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David M. Whitacre
Editor

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Aquatic Toxicology of Perfluorinated Chemicals

John P. Giesy, Jonathan E. Naile, Jong Seong Khim, Paul D. Jones, and John L. Newsted

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1 Introduction

Perfluorinated compounds (PFCs) are fluorinated at all of the valence electrons of the carbon atoms in organic molecules, or at least a portion of the molecule is perfluorinated (Fig. 1). All PFCs are synthetic and many have

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been used in commercially available products or released as byproducts. A partial list of the compounds that are known to have been manufactured and/or released into the environment is given in Table 1. These compounds vary in structure, and thus exhibit different environmental fates and toxicities. Unfortunately, there is presently little information on the chemical–physical properties of most PFCs, and even less toxicity information is available for these compounds. There is some information available on the mechanisms of toxic action and acute and chronic toxicity for a few compounds. Most such information is for the two primary PFCs that have been found as residues in the environment: perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA).

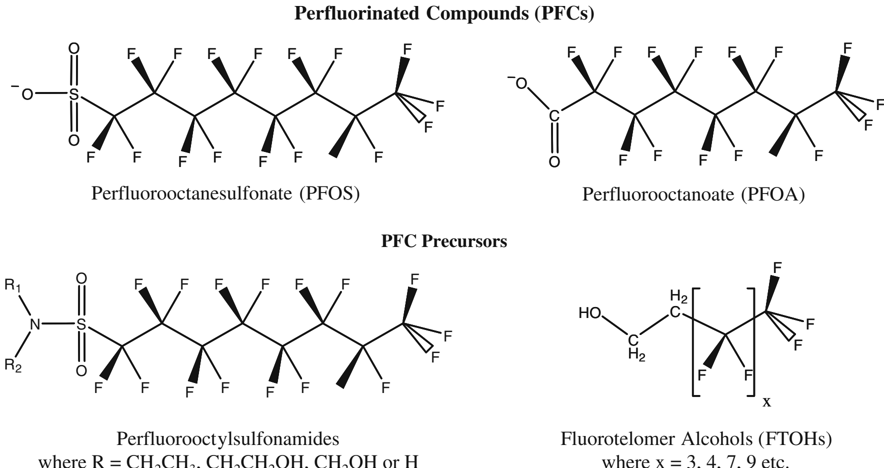


Fig. 1 Structure of perfluorinated compounds (PFCs) and some of their precursors

Among the more prominent PFCs that have been used in the production of commercial or industrial products, and released into the environment, are the perfluorinated fatty acids (PFFAs). The PFFAs are synthetic, fully fluorinated, fatty acid analogues that are characterized by a perfluoro-alkyl chain and a terminal sulfonate or carboxylate group. The high-energy carbon–fluorine (C–F) bond renders these compounds resistant to hydrolysis, photolysis, microbial degradation, and metabolism by animals, which makes them environmentally persistent (Giesy and Kannan 2002). PFCs have been manufactured for over 50 yr and have been used in materials such as wetting agents, lubricants, corrosion inhibitors, stain-resistant treatments for leather, paper and clothing, and in foam fire extinguishers (Sohlenius et al. 1994; Giesy and Kannan 2002). The global environmental distribution, bioaccumulation, and biomagnification

Table 1 Perfluorinated compounds (PFCs) and their precursor molecules

Compound (synonyms)	CAS number	Molecular structure	Molecular wt
PFCs			
Perfluorobutanesulfonate (C4, PFBS)	29420-49-3	$C_4F_9SO_3^-$	299
Perfluorohexanesulfonate (C6, PFHxS)	432-50-7	$C_6F_{13}SO_3^-$	399
Perfluorooctanesulfonate (C8, PFOS)	2795-39-3	$C_8F_{17}SO_3^-$	499
Perfluorooctanesulfonic acid	1763-23-1	$C_8F_{17}SO_3H$	500
Tridecafluoroheptanoate (C7, PFHpA)	–	$C_6F_{13}COO^-$	363
Perfluoroheptanoic acid	375-85-9	$C_6F_{13}COOH$	364
Perfluorooctanoate (C8, PFOA)	–	$C_7F_{15}COO^-$	413
Perfluorooctanoic acid	335-67-1	$C_7F_{15}COOH$	414
Heptadecafluoronoate (C9, PFNA)	–	$C_8F_{17}COO^-$	463
Perfluorononanoic acid	375-95-1	$C_8F_{17}COOH$	464
Nonadecafluorodecanoate (C10, PFDA)	–	$C_9F_{19}COO^-$	513
Perfluorodecanoic acid	335-76-2	$C_9F_{19}COOH$	514
Perfluoroundecanoate (C11, PFUnA)	–	$C_{10}F_{21}COO^-$	563
Perfluoroundecanoic acid	2058-94-8	$C_{10}F_{21}COOH$	564
Perfluorododecanoate (C12, PFDoA)	–	$C_{11}F_{23}COO^-$	613
Perfluorododecanoic acid	307-55-1	$C_{11}F_{23}COOH$	614
Perfluorotridecanoate (C13, PFTrA)	–	$C_{12}F_{25}COO^-$	663
Perfluorotetradecanoate (C14, PFTA)	–	$C_{13}F_{27}COO^-$	713
Perfluorotetradecanoic acid	376-06-7	$C_{13}F_{27}COOH$	714
Perfluoropentadecanoate (C15, PFPA)	–	$C_{14}F_{25}COO^-$	763
PFC precursors			
Perfluorooctane sulfonamide (PFOSA)	754-91-6	$C_8F_{17}SO_2NH_2$	499
n-Methyl perfluorooctane sulfonamidoethanol (n-MeFOSE)	24448-09-7	$C_8F_{17}SO_2N(CH_3)C_2H_4OH$	557
n-Ethyl perfluorooctane sulfonamidoethanol (n-EtFOSE)	1691-99-2	$C_8F_{17}SO_2N(C_2H_5)C_2H_4OH$	571
n-Ethyl perfluorooctane sulfonamidoacetic acid (PFOSAA)	2991-51-7	$C_8F_{17}SO_2N(C_2H_5)CH_2CO_2H$	585
n-Ethyl perfluorooctane sulfonamide (n-EtFOSA)	4151-50-2	$C_8F_{17}SO_2NH(C_2H_5)$	528

Table 1 (continued)

Compound (synonyms)	CAS number	Molecular structure	Molecular wt
Perfluorooctane sulfonylfluoride (POSF)	307-35-7	$C_8F_{17}SO_2F$	502
6:2 Fluorotelomer alcohol (6:2 FTOH)	647-42-7	$CF_3(CF_2)_5C_2H_4OH$	364
8:2 Fluorotelomer alcohol (8:2 FTOH)	678-39-7	$CF_3(CF_2)_7C_2H_4OH$	464
10:2 Fluorotelomer alcohol (10:2 FTOH)	865-86-1	$CF_3(CF_2)_9C_2H_4OH$	564

of several perfluoro-compounds have recently been studied (Giesy and Kannan 2001). PFOS is the most commonly found perfluorinated compound in the tissues of wildlife.

Since PFFAs are chemically stabilized by strong covalent C–F bonds, they were historically considered to be metabolically inert and non-toxic (Sargent and Seffl 1970). Accumulating evidence has demonstrated that PFFAs are actually biologically active and can cause peroxisomal proliferation, increased activity of lipid and xenobiotic metabolizing enzymes, and alterations in other important biochemical processes in exposed organisms (Obourn et al. 1997; Sohlenius et al. 1994). In wildlife, the most widely distributed PFFA, PFOS, accumulates primarily in the blood and in liver tissue (Giesy and Kannan 2001). Therefore, the major target organ for PFFAs is presumed to be the liver. However, this does not exclude other possible target organs such as the pancreas, testis, and kidney (Olson and Anderson 1983). Until recently, most toxicological studies have been conducted on PFOA and perfluorodecanoic acid (PFDA), rather than on the more environmentally prevalent PFOS. However, PFOS appears to be the ultimate degradation product of several commercially used perfluorinated compounds, and the concentrations of PFOS found in wildlife are greater than those of other PFCs (Giesy and Kannan 2002; Kannan et al. 2001a,b).

A large body of ecotoxicological information, generated over a period of more than 20 yr, exists for various salts of PFOS. However, until recently, definitive information was not available on chemical purity, and validated analytical methodology did not exist to measure exposure concentrations in many of the early studies. Therefore, data generated prior to 1998 were less reliable as to the nature of substance(s) tested, and exposure concentrations were not measured as part of these studies. Because it is the most prominent of all the PFOS salts produced, the potassium salt of PFOS was chosen for many of the laboratory studies that have been cited in this chapter. The commercially prepared potassium product was available as a full-strength salt. For example, in 1997, PFOS-K^+ accounted for $>45\%$ of all PFOS salts produced

(US EPA 2001). The primary ecotoxicological data used in this chapter are based in a series of studies utilizing a well-characterized sample of PFOS potassium salt. Although the lithium, ammonium, diethanolamine, and didecyldimethylammonium salts have been tested, many of the studies on these salts utilized mixtures containing only 25–35% active ingredients. The majority of these studies were conducted in accordance with US EPA and/or OECD Good Laboratory Practices. Older studies have also been included where more recently generated data were not available for various species. In addition, in this assessment we also examine recent studies published in the open literature that pertain to ecological presence and biochemical modes of action of PFFAs.

2 Environmental Fate

2.1 Physical/Chemical Properties

PFOS is moderately water soluble, non-volatile, and thermally stable. The potassium salt of PFOS has a reported mean solubility of 680 mg/L in pure water. However, PFOS is a strong acid, and in water at a neutral pH it will completely dissociate into ionic forms. Thus, the PFOS anion can form strong ion pairs with many cations, which results in salting out in natural waters that contain relatively great amounts of dissolved solids (Table 2). For example, as the salt content increases, the solubility of PFOS decreases such that PFOS solubility in salt water is approximately 12.4 mg PFOS/L. PFOS has a reported mean solubility of 56 mg PFOS/L in pure octanol. However, due to the surface-active properties of PFOS, when it is added to octanol and water in a standard test system to measure K_{ow}, it forms three layers. Thus, an octanol/water partition coefficient has not been directly measured for PFOS, but has been estimated from its water and octanol solubilities. Other physiochemical properties for this molecule such as bioconcentration factor and soil adsorption coefficient cannot be estimated with conventional quantitative structure activity relationship (QSAR) models. The use of K_{ow} is not appropriate to predict these other properties because PFOS does not partition into lipids, but instead binds to certain proteins in animals (Jones et al. 2003). As a result, use of either water solubility or predicted K_{ow} values may underestimate the accumulation of PFOS into organisms and other environmental media. PFOS is not expected to volatilize, based on its vapor pressure and predicted Henry's Law Constant. OECD (2002) classified PFOS as a type 2, non-volatile chemical that has a very low or possibly negligible volatility. Available physical/chemical properties for the potassium salt of PFOS are presented in Table 2.

Table 2 Physical/chemical properties of the potassium salt of perfluorooctanesulfonate (PFOS)

Parameter	Value	Reference
Melting point	≥400°C	Jacobs and Nixon (1999)
Boiling point	Not calculable	OECD (2002)
Specific gravity[a]	~ 0.6 (7–8)	OECD (2002)
Vapor pressure	3.31×10^{-4} Pa @ 20°C	Van Hoven et al. (1999)
Water solubility		
Pure water	680 mg/L	Ellefson (2001c)
Fresh water	370 mg/L	OECD (2002)
Sea water	12.4 mg/L	Ellefson (2001a)
Octanol solubility	56 mg/L	Ellefson (2001b)
Log K_{ow}[b]	–1.08	OECD (2002)
Henry's law constant[c]	4.34×10^{-7}	OECD (2002)

[a] pH values in parentheses
[b] Log K_{ow} calculated from PFOS solubility in water and *n*-octanol
[c] Henry's law constant calculated at 20°C using solubility in pure water

2.2 Photolysis

No experimental evidence of direct or indirect photolysis of PFOS is yet available (Hatfield 2001a). The indirect photolytic half-life for PFOS, using an iron oxide photo-initiator matrix model, was estimated to be ≥3.7 yr at 25°C. This model was chosen because it minimized the experimental error in this matrix. This half-life is based on the analytical method of detection.

2.3 Hydrolysis

Under experimental conditions (50°C and pH conditions of 1.5, 5, 7, 9, or 11) no hydrolytic loss of PFOS was observed in a 49-d study (Hatfield 2001b). Based on mean values and precision measures, the hydrolytic half-life of PFOS was estimated to be ≥41 yr at 25°C. However, it is important to note that this estimate was influenced by the analytical limit of quantification, and no loss of PFOS was detected in the study.

