) Propyphenazone (90)		AMDOPH[a] (25)		18
Sand filtration		Trimethoprim (60)	Clarithromycin (15)		21
Aluminum treatment – coagulation			17α-Ethinyloestradiol (0) 17β-Oestradiol (2) Caffeine (0) Erythromycin[b] (33) Oestrone (5) Fluoxetine (15)		22
Chlorination (1.2 mg/L free chlorine)	1,7-Dimethylxanthine[a] (100) Acetaminophen (100) Ciprofloxacin (100) Codeine (100) Lincomycin (100) Norfloxacin (100) Oxytetracycline (100) Roxithromycin (100) Sulfamethazine (100) Sulfamethoxazole (100) Tetracycline (100) Trimethoprim (100)		Caffeine (~0) Carbamazepine (0) Cotinine (~0) Erythromycin[b] (~0)		25
Membrane bioreactor	Ibuprofen (99)	Clofibric acid[a] (54) Diclofenac (58)	Carbamazepine (13)		13
Activated carbon : 5 mg/L	Fluoxetine (92) Roxythromycin (90)	17α-Ethinyloestradiol (77) 17β-Oestradiol (84)	Diclofenac (39) Gemfibrozil (37) Iopromide (30)		22, 29 22, 29

Table 12 (continued)

Process	High removal (>90%)	Medium removal (50–89%)	Low removal (<40%)	Variable	Reference
		Acetaminophen (72) Caffeine (70) Carbamazepine (74) Diazepam (67–90) Erythromycin[b] (54) Oestrone (76) Ibuprofen (16–90) Naproxen (52) Sulfamethoxazole (36–90) Trimethoprim (83)			
Activated carbon: 12 mg/L	Carbamazepine (99) Ibuprofen (99) Diazepam (99) Sulfamethoxazole (99) Roxythromycin (99)				29
Ozone pre-treatment for sludge anaerobic digestion	17α-Ethinyloestradiol (>80) 17β-Oestradiol (>80) Oestrone (>80) Sulfamethoxazole (>80)	Carbamazepine (60) Diazepam (50) Diclofenac (60–80) Ibuprofen (20–50)	Iopromide (20)		14
Ozone: low dose (0.2–0.3 mg/L; cont.)	17α-Ethinyloestradiol (99) 17β-Oestradiol (98) Acetaminophen (94) Caffeine (91) Carbamazepine (99) Diclofenac (95) Erythromycin[b] (97) Oestrone (99)	Diazepam (81) Ibuprofen (80) Iopromide (64)			22

Table 12 (continued)

Process	High removal (>90%)	Medium removal (50–89%)	Low removal (<40%)	Variable	Reference
	Fluoxetine (91) Gemfibrozil (98) Naproxen (91) Sulfamethoxazole (91) Trimethoprim (98)				
Ozone: medium dose (1–5 mg/L)	17α-Ethinyloestradiol (90–99) 17β-Oestradiol (90–99) Azithromycin (90–99) Carbamazepine (>98 –100) Clarithromycin (> 76–99) Diclofenac (>96–>99)	Atenolol (61) Caffeine (34–>53) Celiprolol (>82) Clofibric acid[a] (50) Fenofibric acid (> 62) Ibuprofen (48–>82)	Diatrizoate (0) Oestrone (<1) Ibuprofen (<1) Iomeprol (34) Iopadimol (33) Iopromide (14–42)		10, 16, 17, 23
Ozone: medium dose (1–5 mg/L; cont.)	Erythromycin[b] (90–99) Oestrone (>80–99) Fluoxetine (>93) Gemfibrozil (>94) Indomethacin (90–99) Naproxen (>50–99) Roxithromycin (90–99) Sotalol (>96) Sulfadiazine (90–99) Sulfamethoxazole(90–>99) Sulfapyridine (90–99) Sulfathiazole (90–99) Trimethoprim (>85–>99)	Metoprolol (78) Propranolol (>72)			10, 16, 17, 23
Ozone: high dose (>5–7.1 mg/L)	Carbamazepine (>99) Diclofenac (> 98) Erythromycin[b] (>99) Fluoxetine (>99)	Caffeine (>63) Indomethacin (>50) Naproxen (>66)	Ibuprofen (>24)		17

Table 12 (continued)

Process	High removal (>90%)	Medium removal (50–89%)	Low removal (<40%)	Variable	Reference
	Gemfibrozil (>99) Iopromide (91) Sulfamethoxazole (>99) Trimethoprim (97)				
Ozone: very high dose (10–15 mg/L)	Iomeprol (90) Metoprolol (>93) Iopromide (91)	Atenolol (>86) Caffeine (>87) Clofibric acid[a] (>59) Oestrone (>80) Ibuprofen (>62) Iomeprol (73) Iopadimol (57–84) Iopromide (80)	Diatrizoate (13–14)		10
Ozone/ H_2O_2: low (2.1/1.0 mg/L)	Carbamazepine (98) Diclofenac (98) Naproxen (96) Trimethoprim (95)	Erythromycin[b] (79) Oestrone (44) Fluoxetine (81) Gemfibrozil (74) Sulfamethoxazole (83)	Caffeine (4) Ibuprofen (<1) Iopromide (<1)		17
Ozone/H_2O_2: medium (3.6/ 2.5 mg/L)	Carbamazepine (>99) Diclofenac (>98) Erythromycin[b] (> 99) Oestrone (>94)	Caffeine (65)	Ibuprofen (<1) Iopromide (22)		17
Ozone/H_2O_2: medium (3.6/ 2.5 mg/L; cont.)	Fluoxetine (>91) Gemfibrozil (>99) Naproxen (> 98) Sulfamethoxazole (97) Trimethoprim (>99)				17
Ozone/H_2O_2: high (≥7.1/ 3.5 mg/L)	Carbamazepine (>99) Diclofenac (>98)	Caffeine (>68) Iomeprol (85)	Diatrizoate (25) Iopromide (>24)		10, 17

Table 12 (continued)

Process	High removal (>90%)	Medium removal (50–89%)	Low removal (<40%)	Variable	Reference
	Erythromycin[b] (> 99) Oestrone (>94) Fluoxetine (>91) Gemfibrozil (>99) Ibuprofen (>93) Naproxen (>98) Sulfamethoxazole (>99) Trimethoprim (>99)	Iopadimol (80) Iopromide (89)			
Ozone/UV (15 mg/L)	Iopromide (90)	Iomeprol (88) Iopadimol (88)	Diatrizoate (36)		10

Mn – manganes; H_2O_2 – hydrogen peroxide. References: 1 – Ternes (2001a); 2 – Gómez et al. (2006); 3 – Jones et al. (2007); 4 – Yu et al. (2006); 5 – Miao et al. (2005); 6 – Stumpf et al. (1999); 7 – Ternes (1998); 8 – Ternes et al. (1999); 9 – Lindqvist et al. (2005); 10 – Ternes et al. (2003); 11 – Ternes et al. (2007); 12 – Bernard and Gray (2000); 13 – Bernhard et al. (2006); 14 – Carballa et al. (2007); 15 – Bendz et al. (2005); 16 – Huber et al. (2005); 17 – Snyder et al. (2006); 18 – Reddersen et al. (2002); 19 – Vieno et al. (2006); 20 – Lindberg et al. (2006); 21 – Gobel et al. (2005); 22 – Westerhoff et al. (2005); 23 – Andreozzi et al. (2002); 24 – Joss et al. (2004); 25 – Gibs et al. (2007); 26 – Servos et al. (2005); 27 – Andersen et al. (2005); 28 – Andersen et al. (2003); 29 – Poseidon (2005); 30 – Carballa et al. (2007b)

[a]Metabolite

[b]Erythromycin is not detected in environmental samples in its original form but as a degradation product, dehydrated-erythromycin, with the loss of one molecule of water (Hirsch et al. 1999)

[c]<0 – these compounds seem to accumulate in sludge (Bendz et al. 2005)

6.1.1 Conventional Wastewater Treatment

Primary wastewater treatment is also known as mechanical treatment and involves the use of machinery. It removes large objects from the raw influent, including human waste and floating materials and also oils, fats and grease. Typically, there is a grit chamber wherein sands and rocks from the incoming wastewater are allowed to settle, removing them prior to further treatment. Sewage treatment plants also include a primary sedimentation tank where solids can settle out from wastewater; such solids can be treated separately and are usually denominated as primary sludge. Although few pharmaceuticals are removed to any significant extent during primary treatment, the ones that are include the hormone 17β-oestradiol (Carballa et al. 2004), ibuprofen (Tauxe-Wuersch et al. 2005) and ciprofloxacin (Ternes et al. 2004a). Secondary treatment is superior in treating primary sludge, because such sludge has a large fat fraction and few microorganisms (Ternes et al. 2004a).