2.4 Biodegradation

Biodegradation studies in which PFOS was monitored analytically for loss of parent compound have been conducted using a variety of microbial sources and exposure regimes (Lange 2001; Gledhill and Markley 2000a,b,c). In one study with activated sludge, no loss or biotransformation of PFOS was observed over a 20-wk period under aerobic conditions, nor were there any losses observed in

a study conducted for 56 d with activated sludge under anaerobic conditions. The findings from these studies are supported by the results from a MITI-I test (Kurume Laboratory 2002) that showed no biodegradation of PFOS after 28 d, as measured by net oxygen demand, loss of total organic carbon, or loss of parent material. In addition, no losses of PFOS were observed in a biodegradation study conducted with soil under aerobic conditions. Therefore, to date, no laboratory data exist that demonstrates that PFOS undergoes significant biodegradation under environmental conditions.

2.5 Thermal Stability

Several studies suggest that PFOS would have relatively low thermal stability. This conclusion is based on the fact that the carbon–sulfur (C—S) bond energy is much weaker than the carbon–carbon (C—C), or the carbon–fluorine (C—F) bond energies, and as a result, would more easily break under incineration conditions (Dixon 2001). This conclusion is supported by a study by Yamada and Taylor (2003) indicating that PFOS should be nearly completely destroyed when incinerated.

2.6 Adsorption/Desorption

PFOS appears to adsorb strongly to soil, sediment, and sludge (Table 3) with an average distribution coefficient (K_d) greater than 1 ml/g, and an organic carbon normalized adsorption coefficient (K_{oc}) greater than 10,000 ml/g (Ellefson 2001d). Based on these values, PFOS would not be classified as qualitatively mobile, as defined by OECD guidelines. Once adsorbed to these matrices, PFOS does not readily desorb, even when extracted with an organic solvent. The average desorption coefficient (K_{des}) for soils was determined to be less than 0.001 L/g. In these matrices, adsorption and desorption equilibria were achieved in less than 24 hr; moreover, in more than 50% of cases, equilibria

Table 3 Adsorption and desorption of PFOS to sediments and soils[a]

	Adsorption kinetics			Desorption kinetics	
Soil type	K_d (L/g)	K_{oc} (L/g)	K_{adsF}[b]	K_{des} (L/g)	K_{desF}[b]
Clay	0.0183	70.4	0.0560	0.000471	0.222
Clay loam	0.00972	37.4	0.0421	0.0000158	0.082
Sandy loam	0.0353	126	0.0919	0.0000349	0.104
River sediment	0.00742	57.1	0.0094	0.0000100	0.039
Domestic sludge	<0.120	NC[c]	0.0568	<0.000237	29.5

[a]Values of K_d, K_{oc}, and K_{des} are averaged values
[b]Freundlich coefficient
[c]NC = not calculable

were achieved after approximately 1 min of contact with the test adsorbents. As a result, PFOS exhibited little mobility in all matrices tested and would not be expected to migrate any significant distance. The shape of the adsorption isotherm (H-type) indicates a very strong chemical/adsorption interaction. Since PFOS is a strong acid, it probably forms strong bonds in soils, sediments, and sludge via a chemisorption mechanism.

2.7 Bioconcentration

The potential of PFOS to bioaccumulate and bioconcentrate into fish and the relative importance of dietary and waterborne sources of PFOS to fish accumulation have been evaluated. In a bioaccumulation study with juvenile rainbow trout (*Oncorhynchus mykiss*), fish were exposed to 0.54 μg PFOS/g in the diet for 34 d, followed by a 41 d depuration phase (Martin et al. 2003a). PFOS was accumulated in and depurated from the liver and carcass in a time-dependent manner. The predicted time to reach 90% steady state would be 43 d, which was approximately the same as the exposure duration in the study. The liver and carcass depuration rate constants were 0.035 and 0.054/d, representing depuration half-lives of 20 and 13 d, respectively. The assimilation efficiency was 120 $\pm$ 7.9%, which indicates efficient absorption of PFOS from ingested food. This assimilation efficiency is greater than that observed with chlorinated contaminants such as polychlorinated biphenyls (PCBs), where efficiencies in trout can range from 20 to 60% (Fisk et al. 1998). In addition, this assimilation efficiency of PFOS is indicative of enterohepatic recirculation, which could affect the disposition of PFOS in fish. Evidence of enterohepatic recirculation in rats has been demonstrated to affect the rate of elimination (Johnson et al. 1984). As a result, this process may also be an important mechanism that helps to maintain PFOS concentrations in fish beyond what is predicted from K_{ow} or water solubility values. The bioaccumulation factor (BAF) for PFOS was 0.32 $\pm$ 0.05, which indicates that dietary exposure did not result in biomagnification in trout. This small BAF probably resulted from several factors, including a relatively low experimental feeding rate ($F = 1.5\%$ body wt) coupled with a relatively rapid rate of depuration. Taken together, these data show that under these experimental conditions, the diet would not be a major route of PFOS exposure for fish.

Studies conducted with other fish species have shown that PFOS will bioconcentrate in tissues from waterborne exposures (Table 4). Bluegill exposed to 0.086 or 0.87 mg PFOS/L in a flow-through system accumulated PFOS into edible and non-edible (fins, head, and viscera) tissues in a time-dependent manner (Drottar et al. 2001). In this bluegill study, fish were exposed to 0.086 mg PFOS/L for 62 d, but were only exposed to 0.87 mg PFOS/L for 35 d, because of excessive mortality. At the end of the exposure phase of both treatments, PFOS tissue concentrations appeared to still be increasing. As a

Table 4 Kinetic parameters and bioconcentration factors (BCF) of PFOS in fish

Species	Tissue	Apparent BCF[a]	Kinetic parameters			
			K_u (L/kg × d)	K_d (L/d)	BCF_K[b] (L/kg)	Half-life (d)
Bluegill	Edible	484	8.9	0.0047	1,866	146
	Unedible	1,124	22	0.0052	4,312	133
	Whole	856	16	0.0045	3,614	152
Rainbow trout	Carcass	–	53	0.048	1,100	15
	Blood	–	240	0.057	4,300	12
	Liver	–	260	0.050	5,400	14

[a]Apparent BCF was calculated as the concentration in fish at the end of the exposure phase divided by the average water concentration
[b]BCF_K was estimated as K_u/K_d

result, kinetic analyses of the data were conducted to calculate the kinetic bioconcentration factor (BCF_K) from estimated uptake and depuration rate constants. Fish exposed to 0.87 mg PFOS/L were not used to estimate these parameters. The BCF_K values for edible, inedible, and whole fish tissues were calculated to be 1,866, 4,312, and 3,614, respectively. During the elimination phase of the study, PFOS depurated slowly and the time to reach 50% clearance for edible, non-edible, and whole fish tissues were 146, 133 and, 152 d, respectively.

Tissue distribution and accumulation kinetics were determined in rainbow trout exposed to 0.35 μg PFOS/L (Martin et al. 2003b). The magnitude of PFOS concentrations in tissues were in the order of blood > kidney > liver> gall bladder. The least concentrations of PFOS were observed in the gonads, followed by adipose, and then muscle tissue (Table 4). In blood, approximately 94–99% of the PFOS was associated with plasma, and only a minor amount was associated with the cellular fraction. PFOS also accumulated in the gills, indicating their importance in the uptake and depuration in trout. In general, the depuration rate constants determined for carcass, blood, and liver showed that PFOS was more rapidly depurated than are some organochlorine contaminants (PCBs and toxaphene) but the rate is slower than that observed for other surfactants (Fisk et al. 1998; Tolls and Sijm 1995). When compared to other surfactants, the uptake rate constants were greater than expected and were directly related to greater tissue concentrations (Tolls et al. 1997). BCF_K were 1,100, 4,300, and 5,400 for carcass, blood, and liver, respectively. As was observed for bluegill, steady state PFOS concentrations in tissues were not achieved at the end of the exposure period. The 12-d accumulation ratios (BCF divided by tissue concentration at the end of the exposure period) for carcass, blood, and liver were greater than 600 indicating that the tissue concentrations were far from steady state. However, values of the BCF_K, calculated for rainbow trout, were well within the range of values observed for other species such as bluegill and carp.

In a flow-through bioconcentration study conducted with carp (*Cyprinus carpio*), fish were exposed to 2 or 20 μg PFOS/L, and water and fish tissue samples were collected throughout testing (Kurume laboratory 2001). Upon sampling, fish were separated into parts that included integument (skin except head, scales, fins, alimentary canal, or gills), head, viscera (internal organs except for alimentary canal and liver), liver, and carcass, and then analyzed for concentrations of PFOS. Kinetic analysis was not conducted because the study was not designed to examine uptake from water; rather, BCFs were calculated in all fish tissues at steady state. Steady state was assumed when three or more consecutive sets of tissue PFOS concentrations were not statistically different. In fish exposed for 58 d, the BCFs in carp from the 2 μg PFOS/L treatment ranged from 200 to 1,500. In fish from the 20 μg PFOS/L exposure, BCFs ranged from 210 to 850. PFOS depurated slowly and the time to reach 50% clearance for fish in the 20 μg PFOS/L treatment was 49 d, whereas 152 d was required for fish in the 2 μg PFOS/L treatment to reach 50% clearance.

To date, laboratory studies have demonstrated that PFOS accumulates into fish in a time- and concentration-dependent manner. In addition, these studies suggest that the primary route of accumulation of PFOS into fish is from exposure to aqueous PFOS. Dietary sources of PFOS are secondary and may not significantly enhance the overall accumulation of PFOS by fish. However, what actually happens under natural environmental conditions is yet to be tested. The reason for this is that discrepancies exist between accumulation factors as measured in the laboratory and those estimated in field studies. For example, bioaccumulation factors calculated from liver and surface water PFOS concentrations ranged from 6,300 to 125,000 in the common shiner (*Notropis cornutus*) collected in a Canadian creek (Moody et al. 2001). In contrast, the bioconcentration factor for rainbow trout, based on liver concentrations was 5,400, approximately 23-fold less than the maximal value derived in shiners (Martin et al. 2003b). The discrepancy between laboratory and field accumulation values has also been observed for fish collected from Tokyo Bay, Japan (Taniyasu et al. 2003). In that study, PFOS concentrations in fish livers were similar to those observed in the Great Lakes region of the United States and resulted in bioaccumulation factors that ranged from approximately 1,260 to 19,950. Again, the estimated BAFs were greater than those measured in laboratory studies. In a field study conducted in a reservoir in the Tennessee River, near Decatur Alabama, fish and surface water samples were collected and analyzed for PFOS. Bioconcentration factors from surface water PFOS concentrations and whole body PFOS concentrations in catfish and largemouth bass ranged from 830 to 26,000 (Giesy and Newsted 2001). Although BCF values determined in the laboratory are within the lower range of these values, they are also approximately four-fold less than the greater values estimated with fish from this location. The determination of BCF values from field exposures is complicated by the fact that less polar, PFOS-containing compounds could have been accumulated and then degraded to PFOS. Thus, while there is good agreement between the results of laboratory studies, BCFs and BAFs estimated

from field data vary greatly, and in many cases exceed values calculated from studies conducted under laboratory conditions. Factors contributing to variation in values of BAF and BCF developed from field observations may include interspecies and sex-dependent variation in accumulation. In addition, dietary sources of PFOS may be more important in the accumulation of PFOS by fish over their life cycle than would be expected based on results from laboratory studies conducted with rainbow trout. Finally, the accumulation of PFOS precursors, and their subsequent biotransformation into PFOS, may also be a contributing factor to the greater than expected PFOS concentrations in fish collected from the field. Overall, additional studies will have to be conducted to evaluate the relative importance of different accumulation pathways of PFOS by fish populations under natural environmental conditions.

3 Ecotoxicology

Recently, the toxicity of several PFFAs has been intensively studied, although most work has been limited to either PFOS or PFOA (Hekster et al. 2003). Among the PFFAs, PFOS is the most commonly found perfluorinated compound in environmental samples; this compound is particularly prevalent in the tissues of aquatic organisms (Giesy and Kannan 2001). The finding of such residues, in recent years, has resulted in primary efforts to investigate the toxicity of PFOS to aquatic organisms. From laboratory toxicity studies, the PFOS is known to be moderately acute and slightly chronically toxic to aquatic organisms, in general. In this chapter, the acute and chronic toxicity of PFOS to aquatic organisms, both for freshwater and marine species, is reviewed.

The use of PFOS-based products, or those compounds that can degrade to PFOS, was discontinued in 2000. This was done, in part, because it was possible to substitute the less accumulative and less toxic PFFA, perfluorobutanesulfonate (PFBS). Although PFBS is a widely used replacement for PFFA in many products, and we do review available information, there is considerably less toxicology information on it.

3.1 Acute Toxicity of PFOS to Aquatic Organisms

3.1.1 Aquatic Macrophytes

Data on the acute toxicity of PFOS to aquatic plants are somewhat limited (Table 5). The acute toxicity of PFOS to duckweed (*Lemna gibba*) has been reported; the number of fronds or biomass produced during the 7-d exposure served as an index to relative toxicity. There were two primary conclusions: First, the 7-d IC_{50} was found to be 108 mg PFOS/L, with a 95% confidence interval of 46–144 mg PFOS/L, and a no observable effect concentration

Table 5 Acute toxicity of PFOS to aquatic organisms (95% confidence intervals in parentheses)

Trophic level	Test organism/ species	Test duration	End point	NOEC (mg/L)	LOEC (mg/L)	$EC_{50}/LC_{50}/IC_{50}$ (mg/L)	Reference
Freshwater							
Macroalgae	*Lemna gibba*	7 d	Frond number	15		108 (46–144)	Desjardins et al. (2001c)
		7 d	Frond number	29.2		59.1 (51.5–60.3)	Desjardins et al. (2001c)
		7 d	Biomass	6.6		31.1 (22.2–36.1)	Boudreau et al. (2003a)
Invertebrate	*Daphnia magna*	48 hr	Survival	33.1 (32.8–34.1)		130 (112–136)	Boudreau et al. (2003a)
		48 hr	Immobility	0.8 (0.6–1.3)		67.2 (31.3–88.5)	Boudreau et al. (2003a)
		48 hr	Survival/immobility	32		61 (33–91)	Drottar and Krueger (2000b)
		48 hr	Survival			58 (46–72)	Robertson (1986)
		48 hr	Survival			67 (48–92)	Robertson (1986)
		48 hr	2nd-generation survival	12			Drottar and Krueger (2000f)
	Daphnia pulicaria	48 hr	Survival	46.9 (33.1–65.3)		169 (136–213)	Boudreau et al. (2003a)
		48 hr	Immobility	13.6 (2.2–33.1)		134 (103–175)	Boudreau et al. (2003a)
	Unio complanatus	96 hr	Survival	20		59 (51–68)	Drottar and Krueger (2000c)
Amphibians	*Xenopus laevis*	96 hr	Growth	4.82	7.97	15.6	Palmer and Krueger (2001)
Fish	*Pimephales promelas*	96 hr	Survival	3.2	5.4	9.1 (7.7–11)	Drottar and Krueger (2000h)

Table 5 (continued)

Trophic level	Test organism/species	Test duration	End point	NOEC (mg/L)	LOEC (mg/L)	$EC_{50}/LC_{50}/IC_{50}$ (mg/L)	Reference
	Oncorhynchus mykiss	96 hr	Survival			7.8 (6.2–9.8)	Robertson (1986)
		96 hr	Survival			9.9 (7.5–13.4)	Robertson (1986)
		96 hr	Survival	6.3	13.0	22 (18–27)	Palmer et al. (2002a)
Marine							
Invertebrate	*Artemia salina*	48 hr	Survival			9.4 (7.4–12.1)	Robertson (1986)
		48 hr	Survival			9.4 (7.3–12.2)	Robertson (1986)
		48 hr	Survival			8.9 (6.7–11.9)	Robertson (1986)
	Mysidopsis bahia	96 hr	Survival	1.1		3.6 (3.0–4.6)	Drottar and Krueger (2000d)
		96 hr	Second-generation survival	0.53			Drottar and Krueger (2000g)
	Crassostrea virginica	96 hr	Shell growth	1.8		>3.0	Drottar and Krueger (2000)e
Fish	*Oncorhynchus mykiss*	96 hr	Survival			13.7 (10.7–17.7)	Robertson (1986)
		96 hr	Survival			13.7 (10.7–17.8)	Robertson (1986)
	Cyprinodon variegatus	96 hr	Survival	<15		>15	Palmer et al. (2002b)

(NOEC) of 15 mg PFOS/L, based on frond number (Desjardins et al. 2001c). The sub-lethal effects noted in *L. gibba,* exposed to concentrations $\geq$31.9 mg PFOS/L, included root destruction and/or cupping of the plant (fronds) downward (convex) on the water surface. There was a concentration-dependent increase in dead, chlorotic, and necrotic fronds at greater PFOS concentrations (147 and 230 mg PFOS/L). A recovery period was not evaluated in this study. Second, *L. gibba* exposed to PFOS showed a 7-d IC_{50} of 59 mg PFOS/L (52–60 mg PFOS/L) based on the frond number and a 7-d IC_{50} of 31 mg PFOS/L (22–36 mg PFOS/L) based on the biomass, wt/wt (Boudreau et al. 2003a). The values, based on frond number and biomass were 29 and 6.6 mg PFOS/L, respectively. At the greatest concentration tested (160 mg PFOS/L), the plant fronds exhibited both high percentages of chlorosis and necrosis.

3.1.2 Invertebrates

Several studies on the acute toxicity of PFOS have been conducted with the cladoceran *Daphnia magna* (Table 5). *D. magna* is known to be a representative species among the aquatic invertebrates that are commonly used in standardized toxicity testing. In these acute toxicity studies, cladocerans were exposed to various concentrations of PFOS for 48 hr, and survival (mortality) and immobility were used as end points to calculate LC_{50} or EC_{50} values. Several earlier studies had reported that the LC_{50} for *D. magna* was 58–67 mg PFOS/L (Robertson 1986; Drottar and Krueger 2000b; Boudreau et al. 2003a). However, water concentrations of PFOS were not verified in these studies. Later in 2000, a similar finding was observed in a separate acute toxicity test with *D. magna*, where the 48-hr LC_{50} was reported to be 61 mg PFOS/L with a 95% confidence interval of 33–91 mg PFOS/L (Drottar and Krueger 2000b). The NOEC, based on survival/immobility, was 32 mg/L in that study.

Recently, additional acute toxicity tests with *Daphnia* species have been performed following ASTM guidelines (Boudreau et al. 2003a) (Table 5). In these studies, the 48-hr LC_{50} for *D. magna* was determined to be 130 mg PFOS/L, and the 48-hr LC_{50} for *D. pulicaria* was determined to be 169 mg PFOS/L. Based on immobility of the cladocerans, the 48-hr EC_{50} values for *D. magna* and *D. pulicaria* were determined to be 67.2 and 134 mg PFOS/L, respectively. NOEC values for *D. magna* (0.8 mg PFOS/L) and *D. pulicaria* (13.6 mg PFOS/L) significantly differed from each other. The differences between studies in reported LC_{50} and NOEC values for PFOS-exposed *Daphnia* species could result from uncertainty in differentiating between the immobility and the lethality end point. *D. magna* appeared to be more sensitive than *D. pulicaria* where the end point was 48-hr immobility (Boudreau et al. 2003a).

In another acute toxicity test with the freshwater mussel (*Unio complanatus*), the mussels were exposed to various concentrations of PFOS for 96 hr (Table 5). The 96-hr LC_{50} was determined to be 59 mg PFOS/L (51–68 mg PFOS/L), whereas the 96-hr NOEC, based on mortality, was 20 mg PFOS/L (Drottar and Krueger 2000c). Mussel tissues were analyzed for PFOS

content in this study. Chemical analysis of tissue showed that there was no mortality associated with 96-hr PFOS exposure of <7.3 mg/kg, wt/wt. In contrast, 90% mortality was observed in mussels containing >88 mg PFOS/kg, wt/wt after 96 hr of exposure.

In addition to freshwater invertebrate toxicity testing, PFOS toxicity to marine species has also been evaluated (Table 5). In a series of acute toxicity tests with brine shrimp (*Artemia salina*), the average ($n = 3$) 48-hr LC_{50} was 9.2 $\pm$ 0.29 mg PFOS/L (Robertson 1986). In an acute toxicity test with the saltwater mysid (*Mysidopsis bahia*), the 96-hr LC_{50} was 3.6 mg PFOS/L, and the NOEC was determined to be 1.1 mg PFOS/L, based on mortality (Drottar and Krueger 2000d). The effect of PFOS exposure on a benthic marine invertebrate has also been reported. Shell deposition in the eastern oyster (*Crassostrea virginica*) was examined in this study; shell growth was inhibited at a concentration of 1.8 mg PFOS/L, by 20% compared to controls (Drottar and Krueger 2000e). However, an EC_{50} could not be calculated in this study because growth was only inhibited by 28% at the greatest PFOS concentration of 3.0 mg/L tested. In summary, the acute invertebrate toxicity data indicated that, in short-term exposures, marine invertebrates are more sensitive to PFOS exposure than are freshwater ones.

3.1.3 Amphibians

The developmental effects of PFOS on the African-clawed frog (*Xenopus laevis*) have been investigated by the Frog Embryo Teratogenesis Assay-Xenopus (FETAX) (Palmer and Krueger 2001). In this assay, frog embryos and tadpoles were exposed to various concentrations of PFOS (0.0–24 mg PFOS/L) for 96 hr, and the end points of survival, growth, and developmental anomalies were examined during early stages of development. Significant mortality occurred at concentrations >14.4 mg PFOS/L and the 96-hr LC_{50} was found to be 14–18 mg PFOS/L, for the three replicate assays. There was a correlation between PFOS exposure and malformations in each of the three assays, and the most commonly observed malformations were improper gut coiling, edema, as well as notochord and facial abnormalities. The 96-hr EC_{50} for malformations was 12–18 mg PFOS/L. Finally, tadpole growth was affected in the second and third assays, and the minimum concentrations inhibiting growth were determined to be 8.0 and 8.3 mg PFOS/L. The NOEC for growth was determined to be 5.2 mg PFOS/L.

3.1.4 Fish

Several acute toxicity studies with PFOS have been conducted on fish including fathead minnows (*Pimephales promelas*), sheepshead minnows (*Cyprinodon variegatus*), bluegill sunfish (*Lepomis macrochirus*), and freshwater and marine rainbow trout (*Oncorhynchus mykiss*) (Table 5). Of the freshwater fish exposures, the fathead minnow was the most sensitive species with a 96-hr LC_{50} of

9.1 mg PFOS/L and an NOEC of 3.2 mg PFOS/L. After 96 hr of exposure, the sub-lethal effect of erratic swimming was noted in fathead minnows exposed to concentrations >5.6 mg PFOS/L (Drottar and Krueger 2000 hr).

Two acute toxicity tests with PFOS have been performed with rainbow trout in freshwater (Robertson 1986; Palmer et al. 2002a). Although the 96-hr LC_{50} values for PFOS in rainbow trout differed more than two-fold between these two studies, the LC_{50} of 22 mg PFOS/L, as reported in the Palmer et al. (2002a) study, is more reliable than that reported in Robertson (1986), because the LC_{50} value in the Palmer et al. (2002a) study was calculated with measured PFOS concentrations rather than being based on nominal concentrations.

The sheepshead minnow, a brackish-marine species, has also been tested for PFOS acute toxicity, but was exposed to only one concentration of PFOS, 15 mg PFOS/L. This was the greatest concentration attainable in saltwater and required the addition of methanol (0.05%). No mortality was observed at this concentration after 96 hr of exposure, thus the 96-hr LC_{50} was reported as >15 mg PFOS/L, and the NOEC for sub-lethal effects was reported to be <15 mg PFOS/L (Palmer et. al 2002b). In another study, freshwater rainbow trout were acclimated over 5 d to a final salinity of 30% and were exposed to PFOS for 96 hr (Robertson 1986). For rainbow trout exposed to PFOS in saltwater, the 96-hr LC_{50} was calculated as 14 mg PFOS/L, and no sub-lethal effects were observed among rainbow trout at any PFOS concentration tested in this study. It should be noted that PFOS concentrations were not measured in this study and some of the nominal exposure concentrations were greater than the solubility of PFOS in saltwater.

3.2 *Chronic Toxicity of PFOS to Aquatic Organisms*

3.2.1 Microorganisms

The potential effects of PFOS on microorganisms in activated sludge have been determined by exposing microbes from a municipal wastewater treatment plant to various concentrations of PFOS (0.9–870 mg PFOS/L) (Schafer and Flaggs 2000). After 3 hr of exposure, there was a 39% inhibition of the respiration rate, compared to controls, at the greatest concentration. However, the test concentration in this study exceeded the water solubility for PFOS, and as a result, based on known environmental concentrations PFOS would not be expected to cause any effects to microorganism communities (Table 6).