Secondary treatment is a biological treatment that is designed to substantially degrade sewage through aerobic biological processes. The more sorptive pharmaceuticals are likely to adsorb onto the sludge (Daughton and Ternes 1999). For example, adsorption to sewage sludge is the major removal process for fluoroquinolones (Golet et al. 2003) and tetracyclines (Kim et al. 2005), but is negligible for most polar pharmaceuticals, where the main removal mechanism is biodegradation (Ternes et al. 2004b). In secondary treatment, different processes are used and include activated sludge and biological filtres (Stumpf et al. 1999). Activated sludge has been reported to be more effective in the removal of pharmaceuticals than are biological filters (Stumpf et al. 1999).

Most studies focus on removing pharmaceuticals through reliance on primary and secondary treatment. Many pharmaceuticals including acetaminophen, caffeine, salbutamol and salicylic acid are reported to be substantially removed (>90%) during secondary treatment with activated sludge (Ternes 1998; Gómez et al. 2006; Jones et al. 2007), while others are removed less efficiently (50–89%). Those that are not efficiently removed include the following: gemfibrozil and fenofibric acid (Stumpf et al. 1999; Bendz et al. 2005; Ternes 1998), the β-blockers acebutolol and sotalol (Vieno et al. 2006), the fluoroquinolones ciprofloxacin and norfloxacin (Vieno et al. 2006; Lindberg et al. 2006) and the iodinated X-ray contrast media iomeprol and iopromide (Ternes et al. 2007). Very low removal (<40%) was reported from use of activated sludge as a secondary treatment in a wastewater treatment plant, for carbamazepine, diatrizoate, iopamidol and roxithromycin (Vieno et al. 2006; Ternes et al. 2007; Bernhard et al. 2006; Bendz et al. 2005). Among pharmaceuticals reported to have quite variable removal efficiencies are the following: the hormones 17α-ethinyloestradiol, 17β-oestradiol and oestrone (Ternes et al. 1999; Andersen et al. 2003; Servos et al. 2005; Joss et al. 2004), the β-blockers atenolol, metoprolol and propranolol (Ternes et al. 2007; Vieno et al. 2006; Bendz et al. 2005), clofibric acid and bezafibrate (Ternes 1998; Bernhard et al. 2006), ibuprofen, naproxen and diclofenac (Stumpf et al. 1999; Ternes 1998;

Bendz et al. 2005; Lindqvist et al. 2005), sulfamethoxazole (Bendz et al. 2005; Göbel et al. 2005) and trimethoprim (Lindberg et al. 2006; Bendz et al. 2005; Ternes et al. 2007).

6.1.2 Advanced STPs

In more advanced STPs, membranes (or the so-called membrane bioreactors or suspended biofilm reactors) can be substituted for the conventional secondary sedimentation tank step (Larsen et al. 2004; Joss et al. 2005). Although membrane bioreactors are more effective than activated sludge systems for removing pharmaceuticals, they are still not very efficient (Bernhard et al. 2006; Urase et al. 2005). Nevertheless, Joss et al. (2005) reported similar performances for activated sludge, membrane bioreactors and suspended biofilm reactors. Usually membranes do not allow retention of pharmaceuticals due to size exclusion (Clara et al. 2005). However, dense membranes such as nanofiltration and especially reverse osmosis are much more efficient in removing organic compounds, including pharmaceuticals (Poseidon 2005; Sedlak and Pinkston 2001).

Tertiary treatment is the final stage before treated wastewater is released into the environment. In conventional wastewater treatment, tertiary treatment may be used for nutrient removal. Therefore, nitrogen and phosphorus are removed from the wastewater. Sludges accumulated in the wastewater treatment processes are further treated to provide for safe disposal. Treatment may be achieved through aerobic or anaerobic digestion and composting. Under aerobic conditions, in the presence of oxygen, bacteria consume organic matter and convert it to carbon dioxide, whereas during anaerobic digestion, in the absence of oxygen, the sludge can be fermented in tanks at a temperature of 55°C (thermophilic digestion) or at 36°C (mesophilic digestion; Carballa et al. 2007). Sulfamethoxazole and trimethoprim seem to be unstable in anaerobic mesophilic digestion, whereas sulfapyridine appears to be resistant (Göbel et al. 2005). Another study confirmed the elimination of sulfamethoxazole and several other pharmaceuticals (roxithromycin, naproxen and the oestrogens oestrone 17β-oestradiol and 17α-ethinyloestradiol) using sludge anaerobic digestion (Carballa et al. 2007). In the same study, removal efficiency of ibuprofen, diclofenac, diazepam and iopromide ranged from 20 to 60%, whereas carbamazepine was not removed.

6.2 Fate in the Aquatic Environment

The fate of pharmaceuticals in the aquatic environment is determined by sorption to sediments and/or degradation by abiotic and/or biotic processes (Andreozzi et al. 2003; Ferrer et al. 2004). The degradation of pharmaceuticals in sewage treatment plants, water systems, laboratory tests and soils is reported in several studies (Table 13).

Table 13 Degradation of pharmaceutical compounds under different conditions

Compound	Sphere/conditions	Half-life (d)	Reference
Analgesics and anti-inflammatories			
Acetaminophen	Sewage treatment	Readily biodegradable	1
	Outdoor microcosms	0.9 ± 0.2	2
	Aerobic batch biodegradation	4[a]	3
	Water/sediment system	3.1 ± 0.2	4
	Wastewater	7.2 min	5
Acetylsalicylic acid	Sewage treatment	Readily biodegradable	1
Codeine	Sewage treatment	Non-biodegradable	1
Dextropropoxyphene	Sewage treatment	Non-biodegradable	1
Diclofenac	Organic and salt-free water – photodegradation	5.0[b]	6
	Surface water – photodegradation	39 min	7
	Lake Greifensee – water – photodegradation	Less than 1 hr	8
	Aerobic batch biodegradation	30%[a] biodegraded after 50 d incubation	3
Ibuprofen	Sewage treatment	Inherently biodegradable	1
	Aerobic batch biodegradation	4[a]	3
	Water/sediment system	<6	4
	Water from water/ sediment system	10	4
Ketoprofen	Aerobic batch biodegradation	>99%[a] biodegraded after 50 d incubation	3
Naproxen	Sewage treatment	Non-biodegradable	1
	Surface water	42 min	7
	Aerobic batch biodegradation	80%[a] biodegraded after 50 d incubation	3
	Soil	2	9
Metabolite – analgesics and anti-inflammatories			
Hydroxy-ibuprofen	Water/sediment system	7 ± 2	4
	Water from water/ sediment system	7 ± 2	4
Fluoroquinolone antibiotics			
Levofloxacin	Outdoor microcosms	5.0 ± 0.1	2
Ofloxacin	Closed Bottle Test	Non-biodegradable[c] in 28 d	10
	Organic and salt-free water – photodegradation	10.6[b]	6
Lincosamide antibiotics			
Clindamycin	Closed Bottle Test	Non-biodegradable[b] in 28 d	10

Table 13 (continued)

Compound	Sphere/conditions	Half-life (d)	Reference
Lincomycin	Solar irradiation – photodegradation	1760 (pH 7.5)–2033 (pH 5.5)	11
Macrolide antibiotics			
Clarithromycin	Closed Bottle Test	Non-biodegradable[b] in 28 d	10
Erythromycin[d]	Closed bottle Test	Non-biodegradable[C] in 28 d	10
	Sewage treatment	Non-biodegradable	1
	Soil	20	12
Oleandomycin	Soil	27	12
Roxithromycin	Soil	>>120	12
Penicillin antibiotics			
Amoxicillin	Closed Bottle Test	Non-biodegradable[c] in 28 d	10
Ampicillin	Sewage treatment	48% biodegradable	1
Penicillin G	Closed Bottle Test	Non-biodegradable[c] in 28 d	10
Sulfonamide antibiotics	Respirometer screening test	Non-biodegradable in 28 d	13
	Activated sludge – non-adapted bacteria	5–10 (12 sulfonamides)	13
	Activated sludge-adapted bacteria	0.2–4.1 (12 sulfonamides)	13
Sulfachloropyridazine	Sandy loam soil	3.5	
Sulfamethoxazole	Closed Bottle Test	Non-biodegradable[c] in 28 d	10
	Organic and salt-free water – photodegradation	2.4[b]	6
	Sewage treatment	Non-biodegradable	1
	Outdoor microcosms	19.0 ± 1.2	2
Sulfasalazine	Sewage treatment	Non-biodegradable	1
Tetracycline Antibiotics			
Chlortetracycline	Closed Bottle Test	Non-biodegradable[c] in 28 days	10
Oxytetracycline	Sandy loam soil	21.7	
Tetracycline	Closed Bottle Test	Non-biodegradable[c] in 28 d	10
	Sewage treatment	Non-biodegradable	1
Other antibiotics			
Metronidazole	Closed Bottle Test	Non-biodegradable[c] in 28 d	10
	Sewage treatment	Non-biodegradable	1
	Outdoor microcosms	5.7 ± 0.1	2
Trimethoprim	Closed Bottle Test	Non-biodegradable[c] in 28 d	10
	Outdoor microcosms	5.7 ± 0.1	2

Table 13 (continued)

Compound	Sphere/conditions	Half-life (d)	Reference
Antidepressants			
Amitriptyline	Sewage treatment	Non-biodegradable	1
Sertraline	Outdoor microcosms	6.3 ± 0.2	2
Antiepileptic			
Carbamazepine	Organic and salt-free water – photodegradation	100[b]	6
		82 ± 11	2
	Outdoor microcosms		
	Water/sediment system	328	4
	Water from water/ sediment system	47	4
	River water – photodegradation	907 sunlight hours	14
Metabolite – antiepileptic			
CBZ – DiOH	Water/sediment system	8	4
β-Vlocker			
Propranolol	Organic and salt-free water – photodegradation	16.8[b]	6
Hormone			
17α-Ethinyloestradiol	Water – ozonation (1 mg/L)	10 min	15
Iodinated X-ray contrast media			
Iopromide	Water from water/ sediment system	29 ± 4	4
Lipid regulators			
Atorvastatin	Outdoor microcosms	6.6 ± 0.2	2
Clofibrate	Sewage treatment	Non-biodegradable	1
Gemfibrozil	Aerobic batch biodegradation	>99%[a] biodegraded after 50 d incubation	3
Metabolite – lipid regulators			
Clofibric acid	organic and salt-free water –photodegradation	100[b]	6
	surface water – photodegradation	50 hr	7
	water/sediment system	119 ± 7	4
	water from water/sediment system	82 ± 12	4
Other Pharmaceuticals			
Caffeine (psychomotor stimulant)	Sewage treatment	Readily biodegradable	1
	Outdoor microcosms	1.5 ± 0.4	2
Diazepam	Water/sediment system	311 ± 25	4
	Water from water/ sediment system	34 ± 5	4

Table 13 (continued)

Compound	Sphere/conditions	Half-life (d)	Reference
Ephedrine (anti-asthmatic)	Sewage treatment	Readily biodegradable	1
Meprobamate (hypnotic)	Sewage treatment	Non-biodegradable	1
Methyldopa (antihypertensive)	Sewage treatment	Non-biodegradable	1
Theobromine (antihypertensive)	Sewage treatment	Readily biodegradable	1
Tolbutamide (antidiabetic)	Sewage treatment	Non-biodegradable	1

References: 1 – Richardson and Bowron (1985); 2 – Lam et al. (2004); 3 – Yu et al. (2006); 4 – Löffler et al. (2005); 5 – Bedner and MacCrehan (2006); 6 – Andreozzi et al. (2003); 7 – Packer et al. (2003); 8 – Buser et al. (1998b); 9 – Topp et al. (2008b); 10 – Alexy et al. (2004); 11 – Andreozzi et al. (2006); 12 – Schlüsener and Bester (2006); 13 – Ingerslev and Halling-Sørensen (2000); 14 – Andreozzi et al. (2002); 15 – Huber et al. (2004)

[a]Aerobic batch biodegradation inoculated with diluted waste activated sludge

[b]50° North in winter – photodegradation

[c]OECD 301D 1992 (biodegradability)

[d]Erythromycin is not detected in environmental samples in its original form but as dehydrated Erythromycin, with the loss of one molecule of water (Hirsch et al. 1999)

6.2.1 Sorption onto Sediments

Hydrophobic compounds can sorb to sediments (Ferrer et al. 2004; Löffler et al. 2005). For example, diphenhydramine was found to sorb onto aquatic sediments and may be concentrated as much as one thousand times over its concentration in the water phase, thereby demonstrating an accumulation effect (Ferrer et al. 2004). Alternatively, diclofenac was not detected in sediments from the Greifensee Lake, and in laboratory experiments it showed negligible adsorption onto sediments (Buser et al. 1998). Low adsorption coefficients for diclofenac to sediments have been reported (Scheytt et al. 2005; Table 14). In the same study, carbamazepine was reported to sorb little to sediments, which was confirmed by Löffler et al. (2005). Low sorption coefficients to sediments have also been reported for a carbamazepine metabolite (CBZ-diol), diazepam, clofibric acid, oxazepam (Löffler et al. 2005) and ibuprofen (Scheytt et al. 2005); high adsorption coefficients were measured for oestriol, norethindrone and progesterone in sediments (López de Alda et al. 2002).

6.2.2 Biodegradation

In surface waters, microbial degradation is usually much slower than during sewage treatment, because surface waters have much less diversity and density of bacteria (Kümmerer 2004). Biodegradability of pharmaceuticals in aquatic environments has not been extensively studied (Kümmerer et al. 2000).

Table 14 Sorption data for selected pharmaceutical compounds to soil, sludge, and sediment

Compound	K_d[a] soil (L/kg)	K_{oc}[b] soil (L/kg)	K_d sludge (L/kg)	K_{oc} sludge (L/kg)	K_d sediment (L/kg)
Analgesics and anti-inflammatories					
Acetaminophen			0.414 (predicted)[1]		
Acetylsalicylic acid			2.22 (predicted)[1]		
Diclofenac	0.45[c] ± 0.03/164.5 ± 6.6[2]	121[b] ± 8/2310 ± 93[2]	459[c] ± 32/16 ± 3[3]	1310[c] ± 180/47 ± 32[3]	0.55–4.66[4]
Ibuprofen			453.79 (predicted)[1]	na[c]/21 ± 4[3]	0.18–1.69[4]
			na[c]/7.1 ± 2.0[3]		
Naproxen	10.13 ± 0.36–252.90 ± 4.77[5]	445.86 ± 47.88–3743.23 ± 184.19[5]	217.20 (predicted)[1]	217.20 (predicted)[1]	
			42.46 ± 2.19[5]	128.65 ± 6.64[5]	
Metabolite analgesics and anti-inflammatories					
Salicylic acid	3.6–397[6]				
Fluoroquinolone antibiotics					
Ciprofloxacin	427.0[7]		416.9[8]		
Enrofloxacin	260–6310[7]				
Ofloxacin	309[7]	322162[c] ± 3297/50056 ± 2732[2]			
	1192[c] ± 122/3554 ± 194[2]				
Macrolide antibiotic					
Erythromycin	164.76 (predicted)[1]				
Sulfonamide antibiotics					
Sulfamethazine	1.68 ± 0.13–98.25 ± 4.68[5]	80.41 ± 6.22–1355.21 ± 64.57[5]	42.51 ± 2.30[5]	128.81 ± 6.97[5]	
Sulfamethoxazole	0.23[b] ± 0.08/37.6 ± 1.2[2]	62.2[b] ± 21.6/530 ± 16.9[2]			
Sulfapyridine	3.47				
Tetracycline antibiotic					
Oxytetracycline	417 ± 97–1026 ± 374[9]	27792 ± 6386–93317 ± 34130[9]	0.02 (predicted)[1]		0.3[10]

Table 14 (continued)

Compound	K_d[a] soil (L/kg)	K_{oc}[b] soil (L/kg)	K_d sludge (L/kg)	K_{oc} sludge (L/kg)	K_d sediment (L/kg)
Other antibiotic					
Metronidazole	0.5–0.7[9]	38–56[9]			
Antidepressant					
Fluoxetine	134.44 ± 0.90–234.83 ± 2.36[5]	2746.33 ± 9.72 –7553.34 ± 89.68[5]	176.75 ± 2.06[5]	535.59 ± 6.25[5]	
Antiepileptic					
Carbamazepine	4.66 ± 0.18–32.78 ± 1.01[5] 0.49[b] ± 0.01/37 ± 1.6[2]	253.55 ± 9.59 – 584.61 ± 16.45[5] 132[b] ± 2.7/521 ± 23[2]	75.33 ± 0.84[5] 25.52 (predicted)[1] na[c]/1.2 ± 0.5[3]	228.26 ± 2.53[5] na[c]/3.5 ± 1.5[3]	0.21–5.32[4] 1.3[11]
Antiepileptic – metabolite					
CBZ-diol					0.3[2]
Antineoplastic agents					
Cyclophosphamide			55[c] ± 20 / 2.4 ± 0.5[3]	158[c] ± 58/7.1 ± 1.7[3]	
Ifosfamide			22[c] ± 14/1.4 ± 0.4[3]	62[c] ± 40/4.1 ± 1.2[3]	
Beta-blockers					
Atenolol			0.21 (predicted)[1]		
Propranolol	16.3[b] ± 1.4/199 ± 9.6[2]	4405[b] ± 378/2803 ± 135[2]			
Hormones					
17α-Ethinyloestradiol		3.35 (log)[12]	584 ± 136[13] 278[c] ± 3/349 ± 37[3]	3.32 (log)[13] 794[c] ± 95/860 ± 140[3]	
17β-Oestradiol		3.30 (log)[12]	476 ± 192[13] 1468[8]	3.24 (log)[13]	
Oestriol					479[14]
Oestrone		3.14 (log)[12]	402 ± 126[13]	3.16 (log)[13]	
Norethindrone					128[14]