3.2.2 Microalgae

Many studies have been conducted to determine the toxicity of PFOS to aquatic microalgal species including phytoplankton and diatoms (Table 6). Since the life cycle of most of these species is quite short (ranging from hr to d), these studies represent the measurement of chronic effects on multiple generations,

Table 6 Chronic toxicity of PFOS to aquatic organisms (95% confidence intervals in parentheses)

Trophic level	Test organism/species	Test duration	End point	NOEC (mg/L)	LOEC (mg/L)	$EC_{50}/LC_{50}/IC_{50}$ (mg/L)	Reference
Freshwater							
Microorganisms	Microorganism community	96 hr	Respiratory inhibition			>870	Schaefer and Flaggs (2000)
Microalgae	*Selenastrum capricornutum*	96 hr	Growth (cell density)	42		68 (63–70)	Drottar and Krueger (2000a)
		96 hr	Inhibition of growth rate	42		121 (110–133)	Drottar and Krueger (2000a)
		96 hr	Growth (cell density)	5.3 (4.6–6.8)		48.2 (45.2–51.1)	Boudreau et al. (2003)
		96 hr	Growth (chlorophyll a)	16.6 (8.5–28.1)		59.2 (50.9–67.4)	Boudreau et al. (2003)
	Navicula pelliculosa	96 hr	Growth (cell density)	150		263 (217–299)	Sutherland and Krueger (2001)
		96 hr	Inhibition of growth rate	206		305 (295–316)	Sutherland and Krueger (2001)
	Chlorella vulgaris	96 hr	Growth (cell density)	8.2 (6.4–13.0)		81.6 (69.6–98.6)	Boudreau et al. (2003)
	Zooplankton community	35 d	Community structure	3.0			Boudreau et al. (2003b)
Macroalgae	*Myriophyllum spicatum*	42 d	Biomass (dwt)	11.4		12.5 (6–18.9)	Hanson et al. (2005)
		42 d	Root length (cm)	11.4		16.7 (10.8–22.5)	Hanson et al. (2005)
	Myriophyllum sibiricum	42 d	Biomass (dw)	2.9		3.4 (1.6–5.3)	Hanson et al. (2005)
		42 d	Root length (cm)	0.3		2.4 (0.5–4.2)	Hanson et al. (2005)
Invertebrate	*Daphnia magna*	21 d	Adult survival	5.3 (2.5–9.2)		42.9 (31.7–56.4)	Boudreau et al. (2003a)

Table 6 (continued)

Trophic level	Test organism/ species	Test duration	End point	NOEC (mg/L)	LOEC (mg/L)	$EC_{50}/LC_{50}/IC_{50}$ (mg/L)	Reference
	Chironomus tentans	10 d	Survival	0.05		>0.15	MacDonald et al. (2004)
		10 d	Growth (chlorophyll a)	0.05		0.087	MacDonald et al. (2004)
		20 d	Survival	0.0		0.092	MacDonald et al. (2004)
		20 d	Growth (chlorophyll a)	0.0		0.094	MacDonald et al. (2004)
Amphibians	*Rana pipiens*	16 wk	Partial life cycle	0.3	3	6.21 (5.12–7.52)	Ankley et al. (2004)
Fish	*Pimephales promelas*	28 d	Microcosm	0.3	3.0	7.2 (5.2–9.2)	Oakes et al. (2005)
		47 d	Early life stage	0.29	0.58		Drottar and Krueger (2000i)
Marine							
Microorganisms	*Anabaena flos-aquae*	96 hr	Growth (cell density)	93.8		131 (106–142)	Desjardins et al. (2001a)
		96 hr	Inhibition of growth rate	93.8		176 (169–181)	Desjardins et al. (2001a)
Microalgae	*Skeletonema costatum*	96 hr	Growth (cell density)	>3.2		>3.2	Desjardins et al. (2001b)
Invertebrate	*Mysidopsis bahia*	35 d	Growth, no. of young produced	0.24			Drottar and Krueger (2000g)

even when the exposure period of these tests are short (72–96 hr). The toxicological end points that have been evaluated in these studies include growth (measured in terms of cell density or chlorophyll a content) and/or area under the growth curve over the test duration. Reported 96-hr EC_{50} values for freshwater microalgae (growth end point as measured by cell density) ranged from 48 to 263 mg PFOS/L. The 96-hr NOEC values for biomass ranged from 5.3 to 150 mg PFOS/L. Using biomass as the end point, the most sensitive species was *Selenastrum capricornutum* (NOEC = 5.3 mg PFOS/L), whereas the diatom *Navicula pelliculosa* was the least sensitive species (NOEC = 150 mg PFOS/L) (Boudreau et al. 2003a; Sutherland and Krueger 2001). When growth rate was evaluated as the test end point, 96-hr EC_{50} values ranged from 121 to 305 mg PFOS/L, and NOEC values ranged from 42 to 206 mg PFOS/L. Again, *S. capricornutum* was the most sensitive species, and *N. pelliculosa* was the least sensitive, using growth rate as the end point. The effects of PFOS on these microalgal species were algistatic, since growth resumed when microalgae from the greatest PFOS treatments were placed in fresh growth media at the end of the exposure period. Furthermore, signs of aggregation or adherence of the cells to the flask were not observed, nor were there any noticeable changes in cell morphology at the end of the studies for any concentration evaluated.

Although concentration–response relationships for growth have been developed for freshwater algae, the marine diatom, *Skeletonema costatum*, was not affected by exposure to PFOS. In this study, a 96-hr EC_{50} could not be determined because at the greatest dissolved concentration attained under test conditions (3.2 mg PFOS/L), growth was not significantly inhibited. As a result, an analysis of the sensitivity between freshwater and marine algae could not be conducted.

In addition to evaluating PFOS toxicity in individual species of microalgae, the effects of PFOS has also been evaluated at the community level. In a controlled freshwater microcosm study, 0, 0.3, 3.0, 10, or 30 mg PFOS/L were administered to a zooplankton community for a total of 35 d. Results indicated that the zooplankton community structure was significantly altered by exposure to 10 or 30 mg PFOS/L. By day 35, the total number of zooplankton species decreased by an average of 45.1 and 74.3% in the 10 and 30 mg PFOS/L treatments, respectively. Thus, the NOEC based on changes in zooplankton community structure was determined to be 3.0 mg PFOS/L (Boudreau et al. 2003b).

3.2.3 Aquatic Macrophytes

The chronic toxicity of PFOS was evaluated for two aquatic macrophytes, *Myriophyllum sibiricum* and *M. spicatum,* in a microcosm study (Hanson et al. 2005; Table 6). Both species were exposed to PFOS concentrations ranging from 0.03 to 30 mg PFOS/L for 42 d; measured test end points were plant length, root number and length, node number, and biomass, expressed as dry weight (dwt). Toxicity was observed at PFOS concentrations of >3 mg PFOS/L

for *M. spicatum*, with the 42-d EC_{50} exceeding 12 mg PFOS/L. The NOEC was found to be consistently >11 mg PFOS/L. Toxicity for *M. sibiricum* was observed at PFOS concentrations of >0.1 mg PFOS/L, and the 42-d EC_{50} value was greater than 1.6 mg PFOS/L. The NOEC values of 2.9 and 0.3 mg PFOS/L were based on biomass and root length, respectively. In general, *M. sibiricum* was more sensitive than *M. spicatum*, regardless of the test end point.

3.2.4 Invertebrates

Life-cycle tests with *D. magna* have been conducted to evaluate the chronic toxicity of PFOS to freshwater aquatic invertebrates (Table 6). In one study, the 21-d LC_{50} was determined to be 43 mg PFOS/L, and the NOEC, based on adult survival, was estimated to be 5.3 mg PFOS/L (Boudreau et al. 2003a). In a separate life-cycle toxicity test of *D. magna*, the LC_{50} and NOEC, based on adult survival, were reported as 12–13 mg PFOS/L, respectively (Drottar and Krueger 2000f). In another life-cycle toxicity test with the saltwater mysid, the 35-d NOEC, based on growth and number of young produced, was found to be 0.24 mg PFOS/L (Drottar and Krueger 2000 g). In the course of the life-cycle tests with both *D. magna* and the saltwater mysid, the young produced were briefly exposed to the same concentrations to which the respective first-generation adults were exposed. Survival was monitored for 48 hr (*D. magna*) or 96 hr (*M. bahia*). After 48 hr of exposure, the results of a daphnid second-generation acute exposure produced an NOEC of 12 mg PFOS/L. The second-generation mysid shrimp were exposed to negative control, 0.055, 0.12, 0.24, or 0.53 mg PFOS/L for 96 hr. Survival was >95% for all second-generation mysids exposed to these test concentrations. The mysid second-generation acute exposure NOEC was 0.53 mg PFOS/L. These results indicated that the saltwater mysid may be more sensitive to PFOS than is freshwater *D. magna*. However, additional studies would need to be conducted to better evaluate the toxicity of PFOS to second-generation organisms. Specifically, a greater range of PFOS concentrations is needed to further define the NOAEC (no observable adverse effect concentration) for second-generation mysid shrimp.

3.2.5 Amphibians

The survival and development of northern leopard frogs (*Rana pipiens*), from early embryogenesis through complete metamorphosis, has been investigated in a water exposure study with PFOS (Ankley et al. 2004; Table 6). In tadpoles exposed to 0.03, 0.1, 0.3, 1.0, 3.0, or 10 mg PFOS/L, mortality was observed within 2 wk of study initiation in the 10 mg PFOS/L treatment; >90% mortality was observed by week 4. Tadpole survival was not affected in any other treatment group. The mean LC_{50} at week 5 was 6.2 mg PFOS/L (5.1–7.5 mg PFOS/L). No statistically significant effects were observed for tadpoles exposed to <1.0 mg PFOS/L. However, there was a slight increase in time to metamorphosis and a decrease in total length of tadpoles at levels >3.0 mg PFOS/L. In

addition, there was a slight increase in the incidence of thyroid follicle cell atrophy that was subtle and difficult to quantify. The PFOS-related chronic effects in leopard frogs occurred within a concentration range that has been shown to cause effects in fish and invertebrates.

3.2.6 Fish

Chronic toxicity data, from an early-life stage toxicity test, are available for fathead minnows (*P. promelas*; Drottar and Krueger 2000i; Table 6). In this study, eggs and larvae were exposed to PFOS in a flow-through system for 47 d. Measured water concentrations of PFOS in the various treatments were <LOQ (limit of quantification), 0.15, 0.30, 0.60, 1.2, 2.4, or 4.6 mg PFOS/L. Fish exposed to PFOS at concentrations <0.30 mg PFOS/L showed no significant reduction in time to hatch, hatching success, and survival or growth. The PFOS did not affect percent hatch or growth of fry at any of the concentrations tested. Survival was the most sensitive end point in this study. Compared to controls, percent survival was significantly reduced among fathead minnows exposed to concentrations >0.60 mg PFOS/L. Thus, the NOEC and LOEC (lowest observable effect concentration) for fathead minnows were determined to be 0.30 and 0.60 mg PFOS/L, respectively (Drottar and Krueger 2000i).

3.3 Toxicity of PFBS

3.3.1 Microorganisms

Effects of PFBS on activated sludge microorganisms have been evaluated by exposing microbes to concentrations of 1–1,000 mg PFBS/L for up to 3 hr (Wildlife International 2001a). The maximal inhibitory effects on respiration was observed at 300 mg PFBS/L, but there was no clear dose response because effects at 1,000 mg PFBS/L were less than that observed at 300 mg PFBS/L. As a result, PFBS was not considered to be inhibitory to sewage microorganisms and had a 3-hr EC_{50} of >1,000 mg PFBS/L.

3.3.2 Aquatic Plants

To date, only one study has been conducted with an aquatic plant, the freshwater alga *S. capricornutum* (Wildlife International 2001e). In this study, PFBS was found to be practically non-toxic with a 96-hr EC_{50} of 2,347 mg PFBS/L, and a NOEC of 1,077 mg PFBS/L, based on reductions in biomass. Using growth of exposed cells during the recovery phase of the study, as the end point, PFBS was found to be algistatic.

3.3.3 Aquatic Organisms

To date, the effects of PFBS have been investigated in only a few freshwater aquatic organisms including the bluegill (*L. macrochirus*), the fathead minnow (*P. promelas*), and the water flea (*D. magna*; Table 7). For the bluegill, the 96-hr LC_{50} was 6,452 mg PFBS/L, and the NOEC was 6,452 mg PFBS/L (Wildlife International 2001a). For fathead minnow, the 96-hr LC_{50} was 1,938 mg PFBS/L, and the NOEC was 888 mg PFBS/L (Wildlife International 2001b). For *D. magna*, the 48-hr LC_{50} was 2,183 mg PFBS/L, and the NOEC was 886 mg PFBS/L. One chronic toxicity test has been conducted with a freshwater organism, *D. magna*. In this study, the 21-d NOEC for reproductive end points was 502 mg PFBS/L, and the LOEC was 995 mg PFBS/L. This resulted in a chronic value of 707 mg PFBS/L. These data indicate that PFBS is not very toxic to freshwater organisms, with effect levels only being observed at a concentration greater than 700 mg PFBS/L.

3.4 Water Quality Criteria for the Protection of Aquatic Life

Multiple approaches are available to derive water quality values; the specific approach will depend upon the regulatory agency involved in the calculation of these values and their environmental policies (US EPA 1985; RIVM 2001; CCME 1999). In the United States, three types of water quality can be derived including numeric, narrative, and operational (US EPA 1985). However, for the purposes of this chapter, only numeric criteria were considered. Numeric criteria are scientifically based numbers that are intended to protect aquatic life from adverse effects of contaminants without consideration of societal values, economics, or other non-scientific considerations.