Table 14 (continued)

Compound	K_d[a] soil (L/kg)	K_{oc}[b] soil (L/kg)	K_d sludge (L/kg)	K_{oc} sludge (L/kg)	K_d sediment (L/kg)
Progesterone					204[14]
Iodinated X-ray contrast media					
Iopromide			na[b]/11 ± 1[3]	na[b]/32 ± 5[3]	
Lipid regulators					
Clofibric acid	na[a]/5.38 ± 0.17[2]	na[a]/75.8 ± 2.5[2]	na[c]/4.8 ± 2.5[3]	na[c]/14 ± 7[3]	0.3[11]
Other pharmaceutical					
Diazepam (anxyolitic)			44[c] ± 26/21 ± 8[3]	125[c] ± 75/62 ± 23[3]	3.0[11]
Oxazepam					0.3[11]

References are given in superscript numbers: [1]Jones et al. (2002); [2]Drillia et al. (2005); [3]Ternes et al. (2004b); [4]Scheytt et al. (2005); [5]Monteiro et al. (in prep); [6]Dubus et al. (2001); [7]Nowara et al. (1997); [8]Ericksson et al. (2002); [9]Rabølle and Spliid (2000); [10]Pouliquen and Le Bris (1996); [11]Löffler et al. (2005); [12]Yu et al. (2004); [13]Andersen et al. (2005); [14]López de Alda et al. (2002)

[a]K_d – adsorption coefficient

[b]K_{oc} – adsorption coefficient corrected for soil organic carbon

[b]A/B – low organic carbon and high clay content / high organic carbon and low clay content

[c]A/B – primary sludge/secondary sludge

Biodegradability of several antibiotics was assessed using the closed bottle test. Results show that none of the antibiotics studied were readily biodegradable after 28 d (Alexy et al. 2004; Kümmerer et al. 2000). By comparing half-lives of several pharmaceuticals in pond vs. autoclaved pond water, in an outdoor microcosm study, biodegradation did not appear to be important over the duration of the study (Lam et al. 2004). In lake water incubations, in the dark, biodegradation of diclofenac was reported to be minimal (Buser et al. 1998b). Nevertheless, in an aerobic batch biodegradation test inoculated with diluted activated sludge, 30% of diclofenac was biodegraded after 50 d of incubation (Yu et al. 2006). In the same study, following 50 d of incubation, 80% of naproxen was biodegraded and ketoprofen, ibuprofen, acetaminophen and gemfibrozil were nearly completely biodegraded.

6.2.3 Abiotic Degradation

In surface waters, abiotic degradation may occur via hydrolysis or photodegradation. Pharmaceuticals are administrated orally and are generally resistant to hydrolysis; therefore, photodegradation is probably the dominant process for their abiotic transformation in the aquatic environment (Andreozzi et al. 2003). Lam et al. (2004) explored the abiotic persistence of eight pharmaceuticals and suggested that hydrolysis does not seem to be an important process for degrading these organic compounds, although penicillins are known to rapidly hydrolyse and degrade, as a result of their unstable β-lactam ring (Hirsch et al. 1999).

6.2.4 Photodegradation

The photodegradation of pharmaceuticals has been investigated in a vast number of studies, and Boreen et al. (2003) have reviewed the status of this knowledge.

Many pharmaceutical classes, including the analgesics, anti-inflammatories and the antibiotics, have been shown to be photodegraded (Arnold et al. 2003; Andreozzi et al. 2004; Latch et al. 2003; Table 15). In an aquatic outdoor microcosm study, photodegradation of acetaminophen and caffeine was

Table 15 Examples of pharmaceuticals that are photodegraded and the mechanism involved

Mechanism	Examples of pharmaceuticals	References
Direct photolysis	Naproxen, diclofenac, sulfamethoxazole, sulfamethizole	1, 2, 3
Direct and indirect photolysis	Clofibric acid, amoxicillin, ranitidine, sulfamethazine, sulfamerazine, sulfadiazine	1, 3, 4, 5
Indirect photolysis	Ibuprofen, cimetidine	1, 5

References: 1 – Arnold et al. (2003); 2 – Buser et al. (1998b); 3 – Packer et al. (2003); 4 – Andreozzi et al. (2004); 5 – Latch et al. (2003)

shown to be very fast. Levofloxacin, trimethoprim, sertraline and atorvastatin were also degraded, but at a slower rate, whereas sulfamethoxazole and carbamazepine were fairly persistent (Lam et al. 2004). Other compounds were also shown to be photodegraded, including ofloxacin, lincomycin, metronidazole and atorvastatin (Andreozzi et al. 2003; Andreozzi et al. 2006; Lam et al. 2004).

Absorption of solar light causes direct photolysis, whereas indirect photolysis involves natural photosensitizers such as nitrate and humic acids (Andreozzi et al. 2003) that can generate strong oxidant species such as hydroxyl radicals and singlet oxygen under solar irradiation (Zepp et al. 1981). Furthermore, the photodegradation of a chemical also depends on conditions such as temperature and light intensity (Alexy et al. 2004). Photodegradation may also result in degradation products. For example, photodegradation of carbamazepine, clofibric acid and iomeprol resulted in the formation of degradation products. For clofibric acid, degradation products were identified as 4-chlorophenol, hydroquinone, *p*-benzoquinone and phenol (Doll and Frimmel 2003). In this same study, the photodegradation rate of carbamazepine and clofibric acid was measured in the presence of other drugs that acted as competitive inhibitors, resulting in slower degradation rate constants (Doll and Frimmel 2003).

In the natural environment, the photodegradation rate is affected by a range of factors, including dissolved organic matter (DOM) (Andreozzi et al. 2003, 2004; Doll and Frimmel 2003) concentration of nitrate ions in solution (Andreozzi et al. 2003, 2004) and pH (Andreozzi et al. 2004; Arnold et al. 2003; Table 16).

DOM was found to decrease photodegradation of diclofenac and carbamazepine by adsorbing UV radiation and thus reducing available energy for these molecules (inner filter) (Andreozzi et al. 2003). In contrast, another study reported an enhancement of the photodegradation rate of carbamazepine with low concentrations of DOM (Doll and Frimmel 2003).

Table 16 Influence of nitrate ions, dissolved organic matter (DOM) and pH on the photodegradation rate of some pharmaceuticals

Pharmaceuticals	Photodegradation rate			Reference
	Nitrate ions	DOM	Basic pH	
Amoxicillin	Not influenced	>	>	1
Carbamazepine	<	< >Low concent.	–	2, 3
Clofibric acid	<	>	–	2
Diclofenac	<	<	–	2
Ofloxacin	<	>	–	2
Propranolol	>	>	–	2
Sulfamethizole	–	–	>	4
Sulfamethoxazole	<	>	>	2, 4

References: 1 – Andreozzi et al. (2004); 2 – Andreozzi et al. (2003); 3 – Doll and Frimmel (2003); 4 –Arnold et al. (2003)

6.2.5 Dissipation in Water-Sediment Systems

In addition to the studies described above, laboratory, mesocosm and field studies have been performed to explore the fate of pharmaceuticals in more natural systems involving a variety of dissipation processes. For example, Löffler et al. (2005) investigated the fate of a number of pharmaceuticals in laboratory water/sediment systems and analysed both the water and the sediment over time. In this study, the persistence of carbamazepine was confirmed in both phases. Although the metabolite 10,11-dihydro-10,11-dihydroxycarbamazepine seems to disappear from the water/sediment compartment with a DT_{50} of around 8 d, it was found to be very persistent with DT_{90} values exceeding 365 d. A low persistence was found for ibuprofen 2-hydroxy-ibuprofen and paracetamol, whereas a high persistence was measured for diazepam, carbamazepine and its metabolite and clofibric acid, which could be detected in the water/sediment system after 365 d. Moderate persistence was found for oxazepam and iopromide, which was transformed into at least four transformation products (Löffler et al. 2005). Two compounds, carbamazepine and clofibric acid (Buser et al. 1998a), were reported to be very persistent in the aquatic environment. Even if pharmaceuticals are degraded in the aquatic environment, their continuous emission from STPs renders them persistent contaminants (Daughton 2005; Petrovic et al. 2003).

6.3 Fate in Soils

The fate of pharmaceuticals in soil involves primarily two important processes: sorption and degradation (Beausse 2004; Díaz-Cruz et al. 2003). Sorption of pharmaceutical compounds in soils is an important process because their association with soil particles affect potential mobility (Karthikeyan and Bleam 2003) and availability for degradation (Halling-Sørensen et al. 2002).

6.3.1 Sorption on Soils

Pharmaceuticals display a wide range of sorption to soils (0.2<adsorption coefficients (K_d)a<3600 L/kg; Table 14), and sorption of the same compound in different soil types can vary significantly (Tolls 2001). Different processes are involved in sorption of pharmaceuticals to soils. The more important mechanisms are association with organic matter (OM), ion exchange, surface adsorption to mineral constituents, hydrogen bonding and formation of complexes with ions such as Ca^{2+}, Mg^{2+}, Fe^{3+} or Al^{3+} (Diaz-Cruz et al. 2003; Table 17).

The fluoroquinolone and the tetracycline antibiotics are strongly sorbed to soils, forming stable complexes through cation bridging to clay minerals (Nowara et al. 1997; Rabølle and Spliid 2000). Therefore, these compounds

Table 17 Adsorption mechanisms for acidic and basic compounds (adapted from Kah and Brown 2006)

Acidic compounds		
p*K*a > 10	3 < p*K*a < 10	p*K*a < 3
Dominant form		
AH	Ratio A/AH	A
Adsorption mechanisms		
Hydrophobic interactions (OM, clay) Van der Waals (OM, clay) H-bonding (OM, clay)	Temperate soils	
	Anion repulsion by negatively charged adsorbents Cation (or water) bridging (OM, clay) H bonding Charge transfer (OM) Van der Waals (OM)	
	Tropical soils	
	Anion exchange (Al, Fe (hydr)oxides) Ligand exchange (protonated (oxi)hydroxides, OM) Cation bridging (through ligand exchange: H_2O–metal	
Basic compounds		
p*K*a > 10 (p*K*b < 4)	3 < p*K*a < 10(4<p*K*b<11)	p*K*a < 3(p*K*b > 11)
Dominant form		
BH^+ or B^+	Ratio BH^+/B or B^+/B(OH)	B or B(OH)
Adsorption mechanisms		
Cation exchange (OM, clay) Charge transfer (OM)	Hydrophobic partitioning (OM, clay) Van der Waals (OM, clay) H-bonding (OM, clay) Ligand exchange (OM) Charge transfer (OM)	

A – acid; B – base; H – proton; OM – organic matter

remain in the soil compartment, have very limited mobility and are not detected in leachates (Golet et al. 2003; Karthikeyan and Bleam 2003; Kay et al. 2005; Rabølle and Spliid 2000). The analgesics and anti-inflammatory compounds diclofenac and naproxen, the β-blocker propranolol and the sulfonamides are less sorptive to soils (Drillia et al. 2005; Monteiro et al., in prep.).

Influence of Soil pH and Ionic Strength

Most pharmaceuticals are ionisable, hence, pH is an important parameter when considering their soil sorption. Depending on their particular p*K*a, some pharmaceuticals will be in solution and ionically at equilibrium at soil environmental pH levels. The sorption of acidic compounds, such as clofibric acid, naproxen, sulfonamides, fluoroquinolones and salicylic acid, is pH dependent and they are mainly found in their anionic form at normal soil pH; hence, with the exception of the fluoroquinolones, their adsorption to soils is generally low (Dubus et al. 2001; Monteiro et al., in prep; Nowara et al. 1997; Oppel et al.

2004). Nevertheless, at lower soil pH stronger sorption exists because of higher amounts of the neutral species of these compounds (Drillia et al. 2005; Monteiro et al., in prep). Soil OM is negatively charged; hence, sorption of basic pharmaceuticals is expected to be stronger, since at soil pHs found in the environment, such compounds would be present in their cationic form (e.g., fluoxetine) (Monteiro et al., in prep).

Ionic strength may also affect sorption of ionisable compounds, because an increase of ions in solution gives rise to increasing competition for ion-exchange sites. With increased ionic strength, cations are attracted to negative soil surfaces and may replace already sorbed cationic organic substances. Alternatively, such ionic strength may reduce the negative surface charge and increase sorption of anionic compounds (Ter Laak 2005). Increased ionic strength was reported to significantly decrease sorption of oxytetracycline and did not influence sulfachloropyradizine sorption behaviour (Ter Laak et al. 2006).

Influence of Soil Components

For neutral organic compounds, soil organic carbon (OC) has been shown to be the most important soil property for describing sorption behaviour. However, its use is unsuitable for ionisable compounds, because such compounds can sorb to other soil components (e.g. clay, Al^{3+}, Fe (hydr)oxides; Dubus et al. 2001). Soil OM provides specific adsorption sites for organic compounds that are independent of their polarity (Pignatello 1998). Dubus et al. (2001) reported increased sorption of salicylic acid and clofencet with depth, as OM decreased. In the same study, organic matter did not have a positive influence on the sorption behaviour of these ionisable compounds.

Crystalline and amorphous minerals constitute the clay fraction of soil. The clay fraction has high sorption capacity resulting from its small size and large specific surface area (McGechan and Lewis 2002). Negatively charged clay sorption sites are mostly located on the layer silicates; clay minerals may also provide hydrophobic sorption sites (Kah and Brown 2006). Adsorption of compounds on clay surfaces results from exchangeable cations (Calvet 1989). Sorption of the fluoroquinolone enrofloxacin has been shown to occur at the surface of clay minerals (Nowara et al. 1997).

Aluminium and iron (hydr) oxides, commonly found in tropical soils, may influence sorption. In temperate soils, organic compounds may complex with Al^{3+} and $Fe^{2+/3+}$ and thus prevent the formation of respective hydr(oxides) (Kah and Brown 2006). The charge of their surfaces depends on pH. At pH values lower than the point of zero charge (PZC) of the minerals, the surface is positively charged. Thus, electrostatic attraction of anionic compounds is promoted (Dubus et al. 2001). However, if pH values are above the PZC, then the opposite occurs, i.e., the overall surface is negatively charged and anionic compounds will be repulsed and cationic compounds attracted. The importance of aluminium and iron (hydr)oxides is observed in soils with low OM and clay content, and at pH values in which acidic compounds are mostly in their anionic

form (Kah and Brown 2006). Positively charged oxide surfaces were important for the sorption of salicylic acid and clofencet, with the possible formation of bidentate surface complexes with metals (Dubus et al. 2001).

Effect of Sludge

Addition of sludge to soils introduces other variables that can affect sorption behaviour. A change in solution pH after amendment with sludge or slurry was reported in some studies. While Boxall and co-workers (2002) reported an increase of the pH with sludge amendment, Thiele-Bruhn and Aust (2003) noted a decrease in pH with addition of pig slurry. Therefore, addition of sludge affects solution pH and will therefore affect sorption behaviour of pharmaceuticals. The other parameter that has been reported to change is OC content. Generally, sludge contains much more OC than do soils alone, and with its introduction to soils, an increase of solution OC has been reported (Thiele-Bruhn and Aust 2003; Boxall et al. 2002). Adsorption of compounds to dissolved DOM increases concentrations in the aqueous phase; this decreases sorption coefficients that do not account for chemical fractions that might be sorbed to DOM (Tolls 2001).

Mobility

In a laboratory study to test the leaching behaviour of a range of pharmaceutical compounds in different soils, low mobility was found for diazepam, ibuprofen and carmazepine. The latter has been detected in groundwater and it is believed that the source of this contamination is derived from river sediments (Oppel et al. 2004). In this same study, clofibric acid and iopromide were discovered to be very mobile in soils (Oppel et al. 2004). This mobility was confirmed in a semi-field study for clofibric acid, when it was fully recovered in a soil leachate (Drillia et al. 2005).

Runoff of pharmaceuticals from soils amended with sewage sludge has been reported (Topp et al. 2008a). In fieldwork performed in Canada, sewage sludge was applied using two common practices: broadcast and injection application. In a broadcast application, sludge is applied onto the soil surface and then incorporated into the soil, whereas in an injection application sludge is injected into the soil. In this study, it was concluded that the pharmaceuticals studied, such as carbamazepine, ibuprofen, acetaminophen and naproxen, are subject to runoff following a broadcast application in wet weather (Topp et al. 2008a).