To derive numeric water quality values for those PFCs that have sufficient and appropriate toxicity data, we have relied on the US EPA Great Lakes Initiative (GLI; US EPA 1995). The GLI provides specific procedures and methodologies for utilizing toxicity data to derive water quality values that are protective of aquatic organisms. The GLI presents a two-tiered methodology (Tier I and Tier II), in which the Tier I procedures are essentially the same as the procedures for deriving national water quality criteria (NWQC; US EPA 1985). The Tier II aquatic life methodology is used to derive values when limited toxicity data are available. Because greater uncertainties are associated with limited toxicity data, the Tier II methodology generally produces more stringent values than do the Tier I methodology. EPA has indicated that Tier II values are not intended to be adopted as state water quality standards (US EPA 1995). The guidance provided by the GLI is intended to provide both acute and chronic criteria for the protection of fish, invertebrates, and other aquatic organisms. The final acute value (FAV) is a semi-probabilistic approach that requires data for a range of specified taxa and produces the concentration deemed to be protective of approximately 95% of tested genera. The FAV is

Table 7 Summary of acute and chronic toxicity values for aquatic organisms and plants exposed to perfluorobutanesulfonate (PFBS)

Organism	Genus/species	Test duration	Media	NOEC (mg/L)	LOEC (mg/L)	LC_{50} (mg/L)	Reference
Acute							
Water flea	*Daphnia magna*	48 hr	FW	886	1,707	2,183 (1,707–3,767)	WLI[c] (2001b)
Fathead minnow	*Pimephales promelas*	96 hr	FW	888	1,655	1,938 (888–3,341)	WLI (2001c)
Bluegill	*Lepomis macrochirus*	96 hr	FW	2,715	5,252	6,452 (5,252–9,433)	WLI (2001d)
Algae[a]	*Selenastrum capricornutum*	96 hr	FW	1,077	2,216	2,347 (2,018–2,707)	WLI (2001e)
Mysid	*Mysidopsis bahia*	96 hr	SW	127	269	372 (314–440)	WLI (2001f)
Chronic							
Water flea[b]	*Daphnia magna*	21 d	FW	502	995		WLI (2001 g)

[a]Reported data are based on biomass measurements
[b]Reported data based on reproduction and length measurements
[c]WLI = Wildlife International
FW = Fresh Water
SW = Salt Water

used to establish an acute criterion or criteria maximum concentration (CMC), which is equivalent to one-half the FAV. The chronic criterion or criteria continuous concentration (CCC) represents a concentration of a chemical such that 95% of the genera tested have greater chronic values. The purpose and use of these numerical criteria are not to provide concentrations of a chemical that will be protective of all aquatic species in a specific ecosystem, but to provide reasonable protection to ecologically and commercially important species under most circumstances such that overprotection or under-protection of aquatic species is avoided (US EPA 1985).

The Tier I procedures in the GLI utilize a semi-probabilistic method that requires, at a minimum, results from acceptable acute toxicity tests, with at least one species of freshwater animal in at least eight different families. These families should include the following:

1. the family *Salmonidae* in the class *Osteichthyes*;
2. a second family in the class *Osteichthyes*, preferably a cyprinid;
3. a third family in phylum *Chordata*;
4. a planktonic crustacean (e.g., cladoceran, copepod);
5. a benthic crustacean (e.g., ostracod, isopod, amphipod);
6. an aquatic insect;
7. a family in a phylum other than *Arthropoda* or *Chordata* (e.g., *Annelida*, *Mollusca*); and
8. a family in any order of insect or phylum not already represented.

The guidance for a Tier I assessment also requires data from at least one toxicity test with an alga or a vascular plant and at least one acceptable BCF. In addition, chronic toxicity data are needed from at least three different aquatic animals and should include a planktonic crustacean and a fish species.

When sufficient toxicity data are not available for calculating a national water quality criterion pursuant to EPA Tier I methodology, the GLI guidance provides for calculation of Tier II values. The derivation of Tier II criteria is based on the application of an assessment factor that is used to offset the absence of sufficient toxicity data. However, because of the greater uncertainties associated with limited toxicity data, the Tier II methodology generally produces more stringent values than does the Tier I methodology. Furthermore, EPA has indicated that Tier II values are not intended to be adopted as state water quality standards (US EPA 1995). In both Tier I and Tier II methodologies, water quality criteria that protect against chronic effects can be calculated using available acute data, and an acute–chronic ratio, when sufficient chronic data are not available.

A critical step in deriving either Tier I or II water quality criteria is the evaluation of data usability based on criteria outlined by US EPA (1985) guidance. In this chapter, data were screened to determine usability based on the following: (1) Only data from tests with freshwater organisms were used; (2) Only data on organisms resident in North America were used; species that do not have reproducing wild populations in North America were rejected; (3) Data

with pre-exposed organisms were not used; and (4) Data lacking controls or control treatments, or with unacceptable control results, were not used. Finally, for those studies that meet the requirements listed above, toxicity data were further screened for certain experimental conditions (i.e., water quality considerations, life stage, and measured end points). The water quality criteria values for selected PFCs have been presented and are summarized in Fig. 2.

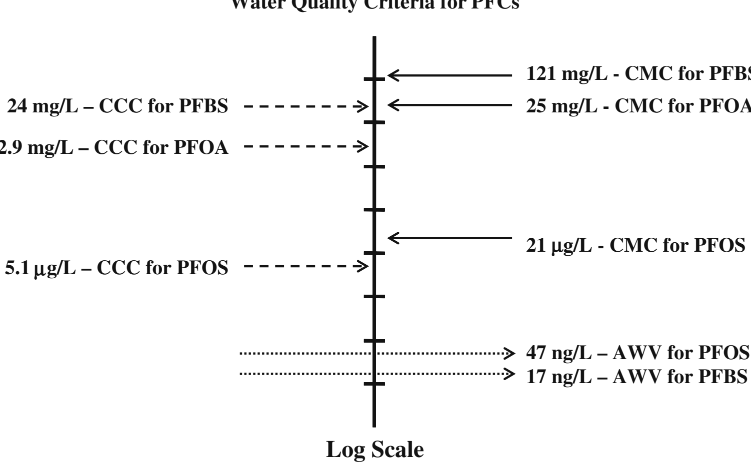


Fig. 2 Comparison of water quality criteria values for the protection of aquatic organisms (CMC: criteria maximum concentration; CCC: criteria continuous concentration) and wildlife (AWV: avian wildlife value) for PFCs, including PFOS, PFBS, and PFOA

3.4.1 PFOS

Collectively, the data on acute toxicity of PFOS meet the GLI species requirements for using Tier I methodology (Table 5). The genus mean acute values (GMAV) for aquatic species are used to calculate a FAV. The GLI Tier I approach for calculating a FAV utilizes a subset of the data nearest the fifth centile of a statistical population of acute toxicity values, in which the data are fitted to a log-triangular distribution, wherein only the four least acute toxicity values nearest the fifth centile are used (US EPA 1995). The specific steps used to calculate the FAV include (1) ranking the GMAV from the greatest to least value and (2) assigning each GMAV a cumulative probability calculated as $P_R = R/(N+1)$, where R is the rank and N is the number of GMAVs in the data set (Table 8). By using the four GMAVs, which have the cumulative probabilities closest to 0.005, one can calculate the FAV as follows (Eqs. 1–4):

$$S^2 = \frac{\sum((\ln \mathrm{GMAV})^2) - ((\sum(\ln \mathrm{GMAV}))^2/4)}{\sum(P) - ((\sum(\sqrt{P}))^2/4)} \quad (1)$$

Table 8 Summary of genus mean acute toxicity values (GMAV) for aquatic organisms exposed to PFOS[a]

Organism	Genus/species	SMAV (mg/L)	GMAV (mg/L)	Rank	Cumulative probability[b]
Water flea	*Daphnia magna*	61	71	10	0.9091
	Daphnia pulicaria	134			
Mussel	*Unio complanatus*	57	57	9	0.8182
Spring peeper	*Pseudacris crucifer*	38	38	8	0.7273
Planarian	*Dugesia japonica*	17	17	7	0.6364
Amphipod	*Hyalella azteca*	15	15	6	0.5455
Rainbow trout	*Oncorhynchus mykiss*	14	14	5	0.4545
Leopard frog	*Rana pipiens*	6.2	6.2	4	0.3636
Oligocheate	*Lumbriculus variegatus*	5.6	5.6	3	0.2727
Fathead minnow	*Pimephales promelas*	2.5	2.5	2	0.1818
Midge	*Chironomus tentans*	0.089	0.089	1	0.0909

[a]Species mean acute values (SMAV) and genus mean acute values (GMAV) calculated as the geometric mean of LC_{50} values from acceptable studies
[b] Cumulative probability calculated as $P = (\text{Rank}/N + 1)$ where N is the number of GMAV

$$L = \sum(\ln \text{GMAV}) - S\left(\sum(\sqrt{P})\right)/4 \quad (2)$$

$$A = S(\sqrt{0.005}) + L \quad (3)$$

$$\text{FAV} = e^{A} \quad (4)$$

Using the GLI methodology, the FAV for the effects of PFOS on aquatic organisms was calculated to be 42 μg PFOS/L (Table 9). This value represents the 95% protection level for aquatic organisms and relies on currently available acute toxicity data. Because the GLI method puts greater emphasis on the four least LC_{50} values used, this criterion is skewed if one genus or species tested is more sensitive than the others. In fact, this is the case for PFOS, wherein there is a difference of approximately 40-fold between the most sensitive genus (*Chironomus*), and the next most sensitive genus (*Pimephales*). In addition, *Chironomus tentans* appear to be uniquely sensitive in that other small, non-predatory white midges, exposed to 30 mg PFOS/L for 10 d, were unaffected by PFOS, whereas at >300 μg PFOS/L all *C. tentans* died. As a result, inclusion of the *C. tentans* acute data in the derivation of the FAV probably results in a conservative water quality value that would be protective of most aquatic organisms.

Depending upon the availability of chronic toxicity data, a final chronic value (FCV) can be calculated in the same manner as is the FAV, or it can be

Table 9 Calculation of a freshwater final acute value (FAV) for PFOS[a]

Rank	GMAV (mg/L)	P	Sqrt (P)	Ln (GMAV)	(Ln GMAV)^2
4	6.2	0.3636	0.6030	1.825	3.3290
3	5.6	0.2727	0.5222	1.723	2.9679
2	2.5	0.1818	0.4264	0.916	0.8396
1	0.089	0.0909	0.3015	–2.414	5.8269
	Sum	0.9091	1.8532	2.0497	12.9634

$S^2 = 235.7512$
$S = 15.3542$
$L = -6.60101$
$A = -3.1667$
Final acute value (FAV) = 42 μg PFOS/L

[a]Only the four most sensitive genera were used in the calculation of the FAV, because the total number of acceptable toxicity results was less than 59

calculated by dividing the FAV by a final acute–chronic ratio (ACR). An ACR can be derived by dividing a species-specific chronic value from an acceptable chronic toxicity test by an LC_{50} from the same species. A chronic value is calculated as the geometric mean of the lower (NOEC) and upper (LOEC) limit from a chronic toxicity test. According to the GLI, the final acute–chronic ratios is calculated as the geometric mean of acute–chronic ratio from at least three different species, a fish, a daphnid, and one other sensitive species. For PFOS, acceptable chronic toxicity studies are available for two freshwater species, *D. magna* and *P. promelas* and one saltwater species, *M. bahia,* for which acute toxicity data are also available. Although saltwater species cannot be used in the derivation of freshwater water quality criteria, these data can be used to calculate an acute–chronic ratio. For *D. magna*, a species mean acute value (SMAV) from acceptable toxicity data was 61 mg PFOS/L, while a chronic value was calculated as 17 mg PFOS/L. This resulted in an ACR of 3.6. For the fathead minnow (*Pimephales promelas*), the SMAV was 8.1 mg PFOS/L, while the chronic value was calculated as 0.48 mg PFOS/L; this resulted in an ACR of 16.9. Finally, for *M. bahia* the SMAV was 3.5 mg PFOS/L, while the chronic value was 0.37 mg PFOS/L and resulted in an ACR of 9.5. The final ACR for PFOS, based on these three ACRs, was 8.3. The FCV was calculated by dividing the FAV (42 μg PFOS/L) by the ACR (8.3) and resulted in a FCV of 5.1×10^{-3} mg PFOS/L (or 5.1 μg PFOS/L).

GLI guidelines require the review of aquatic plant toxicity data, and calculation of a final plant value (FPV), if sufficient data are available. The FPV represents the least concentration from a toxicity test with an important aquatic plant species, in which the concentrations of test material have been measured; the end point monitored in the study is biologically important. For the derivation of a freshwater FPV for PFOS, a chronic study with milfoil, *Myriophyllum sp,* was selected to comply with data acceptability requirements outlined in the GLI. This study

fulfilled all necessary requirements for data acceptability (i.e., measured PFOS water concentrations, biological, and ecologically important end points) and had the least genus mean chronic value (GMAV). Thus, based on the results from the *Myriophyllum* toxicity test, the FPV was determined to be 2.3 mg PFOS/L.

Using the methods outlined in the GLI, a CMC was calculated for PFOS by dividing the FAV (42 μg PFOS/L) by 2, this resulted in a value of 21 μg PFOS/L. The CCC is determined as the lower value between the FCV (5.1 μg PFOS/L) and the FPV (2,300 μg PFOS/L), thus the CCC is 5.1 μg PFOS/L.