6.3.2 Degradation in Soils

It is assumed that pharmaceuticals spread onto soils in sewage sludge do not significantly photodegrade (Thiele-Bruhn 2003). Furthermore, pharmaceuticals may adsorb onto, or penetrate into, soils and be unavailable for degradation (Thiele-Bruhn 2003). The total amount of the substance is assumed to be

available for biodegradation (Artola-Garicano et al. 2003), and because pharmaceuticals are applied to soils in sewage sludge or liquid manure (e.g., sulfonamides and tetracyclines), most studies include the sludge/manure matrix to determine biodegradation rates in soils.

Tetracylines and sulfonamides are used in human therapy but their occurrence in the environment mainly results from veterinary use, thus studies found in the literature are from application of manure or slurry to soils.

Tetracyclines and fluoroquinolones are known to strongly adsorb to soils (Nowara et al. 1997; Rabølle and Spliid 2000), and therefore they may be very persistent in soils. This was confirmed by two studies, in which tetracyclines and fluoroquinolones were found to be very persistent in soils amended with liquid manure and sewage sludge, respectively (Hamscher et al. 2002; Golet et al. 2002b). However, oxytetracycline was reported to be completely degraded within a clay soil column over a period of 4 mon (Kay et al. 2005).

Only a few studies were found in the literature that reported degradation in soils for other classes of pharmaceuticals (Schlüsener and Bester 2006; Topp et al. 2006; Collucci et al. 2001; Topp et al. 2008b). Caffeine was reported to rapidly degrade to carbon dioxide in sandy loam and loam soils, and more slowly in a silt loam soil (Topp et al. 2006); with the exception of roxithromycin, macrolides including erythromycin and oleandomycin are degraded in soils (Schlüsener and Bester 2006).

In laboratory microcosm incubations, degradation in soil of the natural hormones 17β-oestradiol and oestrone was investigated. 17β-Oestradiol was oxidized to oestrone in both autoclaved and non-sterile soils, suggesting an abiotic process, whereas oestrone was stable in autoclaved soil and degraded in the non-sterile soils, suggesting microbial degradation (Collucci et al. 2001). Naproxen was reported to be quickly degraded and mineralized to carbon dioxide in soils (Topp et al. 2008b).

Environmental factors that appear to affect soil degradation of pharmaceuticals are soil type, temperature and moisture (Topp et al. 2008b; Collucci et al. 2001). Dissipation of hormones was slower when soils were air-dried or adjusted to field moisture capacity, but soil pH and OM content had no effect on degradation rates (Collucci et al. 2001). In the same study, temperature only affected mineralization of 17β-oestradiol (Collucci et al. 2001). Naproxen dissipation was reported to be slower at lower temperatures and moisture contents and initially slower in saturated soil, but after 7 d of incubation the degradation rate accelerated and was comparable to the ones detected in moist soils (Topp et al. 2008b).

No effect on biodegradation of veterinary antibiotics, including metronidazole, tylosin and olaquindox in soil was verified after addition of manure (Ingerslev and Halling-Sørensen 2001). Caffeine degradation rates in soils increased with addition of aerobically digested sewage sludge, whereas addition of anaerobically treated sewage sludge did not accelerate caffeine mineralization (Topp et al. 2006). The degradation rate of naproxen was also reported to be increased by the addition of biosolids (Topp et al. 2008b).

The formation of metabolites been only been investigated in a few studies (Topp et al. 2008b; Collucci et al. 2001). No detectable transformation products were found for naproxen or the hormones oestrone and 17β-oestradiol (Topp et al. 2008b; Collucci et al. 2001).

6.4 Fate in Drinking Water Treatment

The advanced methods used in drinking water treatment plants may remove substances by physical separation processes and/or a combination of biological, photochemical and physical processes (Sedlak and Pinkston 2001). Ozone, and advanced oxidation processes (AOPs), such as ozone coupled with peroxide hydrogen or ultraviolet radiation (UV), and processes such as chlorination, membrane bioreactor, reverse osmosis, coagulation and filtration with activated carbon are being used (Boyd et al. 2003; Ternes et al. 2003, 2007; Balcioğlu and Ötker 2003; Westerhoff et al. 2005; Huber et al. 2005).

6.4.1 Physical and Chemical Processes

Bank filtration has been used in drinking water production for many years, although this process only successfully removes a few compounds (e.g. bezafibrate and diclofenac). Another process used in advanced water treatment is filtration with activated carbon. This process has proven to be very effective in removing organic substances including carbamazepine, ibuprofen, diazepam, sulfamethoxazole and roxithromycin; only a few substances such as the iodinated contrast media show low affinity to activated carbon (Poseidon 2005). Stackelberg et al. (2007) performed a study with 113 compounds, including pharmaceuticals, in which filtration with granular activated carbon accounted for 53% of the contaminant removal, whereas only 32% was removed by chlorination. Gibs et al. (2007) investigated the chlorination of 98 pharmaceuticals and other organic compounds, and only 22 would react with free chlorine within 24 hr. Disinfection by chlorination is effective for a number of pharmaceuticals, including sulfonamides, fluoroquinolones and analgesics and anti-inflammatories, whereas no removal was observed for erythromycin, caffeine, carbamazepine or cotinine (Gibs et al. 2007). Therefore, chlorination is not an effective method for the removal of pharmaceuticals in advanced water treatment plants. Furthermore, the disinfection by-products formed during chlorination may be dangerous. Another process employed in STPs for removal of OM and particles is coagulation/flocculation. However, little removal of pharmaceuticals is achieved with this method (Carballa et al. 2005; Poseidon 2005; Westerhoff et al. 2005).

6.4.2 Advanced Oxidation Processes

Advanced oxidation processes (AOPs) produce hydroxyl (OH) radicals, which are very reactive non-selective species that attack the majority of organic substances. Different reactants are used and are usually expensive and include ozone and/or hydrogen peroxide (H_2O_2) (Andreozzi et al. 1999). Some examples of AOPs are ozone (O_3) coupled with H_2O_2, UV radiation, H_2O_2/UV and photocatalysis with titanium dioxide (TiO_2) under UV light and coupled with oxygen (Andreozzi et al. 1999).

The use of AOPs has been reported in several studies to be very effective in removing pharmaceuticals (Ternes et al. 2002b; Balcioğlu and Ötker 2003; Huber et al. 2005; Snyder et al. 2006; Zwiener et al. 2000). Treatment with ozone at low (0.2–0.3 mg/L) and medium (1–5 mg/L) doses has been shown to achieve high removal for a number of pharmaceuticals including the hormones 17α-ethinyloestradiol and 17β-oestradiol, the analgesics and anti-inflammatories naproxen, antibiotics sulfamethoxazole, erythromycin and trimethoprim (Huber et al. 2005; Ternes et al. 2003; Westerhoff et al. 2005); in contrast, very low removal was observed for diatrizoate and iodinated X-ray contrast media (Ternes et al. 2003). However, with increased ozone doses (>10 mg/L) a higher removal was observed for these compounds (Ternes et al. 2003). AOPs using ozone/H_2O_2 at low (2.1/1.0 mg/L) and medium (3.6/2.5 mg/L) doses have been reported to achieve high removal efficiencies for a number of pharmaceuticals including carbamazepine, diclofenac, naproxen, trimethoprim, sulfamethoxazole and fluoxetine, whereas low removal was achieved for diatrizoate, iopromide and ibuprofen (Snyder et al. 2006; Ternes et al. 2003). However, when higher doses were used ($\geq$ 7.1 / 3.5 mg/L) better removal was observed for ibuprofen, diatrizoate and iodinated X-ray contrast media (Snyder et al. 2006; Ternes et al. 2003).

However, at more economic doses, ozone will not result in complete mineralization (break down to carbon dioxide and water) and by-products may be formed (Snyder et al. 2006). Some of the identified by-products do not appear to be toxic (Poseidon 2005). Oestrogenicity also seems to be lost after the ozonation process (Poseidon 2005; Snyder et al. 2006).

The efficiency of AOPs is not influenced by suspended solids and the parameter that has higher effect on AOPs is dissolved organic carbon (DOC) (Huber et al. 2005). Therefore, to reduce pharmaceutical content more than 90%, the ozone concentration used in AOPs must be the same as the DOC value (Zwiener et al. 2000).

7 Recommendations for Further Work

Although considerable information is now available in the public domain on the topic we have reviewed in this article, there are still many data gaps. Based on the findings of this review we would advocate that

1. Reliable usage and consumption data are obtained for pharmaceuticals across the world. This should not only consider prescription medicines but also over-the-counter drugs as well.
2. Studies be performed on the occurrence and fate of a wider range of pharmaceuticals; there are more than 3000 pharmaceuticals currently in use; environmental data are available for only a few of these.
3. Analytical methods be developed to allow detection of a wider range of pharmaceuticals at environmentally realistic concentrations.
4. New studies be performed into the detection, occurrence and fate of transformation products and metabolites of pharmaceuticals.
5. Work be performed to develop a more detailed understanding of the chemical and environmental properties affecting sorption, persistence, transport and accumulation in environmental systems. This knowledge will allow development of modelling approaches for predicting the fate and behaviour of pharmaceuticals for a range of environmental conditions. Data are particularly lacking for terrestrial systems.
6. The available occurrence data be used to evaluate existing regulatory exposure models, and where appropriate, be used to guide the further development of these models. This will assist in better determining the environmental risks of future new pharmaceuticals.

8 Summary

In this chapter, we have reviewed data available on the usage, consumption, sources, occurrence and fate of human-use medicines in the environment. The main conclusions of our review are as follows:

1. Over the past decade, a wealth of data has been produced on the inputs, occurrence and fate of pharmaceuticals in the natural environment. This data set provides an excellent resource to inform the debate on human and environmental impacts of pharmaceuticals. Any unpublished additional information generated by the pharmaceutical industry is not readily available.
2. Pharmaceutically active substances, and other biologically active agents, are widely prescribed and used around the world. The most heavily used pharmaceutical classes include antibiotics, analgesics, anti-inflammatories and beta-blockers. Among the most used active ingredients are amoxicillin, acetaminophen and metoprolol. However, reliable information on consumption of pharmaceuticals in some countries is often difficult to access. Furthermore, many pharmaceuticals are sold as “over-the-counter” drugs, which renders consumption estimates even more difficult to obtain.
3. The main method by which pharmaceuticals are introduced into the environment is probably from sewage treatment plant emissions. Other, more minor sources of environmental contamination by pharmaceuticals include

inappropriate disposal of unused or expired drugs, accidental spills during production or distribution and emissions from manufacturing. Manufacturing releases may be more significant in developing countries. One way to minimize environmental release of pharmaceuticals could be the return of unused medicines to the pharmacy for appropriate disposal. Additional pathways for introduction of drugs to the terrestrial environment may be use of sewage sludge, contaminated with pharmaceuticals, as fertilizer in agriculture and crop irrigation with wastewaters.

4. Over the last decade, more than 100 different drugs have been detected in a range of environmental matrices; among those detected are antibiotics, analgesics, anti-inflammatories, hormones and lipid regulators. In general, the environmental occurrence of drug metabolites has not been much studied, and the environmental metabolic fate of most drugs is unknown.
5. The fate of pharmaceuticals in the environment is dependent on a range of factors, including physico-chemical properties, amount used, amenability to metabolism and treatability in sewage treatment plants. Once released into the environment, other factors dictate the fate of these compounds, including degradation and sorption to components of the aquatic and soil environment, and environmental factors such as pH and climate.
6. Several pharmaceuticals have been shown to resist conventional sewage treatment, although more advanced methods can be used to eliminate these compounds. Advanced oxidation processes were shown to achieve better removal efficiency and may be useful in the future.
7. Once released into the aquatic environment, several pharmaceuticals have been shown to be photodegraded, while others are resistant to the effects of light. Many pharmaceuticals are attenuated in the environment through the action of sorption onto sediments. In the soil environment, there is an evident lack of information on degradation of pharmaceuticals and impact of sludge on dissipation, whereas more information is available on sorption behaviour, even though it is primarily on antibacterials.

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Appendix

Compound	Therapeutic class	CAS[a]
1,7-Dimethylxanthine (caffeine metabolite)	Psychomotor stimulant – metabolite	611-59-6
16α-Hydroxyoestrone	Hormone	566-76-7
17α-Oestradiol	Hormone	57-91-0
17α-Ethinyloestradiol	Hormone	57-63-6

Appendix (continued)

Compound	Therapeutic class	CAS[a]
17β-Oestradiol	Hormone	50-28-2
17β-Oestradiol-17-valerate	Hormone	979-32-8
19-Norethisterone	Hormone	68-22-4
4-Aminoantipyrine (metamizole metabolite)	Analgesic and anti-inflammatory – metabolite	83-07-8
AAA (metamizole metabolite)	Analgesic and anti-inflammatory – metabolite	*N-A*cetyl-4-aminoantipyrine
Acebutolol	Beta-blocker	37517-30-9
Acetaminophen	Analgesic	103-90-2
Acetylsalicylic acid	Analgesic and anti-inflammatory	50-78-2
Albuterol	Beta2-simpathomimetic	18559-94-9
AMDOPH (phenazone-type metabolite)	Analgesic and anti-inflammatory – metabolite	1-Acetyl-1-methyl-2-dimethyl-oxamoyl-2-phenylhydrazide
Amidotrizoic acid	Iodinated X-ray contrast media	50978-11-5
Amitriptyline	Antidepressant	50-48-6
Amoxicillin	Penicillin antibiotic	26787-78-0
AMPH (phenazone-type metabolite)	Analgesic and anti-inflammatory – metabolite	1-Acetyl-1-methyl–2-phenylhydrazide
Ampicillin	Penicillin antibiotic	69-53-4
Androsterone	Hormone	53-41-8
Atenolol	Beta-blocker	29122-68-7
ATH (potential metabolite of iopromide)	Iodinated X-ray contrast media – metabolite	(2,3-Dihidroxypropyl)amide
ATI (potential metabolite of iopromide, iopadimol and iomeprol)	Iodinated X-ray contrast media – metabolite	5-Amino-2,4,6-triiodoisophthalic acid
Atorvastatin	Lipid regulator	134523-00-5
Azithromycin	Macrolide antibiotic	83905-01-5
Benzoylecgonine (cocaine metabolite)	Illicit drug – metabolite	519-09-5
Betaxolol	Beta-blocker	63659-18-7
Bezafibrate	Lipid regulator	41859-67-0
Bisoprolol	Beta-blocker	66722-44-9
Caffeine	Psychomotor stimulant	58-08-2
Carazolol	Beta-blocker	57775-29-8
Carbamazepine	Antiepileptic	298-46-4
Carboxy-ibuprofen (ibuprofen metabolite)	Analgesic and anti-inflammatory – metabolite	15935-54-3

Appendix (continued)

Compound	Therapeutic class	CAS[a]
CBZ-10OH (carbamazepine metabolite)	Antiepileptic – metabolite	10,11-Dihydro-10-hydroxycarbamazepine
CBZ-2OH (carbamazepine metabolite)	Antiepileptic – metabolite	2-Hydroxycarbamazepine
CBZ-3OH (carbamazepine metabolite)	Antiepileptic – metabolite	3-Hydroxycarbamazepine
CBZ-DiOH (carbamazepine metabolite)	Antiepileptic – metabolite	10,11-Dihydro-10,11-dihydroxycarbamazepine
CBZ-EP (carbamazepine metabolite)	Antiepileptic – metabolite	10,11-Dihydro-10,11-epoxycarbamazepine
Celiprolol	Beta-blocker	56980-93-9
Chloramphenicol	Antibiotic	56-75-7
Chlorotetracycline	Tetracycline antibiotic	57-62-5
Cimetidine	Antacid	51481-61-9
Ciprofloxacin	Fluoroquinolone antibiotic	85721-33-1
Citalopram	Antidepressant	59729-33-8
Clarithromycin	Macrolide antibiotic	81103-11-9
Clenbuterol	Beta2-simpathomimetic	37148-27-9
Clindamycin	Lincosamide antibiotic	18323-44-9
Clofibrate	Lipid regulator	637-07-0
Clofibric acid	Lipid regulator – metabolite	882-09-7
Clotrimazole	Fungicide	23593-75-1
Cloxacillin	Penicillin antibiotic	61-72-3
Cocaine	Illicit drug	50-36-2
Codeine	Analgesic	76-57-3
Cotinine	Nicotine metabolite	486-56-6
Cyclophosphamide	Antineoplastic agent	50-18-0
DAMI (potential metabolite of iopromide)	Iodinated X-ray contrast media – metabolite	Desmethoxyacetyl iopromide
Dehydronifedipine (nifedipine metabolite)	Antihypertensive – metabolite	67035-22-7
Democlocycline	Tetracycline antibiotic	127-33-3
Dextropropoxyphene	Analgesic and anti-inflammatory	469-62-5
Diatrizoate	Iodinated X-ray contrast media	117-96-4
Diazepam	Anxyolitic agent	439-14-5
Diclofenac	analgesic and anti-inflammatory	15307-86-5
Dicloxacillin	penicillin antibiotic	3116-76-5
Diethylstilbestrol	Hormone	56-53-1
Digoxigenin (digoxin metabolite)	Cardiac stimulant – metabolite	1672-46-4