3.4.2 Critical Body Burden of PFOS in Fish

The critical body residue (CBR) hypothesis provides a framework for analyzing aquatic toxicity in terms of mode of action and tissue residue concentrations (McCarty and Mackay 1993; Di Toro et al. 2000). The key assumption of the hypothesis is that adverse effects are elicited when the molar concentration of a chemical in an organism's tissues exceeds a critical threshold. Under steady state conditions, the CBR can be expressed mathematically as the end point of the effect concentration (in water) determined in an aquatic test and the BCF:

$$\mathrm{CBR} = \mathrm{BE} \times \mathrm{BCF}$$

where CBR is the critical body residue (mmol/kg), BE is the biological effect level (LC_{50}, EC_{50}, or some chronic level), and BCF is the bioconcentration factor.

The BCF used in this type of analysis can be derived either experimentally or empirically through the use of QSARs. Implicit in this hypothesis is the assumption that a chemical is accumulated in tissues via a partitioning process, and it has reached a steady state within the test period. Thus, the CBR is a time-independent measure of effect for organisms exposed to the chemical. One limitation of this assumption is that, in many cases, organisms may not have achieved a steady state concentration such that using the BCF would overestimate the actual whole body concentration one would expect during a standard aquatic acute toxicity test. In addition, this model does not take into account accumulation of chemicals into target tissues that occurs in a manner different from that observed on a whole body basis (Barron et al. 2002). Thus, these factors may result in an overestimate of the CBR that would underestimate the risk an aquatic organism would be exposed to in a natural setting. For this analysis, kinetic parameters of accumulation have been used instead of the BCF to evaluate tissue concentrations associated with toxicity in bluegill.

To estimate a critical body residue level for PFOS in fish, we used data from a bluegill bioconcentration study in which significant mortality occurred at the greatest dose (Drottar et al. 2001). In this study, bluegill sunfish were exposed to 0.086 or 0.87 mg PFOS/L for up to 62 d, followed by a depuration period. However, at 0.87 mg PFOS/L, mortality was noted by day 12, with 100% mortality being observed by day 35. At this high dose, no fish survived to the

Table 10 Cumulative mortality and whole body PFOS concentrations in bluegill exposed to 1.0 mg/L in a bioconcentration study[a]

Time (d)	PFOS (μg/kg, wt/wt)	Number exposed	Cumulative mortality
0.2	1,577	55	0
1.0	2,519	55	0
3.0	33,703	55	0
7.0	81,690	55	0
14	158,743	55	16
21	177,969	55	35
28	241,799	55	52

[a] PFOS concentration values are means for fish sampled on the indicated dates. Concentrations are expressed on a wet weight basis

end of the uptake phase of the study. Mortality and whole body PFOS concentration data, collected during the study at the 0.87 mg PFOS/L exposure concentration, are given in Table 10. Probit analysis was used to estimate a critical body residue concentration; tissue PFOS concentration was used as the independent variable and mortality as the dependent variable. The use of probit analysis allowed for the calculation of point estimates along the dose–response curve. The 28-d LD_{50}, calculated from whole body concentrations, was 172 mg PFOS/kg, wt/wt. The 95% lower and upper confidence limits for the LD_{50} were 163 and 179 mg PFOS/kg, respectively. As an estimate of a no observable adverse effect level (NOAEL) for PFOS-induced mortality in bluegill, we extrapolated down to the LD_{01}. The LD_{01} was 109 mg PFOS/kg, wt/wt. The 95% lower and upper confidence limits for the LD_{01} were 87 and 123 mg PFOS/kg, wt/wt, respectively. From this statistical evaluation of the data, the tissue concentration that would not be expected to cause adverse effects in fish is 109 mg PFOS/kg. However, due to potential differences in species sensitivity, the lower 95% confidence limit of the LD_{01} was used as a conservative estimate of a NOAEL. Based on this analysis, tissue concentrations less than 87 mg PFOS/kg would not be expected to cause acute effects in fish. However, in this bluegill study no evaluation of other non-lethal end points, including development or reproduction, was made. In addition, there are not sufficient data to critically evaluate differences in accumulation, tissue distribution, or target organ toxicity across fish species. Therefore, it may be necessary to incorporate uncertainty factors in the estimated CBR to take into account interspecies differences.

3.4.3 PFBS

Because acute toxicity data are too limited to calculate a water quality criterion, a Tier II water quality criterion is derived as directed by GLI guidance. In this methodology, a secondary acute value (SAV) is calculated by dividing the least acute toxicity value (LC_{50}) by an application factor or secondary acute factor (SAF). The SAF is a factor used to compensate for the lack of sufficient acute toxicity data that is normally required for calculating Tier I water quality

criteria. The magnitude of the SAF corresponds to the number of satisfied minimum data requirements given in the Tier I methodology and can range from 4.3 up to 21.9 for chemicals that, for example, only meet 7 or 1 of the data requirements, respectively. For PFBS, the lowest acute toxicity value was for the fathead minnow (*P. promelas*) that had a 96-hr LC_{50} of 1,938 mg PFBS/L (Table 11). The SAF, based on the three acceptable acute toxicity data values that meet the Tier I requirements, is 8.0 as prescribed by GLI guidance. Thus, the SAV for PFBS was calculated as shown in Eqs. 5 and 6 below:

Table 11 Summary of genus mean acute values (GMAVs) and genus mean chronic values (GMCVs) for aquatic organisms exposed to PFBS[a]

Organism	Genus/species	Test duration	Media	GMAV (mg PFBS/L)
Acute				
Bluegill	*Lepomis macrochirus*	96 hr	FW	6,452
Water flea	*Daphnia magna*	48 hr	FW	2,183
Fathead minnow	*Pimephales promelas*	96 hr	FW	1,938
Chronic				
Water flea	*Daphnia magna*	21 d	FW	707

[a] Genus mean acute values were based on geometric means of acute toxicity values by genus, whereas genus mean chronic values were based on geometric means of NOAEC values from chronic studies
FW = Fresh Water

$$\text{secondary acute value (SAV)} = \frac{\text{lowest acute value}}{\text{secondary acute factor (SAF)}} \quad (5)$$

$$\text{SAV} = \frac{1938 \text{ mg/L}}{8.0} = 242 \text{ mg PFBS/L} \quad (6)$$

To calculate a secondary chronic value (SCV) the SAV is divided by a final acute–chronic ratio (FACR). However, to date, only one chronic toxicity study, on *D. magna,* could be used to calculate a species-specific ACR, which is needed in the derivation of a FACR. For this species, the SMAV was 1,938 mg PFBS/L, and the chronic value (CV) was 707 mg PFBS/L. The ACR, calculated from these data, was 3.1. However, to calculate a FACR, a minimum of three species-specific ACR values are needed, and as a result, default ACR values are used to replace the missing data as prescribed in the GLI Tier II methodology. The default ACR value of 18 is substituted for each of the two missing ACR values; this resulted in a FACR of 10. The SCV is then calculated by dividing the SAV by the FACR. The SCV for PFBS was calculated as follows in Eqs. 7 and 8:

$$\text{secondary chronic value (SCV)} = \frac{\text{secondary acute value (SAV)}}{\text{final acute to chronic ratio (FACR)}} \quad (7)$$

$$SCV = \frac{242 \text{ mg/L}}{10} = 24 \text{ mg PFBS/L} \quad (8)$$

Using Tier II methodology, the SCV for PFBS was determined to be 24 mg PFBS/L.

As required by the GLI guidance, a FPV needs to be determined to evaluate the potential hazard a chemical may pose to aquatic plant communities. This value can be based on 96-hr tests conducted with an alga, or a chronic test conducted with an aquatic vascular plant. To date, only a single toxicity study has been conducted with the green alga, *S. capricornutum*, on PFBS that meets the data requirements as outlined in the GLI guidance. In this test, the 96-hr EC_{50}, based on cell count, was 2,347 mg PFBS/L, and the NOEC and LOEC values were 1,077 and 2,216 mg PFBS/L, respectively. The chronic value from these data was 1,545 mg PFBS/L. Thus, the FPV for PFBS was determined to be 1,500 mg PFBS/L.

From methods outlined in the GLI, a CMC for PFBS was calculated by dividing the FAV by 2 and produced a value of 120 mg PFBS/L. The secondary continuous criterion (SCC) is determined as the lower value between the SCV (24 mg PFBS/L) and the FPV (1,500 mg PFBS/L); thus, the SCC for PFBS is 24 mg/L.

3.4.4 PFOA

A review of available acute toxicity data for PFOA with freshwater organisms indicates that there is insufficient data to calculate a Tier I water quality criterion, because only five of the data requirements were met. Consequently, a Tier II water quality criterion was derived as provided for in the GLI guidance. For PFOA, the least GMAV was for the water flea (*D. magna*) that had a 48-hr EC_{50} of 297 mg PFOA/L (Table 12). The SAF, based on five Tier I data requirements being met, was 6.1 as prescribed by GLI guidance. Thus, the SAV for PFOA was calculated as shown in Eq. 9:

$$SAV = \frac{297 \text{ mg/L}}{6.1} = 49 \text{ mg PFOA/L} \quad (9)$$

To calculate a SCV, the SAV was divided by a FACR. To date, only two acceptable chronic toxicity studies are available that can be used to calculate the species-specific ACR needed to derive a FACR. For *D. magna*, if a SMAV of 297 mg PFOA/L and a CV of 22 mg PFOA/L are used, the ACR was 10. For *O. mykiss*, the SMAV was 752 mg PFOA/L, and the chronic value was 40 mg PFOA/L. From these two values the ACR was determined to be 19. However, a minimum of three species-specific ACR values are needed to calculate a FACR and as a result, a default ACR value of 18 was used to replace the missing data,

Table 12 Summary of genus GMAVs and GMCVs for aquatic organisms exposed to perfluorooctanoate (PFOA)[a]

Test species	Genus/species	Test duration	Media	GMAV (mg PFOA/L)
Acute				
Midge	*Chironomus tentans*	96 hr	FW	1,090
Rainbow Trout	*Oncorhynchus mykiss*	96 hr	FW	752
Bluegill	*Lepomis macrochirus*	96 hr	FW	601
Fathead minnow	*Pimephales promelas*	96 hr	FW	511
Water flea	*Daphnia magna*	48 hr	FW	297
Chronic				
Rainbow trout	*Oncorhynchus mykiss*	85 d	FW	40[b]
Water flea	*Daphnia magna*	21 d	FW	21[b]

[a]Genus mean acute values were based on geometric means of acute toxicity values by genus
[b]Values represent GMCV and are based on geometric means of NOAEC values from chronic studies
FW = Fresh Water

as provided for in the GLI Tier II methodology. Thus, the FACR, calculated from these three ACR values, was 17. The SCV for PFOA was calculated as shown in Eq. 10:

$$\text{SCV} = \frac{49\ \text{mg/L}}{17} = 2.9\ \text{mg PFOA/L} \tag{10}$$

By using Tier II methodology, the SCV for PFOA was determined to be 2.9 mg PFOA/L.

Sufficient data were available to calculate a FPV for PFOA that would be protective of aquatic plant communities. To date, acceptable toxicity tests have been conducted with the algae (*S. capricornutum*), and with two milfoil species, *M. spicatum* and *M. sibiricum*. *Myriophyllum* was determined from these studies to be the most sensitive aquatic plant genus, with a 42-d EC_{50} of 34 mg PFOA/L, and a NOAEC of 23.9 mg PFOA/L, using reductions of biomass (dry wt) as the end point. Based on the NOAEC for *Myriophyllum* sp., the FPV for PFOA was determined to be 23.9 mg/L.

Using GLI methodology, a CMC for PFOA was calculated by dividing the FAV by 2, this produced a value of 25 mg PFOA/L. The SCC is determined as the lower value between the SCV (2.9 mg PFOA/L) and the FPV (23.9 mg PFOA/L), therefore, the SCC for PFOA is 2.9 mg/L.

3.5 Water Quality Criteria for the Protection of Wildlife

3.5.1 PFOS

Toxicity reference values (TRVs) have been derived from chronic effects on reproduction in which mallards or quail were chronically exposed via the diet (Newsted et al. 2007). The TRVs were based on quail because treatment-related reproductive effects were observed at 10 mg PFOS/kg, wt/wt feed; in contrast, toxicological and ecological effects were not noted in mallards at this dietary concentration. TRVs were derived from dietary exposure and tissue PFOS concentrations with the intention of protecting fish-eating water birds. These species were selected because they harbor some of the greatest liver and serum PFOS concentrations, when compared to lower trophic level avian species; thus, avian TRVs, protective of all avian species, were derived from the characteristics of trophic level IV fish-eating birds such as eagles and ospreys. Many of these bird species are sensitive to other classes of organic compounds and may provide an early warning for the presence and effects of contaminants within contaminated aquatic ecosystems (Ankley et al. 1993; Bowerman et al. 1998). In addition, by factoring in characteristics of predatory birds, such as weights, daily food consumptions, and species-specific transfer coefficients, contributions of PFOS from both aquatic and terrestrial exposure pathways can be incorporated into the derivation of avian TRVs (Giesy et al. 1994; Giesy and Kannan 1998).