Appendix (continued)

Compound	Therapeutic class	CAS[a]
Digoxin	Cardiac stimulant	20830-75-5
Diltiazem	Antihypertensive	42399-41-7
Dimethylaminophenazone (aminopyrine)	Analgesic and anti-inflammatory	58-15-1
Diphenhydramine	Antihistimine	58-73-1
DMOAS (phenazone-type metabolite)	Analgesic and anti-inflammatory – metabolite	Dimethyloxamide acid-(*N*'-methyl-*N*-phenyl)-hydrazide
Doxycycline	Tetracycline antibiotic	564-25-0
Enalapril	Antihypertensive	75847-73-3
Enalaprilat	Antihypertensive – metabolite	76420-72-9
Enoxacin	Fluoroquinolone antibiotic	74011-58-8
Enrofloxacin	Fluoroquinolone antibiotic	93106-60-6
Ephedrine	Anti-asthmatic	299-42-3
Equilenin	Hormone replacement	517-09-9
Equilin	Hormone replacement	474-86-2
Erythromycin	Macrolide antibiotic	114-07-8
Oestradiol	Hormone	50-28-2
Oestriol	Hormone	50-27-1
Oestrogen	Hormone	53-16-7
Oestrone	Hormone	53-16-7
Etofibrate	Lipid regulator	31637-97-5
FAA (metamizole metabolite)	Analgesic and anti-inflammatory – metabolite	*N*-Formyl-4-aminoantipyrine
Fenofibrate	Lipid regulator	49562-28-9
Fenofibric acid	Lipid regulator – metabolite	42017-89-0
Fenoprofen	Analgesic and anti-inflammatory	31879-05-7
Fenoterol	Beta2-simpathomimetic	13392-18-2
Flumequine	Fluoroquinolone antibiotic	42835-25-6
Fluoxetine	Antidepressant	54910-89-3
Flurbiprofen	Analgesic and anti-inflammatory	5104-49-4
Furosemide	Diuretic	54-31-9
Gemfibrozil	Lipid regulator	25812-30-0
Gentisic acid (acetylsalicylic acid metabolite)	Analgesic and anti-inflammatory – metabolite	490-79-9
Glibenclamide	Antidiabetic	10238-21-8
Hydrochlorothiazide	Diuretic	58-93-5

Appendix (continued)

Compound	Therapeutic class	CAS[a]
Hydroxyhippuric acid	Analgesic and anti-inflammatory – metabolite	487-54-7
Hydroxy-ibuprofen (ibuprofen metabolite)	Analgesic and anti-inflammatory – metabolite	51146-55-5
Ibuprofen	Analgesic and anti-inflammatory	15687-27-1
Ifosfamide	Antineoplastic agent	3778-73-2
Indomethacin	Analgesic and anti-inflammatory	53-86-1
Iomeprol	Iodinated X-ray contrast media	78649-41-9
Iopamidol	Iodinated X-ray contrast media	60166-93-0
Iopromide	Iodinated X-ray contrast media	73334-07-3
Iothalamic acid	Iodinated X-ray contrast media	2276-90-6
Ioxitalamic acid	Iodinated X-ray contrast media	28179-44-4
Ketoprofen	Analgesic and anti-inflammatory	22071-15-4
Levonorgestrel	Hormone	797-63-7
Lidocaine	Anaesthetic	137-58-6
Lincomycin	Lincosamide antibiotic	154-21-2
Lofepramine	Antidepressant	23047-25-8
Lomefloxacin	Fluoroquinolone antibiotic	98079-51-7
Lovastatin	Lipid regulator	75330-75-5
MAA (metamizole metabolite)	Analgesic and anti-inflammatory – metabolite	*N*-Methyl-4-aminoantipyrine
Meclofenamic acid	Analgesic and anti-inflammatory	644-62-2
Mefenamic acid	Analgesic and anti-inflammatory	61-68-7
Meprobamate	Hypnotic	57-53-4
Mestranol	Hormone	72-33-3
Metformin	Antidiabetic	657-24-9
Methicillin	Penicillin antibiotic	61-32-5
Methotrexate	Antineoplastic agent	59-05-2
Methyldopa	Antihypertensive	555-30-6
Metoprolol	Beta-blocker	37350-58-6
Metronidazole	Anti-infective	443-48-1
Morphine	Analgesic	57-27-2
N_4-acetyl sulfamethoxazole (sulfamethoxazole metabolite)	Sulfonamide antibiotic – metabolite	21312-10-7

Appendix (continued)

Compound	Therapeutic class	CAS[a]
Nadolol	Beta-blocker	42200-33-9
Nafcillin	Penicillin antibiotic	147-52-4
Naproxen	Analgesic and anti-inflammatory	22204-53-1
Nifedipine	Antihypertensive	21829-25-4
Norethindrone	Hormone	68-22-4
Norfloxacin	Fluoroquinolone antibiotic	70458-96-7
Norfluoxetine (fluoxetine metabolite)	Antidepressant – metabolite	56161-73-0
Ofloxacin	Fluoroquinolone antibiotic	82419-36-1
Oleandomycin	Macrolide antibiotic	3922-90-5
Omeprazole	Antacid	73590-58-6
Oxacillin	Penicillin antibiotic	66-79-5
Oxazepam	Anxyolitic agent	604-75-1
Oxprenolol	Beta-blocker	6452-71-7
Oxyphenbutazone (phenylbutazone metabolite)	Analgesic and anti-inflammatory – metabolite	129-20-4
Oxytetracycline	Tetracycline antibiotic	79-57-2
Paroxetine	Antidepressant	61869-08-7
Penicillin G	Penicillin antibiotic	61-33-6
Penicillin V	Penicillin antibiotic	87-08-1
Pentoxifylline	Vasodilator	6493-05-6
Phenazone (antipyrine)	Analgesic and anti-inflammatory	60-80-0
Phenylbutazone	Analgesic and anti-inflammatory	50-33-9
Primidone	Antiepileptic	125-33-7
Progesterone	Hormone	57-83-0
Propranolol	Beta-blocker	525-66-6
Propyphenazone	Analgesic and anti-inflammatory	479-92-5
Quinidine	Antiarrhythmic agent	56-54-2
Ranitidine	Antacid	66357-35-5
Roxithromycin	Macrolide antibiotic	80214-83-1
Salbutamol	Beta2-simpathomimetic	35763-26-9
Salicylic acid (acetylsalicylic acid metabolite)	Analgesic and anti-inflammatory – metabolite	69-72-7
Sertraline	Antidepressant	79617-96-2
Simvastatin	Lipid regulator	79902-63-9
Sotalol	Beta-blocker	3930-20-9
Spyramycin	Macrolide antibiotic	8025-81-8
Sulfacetamide	Sulfonamide antibiotic	144-80-9

Appendix (continued)

Compound	Therapeutic class	CAS[a]
Sulfadiazine	Sulfonamide antibiotic	68-35-9
Sulfaguanidine	Sulfonamide antibiotic	57-67-0
Sulfamerazine	Sulfonamide antibiotic	127-79-7
Sulfamethazine	Sulfonamide antibiotic	57-68-1
Sulfamethizole	Sulfonamide antibiotic	144-82-1
Sulfamethoxazole	Sulfonamide antibiotic	723-46-6
Sulfanilic acid	Sulfonamide antibiotic	121-57-3
Sulfapyridine	Sulfonamide antibiotic	144-83-2
Sulfathiazole	Sulfonamide antibiotic	72-14-0
Sulfazalazine	Sulfonamide antibiotic	599-79-1
Sulfisoxazole	Sulfonamide antibiotic	127-69-5
Sulfonylamide	Sulfonamide antibiotic	63-74-1
Tamoxifen	Antineoplastic agent	10540-29-1
Terbutaline	Beta2-simpathomimetic	23031-25-6
Testosterone	Hormone	58-22-0
Tetracycline	Tetracycline antibiotic	60-54-8
Theobromine	Antihypertensive	83-67-0
Timolol	Beta-blocker	26839-75-8
Tolbutamide	Antidiabetic	64-77-7
Tolfenamic acid	Analgesic and anti-inflammatory	13710-19-5
Trimethoprim	Antibiotic	738-70-5

[a]Cases where the CAS (Chemical Abstracts Service registration number) is not available the chemical name is given

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