3.6 Derivation of PFOS TRVs for a Level IV Avian Predator

TRVs for level IV birds were developed by using the uncertainty factor (UF) approach, as described in the US EPA GLI methodology (US EPA 1995). In this approach, three categorical uncertainties were delineated. These included the following: (1) uncertainty with LOAEL to NOAEL extrapolation (UF_L), (2) uncertainty related to duration of exposure (UF_S), and (3) uncertainty related to inter-taxon extrapolations (UF_A). In this approach, UFs for each category are assigned values between 1 and 10 that are based on available scientific findings and best professional judgment (Chapman et al. 1998). Using the data from the quail reproduction study, and the characteristics of a level IV avian predator, a final UF of 24 was assigned; this UF accounted for data gaps and extrapolations in the analysis (Table 13). TRVs, that were based on dietary concentrations, average daily intake (ADI), and egg PFOS concentrations, were 0.42 mg PFOS/kg feed, 0.032 mg PFOS/kg bwt/d, and 2.6 μg PFOS/ml egg yolk, respectively (Table 14). Because sex-specific differences in adult serum and liver PFOS concentrations were observed in the toxicity studies, TRVs based on these end points represent a range of values that encompass all avian reproductive conditions. The sex-specific differences in serum and liver PFOS concentrations, at study termination, were probably a

Table 13 Assignment of uncertainty factors for the calculation of a generic trophic level IV avian predator toxicity reference value (TRV) for PFOS[a]

Uncertainty factors	Notes
Inter-taxon extrapolation (UF_A)	The laboratory study used to determine a threshold dose was from northern bobwhite quail; this species belongs to the same taxonomic class but is in a different order, $UF_A = 6$
Toxicological end point (UF_L)	An LOAEL, but not a NOAEL, was determined in the quail study, based on multiple end points that included reproduction. Furthermore, the difference between the LOAEL and the control was less than 20% for the affected reproductive end points. Taken together with other study data, the $UF_L = 2$
Exposure duration (UF_S)	The quail reproductive study was conducted for 20 wk; several important life stages were evaluated including embryonic development and offspring growth and survival, so $UF_s = 2$
Overall UF for TRV	$UF = 6 \times 2 \times 2 = 24$

[a]Selection of uncertainty factors based on the Great Lake Initiative (US EPA 1995)

Table 14 PFOS toxicity reference values (TRVs) for a generic trophic level IV avian predator based on dietary, liver, and serum toxic doses[a]

	Male LOAEL	TRV[b]	Female LOAEL	TRV[b]
ADI (mg PFOS/kg bwt/d)[c]	0.77	0.032	0.77	0.032
Liver (μg PFOS/g, wt/wt)	88	3.7	4.9	0.20
Serum (μg PFOS/ml)	141	5.9	8.7	0.36
Egg Yolk (μg PFOS/ml)			62	2.6

[a]LOAEL values based on bobwhite quail definitive study
[b] TRV estimated with total uncertainty factor of 24 derived using the US EPA GLI protocol
[c]ADI= Average daily intake (mg PFOS/kg bwt/d); estimates were based on pen averages

result of PFOS being transferred to eggs from adult females during egg-laying. This is substantiated by the fact that during the pre-reproductive phase of the study, serum concentrations in females were similar to those observed in males (Newsted et al. 2007). Therefore, the reproductive condition of the bird affects the relevant serum and liver values.

Water quality criteria for the protection of avian species can be calculated using modified procedures that are explained in GLI guidance (US EPA 1995). Modifications to the GLI procedures were focused primarily on the derivation of BAFs that are used to model the accumulation of residues from water in trophic level III and IV fish. The procedures outlined in the GLI for deriving these BAFs are based on chemical-specific K_{ow} values. However, because PFOS has surfactant qualities, a K_{ow} value has not been directly measured in the laboratory. Consequently, literature values were used to estimate the potential biomagnification of PFOS into upper trophic level fish. The site-specific nature of most field-derived BAF values resulted in a baseline BAF being calculated from laboratory BCF values. Several laboratory BCF values have been determined for fish exposed to waterborne PFOS (Drottar et al. 2001; Martin et al.

2003b). For bluegill (*L. macrochirus*), a BCF of 3,614, based on whole body PFOS concentrations, was derived by kinetic analysis (Drottar et al. 2001). In rainbow trout (*O. mykiss*), a BCF of 1,100 was derived from carcass PFOS concentrations (Martin et al. 2003b). The baseline BAF for PFOS was calculated as the geometric mean of these BCF values (BAF=1,994). To address potential biomagnifications rates into trophic level IV fish, literature values from a Laurentian Great Lakes food chain study were used (Kannan et al. 2005). In this study, PFOS concentrations in predatory fish, including whitefish and Chinook salmon, were approximately 10–20 times greater than that measured in prey fish. However, PFOS concentrations in the predatory fish were based on liver concentrations, a tissue for which PFOS is preferentially accumulated compared to whole body concentrations. As a result, the biomagnification factor (BMF) from this study could have been approximately four to five times greater if whole-body PFOS concentrations had been used in these analyses (Martin et al. 2003b). A BMF value of 5 was used to predict the concentration of PFOS in trophic level IV. Finally, for the consumption of piscivorous birds by upper trophic level avian predators (e.g., herring gull by eagles), the BAF is derived by multiplying the baseline BAF for fish by a BMF to account for the biomagnification from fish into birds. Currently, there are few reliable data from field studies that can be used to derive a BMF. As a result, the data from the mallard and northern bobwhite definitive reproduction studies were used to calculate a BMF (Newsted et al. 2007). Based on the results of the definitive reproduction study with bobwhite quail and mallards, BMFs were calculated by dividing the mean concentration of PFOS in liver by the concentration of PFOS in the diet (Leonards et al. 1997). Liver concentrations were used to calculate the BMF, because liver PFOS concentrations were less variable than serum concentrations and would be a better measure of accumulation. Finally, only the male liver PFOS concentrations were used in the calculation of the BMF, because their liver concentrations were unaffected by laying of eggs, as was observed in females from these treatment groups. The effect of laying eggs and the resulting loss of PFOS from the hens would introduce a bias and underestimate the actual BMF. In northern bobwhites males from the 10 ppm PFOS treatment, an average liver concentration of 88 μg PFOS/g resulted in a BMF of 8.8. For mallards from the 10 ppm treatment group, an average liver concentration of 61 μg PFOS/g resulted in a BMF of 6.1. Using the geometric mean of the northern bobwhite and mallard BMF values, an overall BMF of 7.3 was calculated, and this value was used in the water quality criterion calculations. This value is similar to that observed for bald eagles from the Great Lakes, where PFOS concentrations in the livers of bald eagles were 10–20 times greater than that measured in the livers of salmon (Kannan et al. 2005).

According to the GLI guidelines, three avian species are selected to represent avian wildlife in the WQC calculations. The use of these representative species is meant to be protective of all avian wildlife. The three species are the bald eagle, the herring gull, and the belted kingfisher. These birds are all residents of the

Great Lakes basin and are likely to experience the greatest exposures to contaminants through the food web. Exposure parameters, including body weights (BW), feeding rates (F_{TLi}), drinking rates (W), and trophic level dietary composition (as food ingestion rate and food item percent in the diet), for each representative avian species are listed in Table 15. Calculation of a water quality criteria for the protection of avian species were based on these species-specific parameters, as shown in Eq. 11:

$$WV = \frac{\frac{TD}{UF_A\ xUF_S\ xUF_L} x\ BW}{\mathrm{W} + \sum\left(\mathrm{F_{TLi}\ xBAF_{TLi}^{WL}}\right)} \tag{11}$$

where WV = wildlife value in milligrams of PFOS per liter (mg PFOS/L); TD = test dose or threshold dose in mg of PFOS per kg per day (mg PFOS/kg, bwt/d) for the test species; UF = uncertainty factor for extrapolating toxicity across species (UF_A), for sub-chronic to chronic exposures (UF_S), and for LOAEL to NOAEL extrapolations (UF_L). All UF values are unit-less; BW = average body weight in kilograms (kg) for the representative species; F_{TLi} = species-specific average daily amount of food consumed (kg/d) for trophic level (i); W = species-specific average daily amount of water consumed (L/d); ${BAF^{WL}}_{TLi}$ = bioaccumulation factor for wildlife food in trophic level (i). For consumption of piscivorous birds by other birds, the BAF is derived by multiplying the trophic level III BAF by the biomagnification factor (L/kg).

WVs for the three avian species were calculated from exposure values given in the GLI guidance (Table 15), and using the following fate and toxicological properties for PFOS.

Fate properties:		Toxicological properties	
BAF_3	1,994	$ADI_{(LOAEL)}$	0.77 mg PFOS/kg bwt/d
BAF_4	9,970	Total UF	24
BMF	7.3		
BMF_{other}	0		

Using these data, the calculated wildlife values for the individual species were the following:

Herring gull:	41 ng PFOS/L
Bald eagle:	71 ng PFOS/L
Kingfisher:	36 ng PFOS/L

The final avian wildlife value was calculated as the geometric mean of all three avian wildlife values, thus

Avian wildlife value: 47 ng PFOS/L

Table 15 Exposure parameters for three avian surrogate species identified for protection

Species	Adult body wt (kg)	Water ingestion rate (L/d)	Food ingestion rate of each prey in each trophic level (kg, wt/wt/d)	Trophic level of prey (% diet)
Herring gull	1.1	0.063	TL3: 0.192; TL4: 0.0480; Other: 0.0267	Fish: 90 (TL3: 80; TL4: 20). Other: 10
Bald eagle	4.6	0.160	TL3: 0.371; TL4: 0.0929 PB: 0.0283; Other: 0.0121	Fish: 92 (TL3: 80; TL4: 20). Birds: 8: (PB: 70; other: 30)
Belted Lingfisher	0.15	0.017	TL3: 0.0672	TL3: 100

TL3 or TL4 = trophic level III or IV fish; PB = piscivorous birds; Other = non-aquatic birds and mammals

3.7 Derivation of PFBS TRVs for a Level IV Avian Predator

As with PFOS, the TRV was derived by using the UF methodology described in the US EPA GLI methodology (US EPA 1995). Using the data from the quail reproduction study (Newsted et al. 2008), and the characteristics of a level IV avian predator, a final UF of 12 was assigned to account for data gaps and extrapolations in the analysis (Table 16). TRVs, based on dietary, ADI, and egg PFOS concentrations, were 50 mg PFBS/kg feed, 7.3 mg PFBS/kg bwt/d, and 5.7 mg PFBS/ml whole egg, respectively (Table 17). Unlike PFOS, sex-specific differences in accumulation of PFBS from the diet into blood serum and liver of quail were not great and were generally less than 1.6-fold. Thus, the reproductive condition of the bird may not be important in determining concentrations of PFBS in serum and liver; however, because sample size was small, the toxicological or ecological significance of these differences is unknown.

Table 16 Assignment of uncertainty factors for the calculation of a generic trophic level IV avian predator toxicity reference value (TRV) for PFBS[a]

Uncertainty factors	Notes
Inter-taxon extrapolation (UF_A)	The laboratory study used to determine a threshold dose was from northern bobwhite quail; this species belongs to the same taxonomic class but is in a different order, $UF_A = 6$
Toxicological end point (UF_L)	A NOAEL was determined from a quail study and was based on multiple end points that included reproduction. Taken together with other study data, the $UF_L = 1$
Exposure duration (UF_S)	The quail reproductive study was conducted for 20 wk and evaluated several important life stages including embryonic development and offspring growth and survival, so $UF_s = 2$
Overall UF for TRV	$UF = 6 \times 1 \times 2 = 12$

[a]Selection of uncertainty factors based on the Great Lake Initiative (US EPA 1995)

Table 17 PFBS TRVs for a generic trophic level IV predator based on dietary, liver, and serum toxic doses[a]

	Male		Female	
	NOAEL	TRV[b]	NOAEL	TRV[b]
ADI (mg PFBS/kg bwt/d)[c]	87.7	7.3	87.8	7.3
Liver (mg PFBS/g, ww)	16	1.3	30	2.5
Serum (mg PFBS/ml)	68	5.7	104	8.7
Egg yolk (mg PFBS/ml)			68	5.7

[a]NOAEL values based on bobwhite quail definitive study
[b]TRV estimated with total uncertainty factor of 12 derived using the US EPA GLI protocol
[c]ADI = average daily intake (mg PFBS/kg bwt/d); estimates were based on pen averages

3.8 PFBS Water Quality Criteria for Protection of Aquatic Predatory Birds

A baseline BAF for PFBS was calculated from laboratory BCF values (Wildlife International 2001a–g; Martin et al. 2003b). For bluegill (*L. macrochirus*), a steady state BCF of less than 1, based on whole body PFOS concentrations, was derived by kinetic analysis (WLI 2001d). This result was similar to that found in rainbow trout (*O. mykiss*), where a BCF was also determined to be less than 1 (Martin et al. 2003b). Thus, as a conservative measure, the baseline BAF was estimated to be 1 for PFBS. Unlike PFOS, no biomagnification of PFBS into upper trophic level fish was assumed, since laboratory studies have not indicated that PFBS is bioaccumulated via the diet (Martin et al. 2003b); the BAF for upper trophic level was also assumed to be 1.0.

The biomagnification of PFBS into avian species from consumption of fish was determined from the quail dietary reproduction study (Newsted et al. 2008). In this study, liver concentrations in both adult male and female quail were approximately 30-fold less than that measured in the feed, indicating that biodimunition may have occurred. In addition, no significant sex-related differences were observed in the study; this indicated that reproductive condition may not be important in predicting bird tissue concentrations. A BMF of 1.0 was used as conservative value to account for potential food web accumulation of PFBS into upper trophic level birds.

WV values for the three avian species were calculated from exposure values given in the GLI guidance (Table 15) and from the following fate and toxicological properties for PFBS.

Fate properties:		Toxicological properties	
BAF_3	1	$ADI_{(LOAEL)}$	87.8 mg PFBS/kg bwt/d
BAF_4	1	Total UF	12
BMF	1		
BMF_{other}	0		

Using these data, the calculated wildlife values for the individual species were the following:

Herring gull:	24 mg PFBS/L
Bald eagle:	16 mg PFBS/L
Kingfisher:	13 mg PFBS/L

The final avian wildlife value was calculated as the geometric mean of all three avian wildlife values, thus

Avian Wildlife Value: 17 mg PFBS/L

3.9 QSAR Analyses

Little toxicity information exists for many PFCs, especially in vivo toxicity data. Therefore, QSARs were developed to estimate the toxicity of PFCs for which no measured information is available. The results of in vitro and in vivo toxicity studies with PFCs have shown that the two principle determinants of biological activity and bioaccumulation are (1) the length of the fluorinated carbon chain and (2) the functionality of the head group (Goecke-Flora and Reo 1996; Hu et al. 2002; Lau et al. 2007). Specifically, the results of these studies have shown that the bioaccumulation potential and toxicity of PFCs increase with increasing fluorinated carbon chain length and that, in general, compounds that have sulfonic acid moieties tend to be more toxic than their carboxylic acid counterparts. In addition, the presences of primary and secondary amides have a significant effect on the toxicity of these compounds (Starkov and Wallace 2003). These findings can also be extended to aquatic organisms, where chain length, head group functionality, as well as the presence of amide groups, can also influence the toxicity and bioaccumulation potential of fluorochemicals.

Although few bioconcentration studies with PFCs in aquatic organisms exist, laboratory studies with fish have shown that the bioaccumulation potential of perfluorinated carboxylates (PFCAs) and perfluorinated sulfonates (PFAS) is related to chain length, with the greatest accumulation being observed for those compounds with the longest fluorinated carbon chains (Martin et al. 2003a, 2003b; Condor et al. 2008). In rainbow trout, PFCA and PFAS compounds, with fluorinated carbon chains shorter than seven and six, respectively, do not bioaccumulate and typically have BCFs less than 1.0 (Fig. 3). Bioconcentration factors were found to increase by a factor of approximately 8 for each additional fluorinated carbon for PFCAs with chain lengths of 8–12 (Martin et al 2003b). However, PFCAs with fluorinated carbon chains greater than 12 accumulated in rainbow trout to a lesser degree than did PFCAs with shorter carbon chains; this suggests that bioaccumulation potential may be limited by molecular size. Although only limited laboratory data are available for PFAS compounds, the general relationship

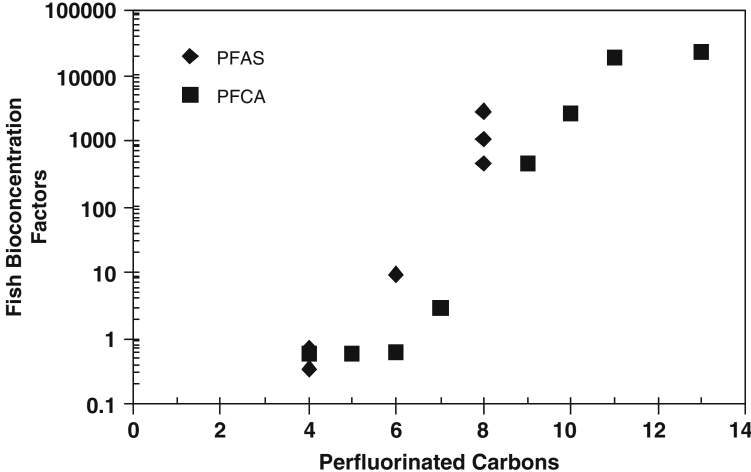


Fig. 3 Relationship between fluorinated carbon chain length of perfluorinated sulfonates (PFAS) and perfluorinated carboxylates (PFCA), and bioconcentration in several fish species including rainbow trout, fathead minnow, and bluegill

between fluorinated carbon chain length and bioaccumulation potential for these compounds is similar to that of the PFCAs, wherein both BCF and BAF values increase with chain length. For rainbow trout, a comparison of BCFs for PFBS (4 carbons), perfluorohexane sulfonate (PFHxS; 6 carbons), and PFOS (8 carbons) indicated that the BCF for PFHS was approximately 100-fold less than PFOS (8 carbons), whereas the BCF value for PFBS was at least 1,500-fold less than the PFOS BCF value. However, because a measurable BCF for PFBS may result from tissue concentrations being less than the method detection limit (MDL) (Martin et al. 2003b), a definitive evaluation could not be made. However, in studies with bluegill, the BCF value for PFOS was shown to be approximately 11,000-fold greater than the value determined for PFBS (3M 2003; NICNAS 2005). Collectively, these data indicate that, for PFAS compounds, an approximately 100-fold increase in bioaccumulation potential occurs when two fluorinated carbons are added to the chain length (for PFAS with 4–8 carbons). However, bioconcentration studies have not yet been conducted with PFAS with greater than eight fluorinated carbons, and it is, therefore, not known if this relationship will be borne out in future studies. Moreover, molecular size limitations may affect the bioaccumulation potential of PFAS compounds as it does with PFCAs. Finally, a comparison of bioconcentration and bioaccumulation factors of PFCA and PFAS compounds, with carbon chain lengths of five or greater, indicates that PFAS compounds tend to have greater bioaccumulation potentials than do PFCA compounds of the same carbon chain lengths, in a manner that is similar to that observed for mammalian species (Ohmori et al. 2006; Lau et al. 2007).

Studies conducted in vitro with several different mammalian cell lines have shown that the length of the carbon chain of fluorinated compounds is related to their potency as measured by cytotoxicity or inhibition of gap junctional intercellular communication (GJIC) (Fig. 4). GJIC is a process by which cells exchange small molecules (ions, second messengers, low molecular weight metabolites, etc.) and is involved in normal growth, development, and differentiation of tissues (Trosko and Rush 1998). In a study with rat liver epithelial cells (WB-F344), PFCAs with carbon chain lengths of 7–10 rapidly and reversibly inhibited GJIC in a dose-dependent manner. In contrast, PFCAs with carbon chain lengths of 2–5, 16, or 18 did not appreciably inhibit GJIC (Upham et al. 1998). In addition, PFOS also inhibited GJIC in a dose-dependent manner and was more potent than PFOA, a C7 carboxylate. In a subsequent study, PFOS, perfluorooctane sulfonamide (PFOSA), and PFHS all inhibited GJIC in a dose-dependent manner, whereas exposure to PFBS, a 4-carbon PFAS, did not affect GJIC (Hu et al. 2002). The toxicity of PFCs to mammalian cells is also directly proportional to the length of the fluorinated carbon chain, and such chain length is the primary determinant of toxicity (Fig. 4). In the study by Hu et al. perfluorinated carboxylates with carbon chain lengths less than five were not cytotoxic; toxicity increased with increasing carbon chain lengths for those compounds with chain lengths of 5–13 (Kleszczynski et al. 2007; Mulkiewicz et al. 2007). However, for PFCAs with greater than 13 fluorinated carbons, the relationship between chain length and toxicity deviated from linearity, with potency actually being less than that observed for

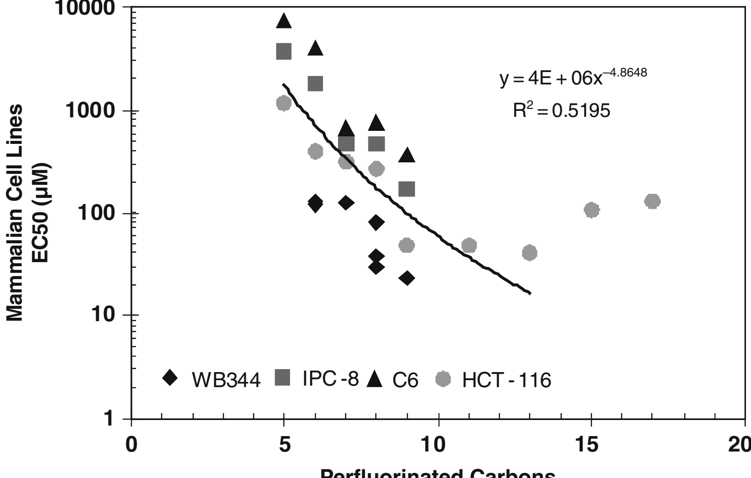


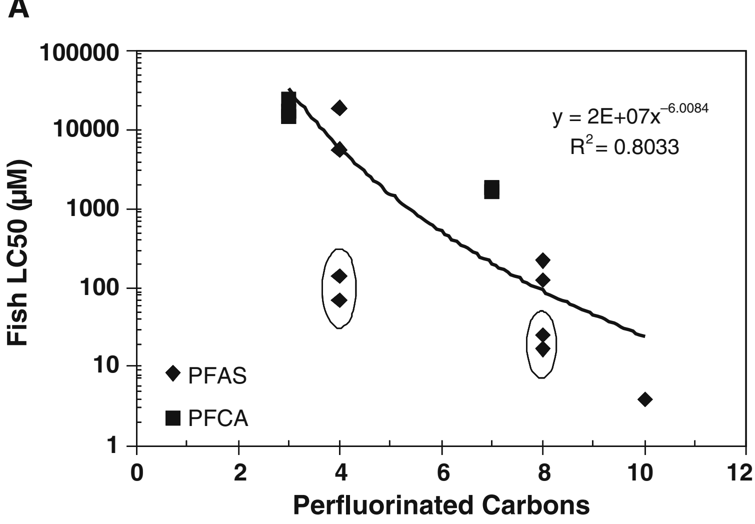
Fig. 4 Relationship between cytotoxicity and gap junctional intercellular communication (GJIC) inhibition and fluorinated carbon chain length of PFAS and PFCA in several mammalian cell lines. Regression model includes all perfluorinated compounds except for those with carbon chain lengths greater than 13

perfluorotetradecanoic acid (PFTeDA: C13). In summary, the results from both the GJIC and the cytotoxicity assays show that the primary determinant of perfluorinated compound potency is the length of the fluorinated carbon chain, and although the functionality of the head group may influence potency, the significance of this influence can only be ascertained when additional in vitro toxicity data are available.

The length of the fluorinated carbon chain and functionality of the head group are also related to the aquatic toxicity of perfluorinated chemicals, as affirmed in several freshwater species, including rainbow trout, bluegill, and fathead minnow (Fig. 5A), and the cladoceran *D. magna* (Fig. 5B). In fish, the toxicity of both PFAS and PFCA compounds was directly related to carbon chain length; PFCA compounds were less toxic than PFAS compounds with equivalent carbon chain lengths.

Results of acute toxicity studies on *D. magna*, with PFAS and PFCA compounds, have shown increased toxicity as carbon chain length increases; the PFAS compounds tend to be more toxic than PFCA compounds with equivalent chain lengths. Interestingly, the toxicity of saturated (FTCA) and unsaturated (FTUCA) fluorotelomer carboxylic acid was related to the length of the carbon chain, with toxicological potency increasing with increasing chain length (Boudreau et al. 2002; Phillips et al. 2007). When all groups of PFCs were compared as to chain length of their fluorinated carbons, FTCA and FTUCA compounds were generally more toxic than were PFAS or PFCA compounds. Although the basis for the greater toxicity of these fluorotelomers to *D. magna* has not yet been fully examined, insight may be gained from results of a metabolic study with rat hepatocytes, in which the metabolism and disposition of fluorotelomer alcohols were evaluated (FTOH; Martin et al. 2005). In this study, 8:2 FTOH was first oxidized to a transient fluorotelomer aldehyde or and then was further oxidized to either an unsaturated aldehyde, 8:2 FTCA that could then be converted to its unsaturated form, 8:2 FTUCA. These unsaturated fluorotelomer metabolites eventually react with glutathione. Because these compounds may also react with other cellular nucleophiles, such reactivity could result in toxicity, as was observed in studies of the effects of PFCs on *D. magna*. However, more detailed, mechanistic studies are needed before the underlying basis for the toxicity of these compounds to aquatic organisms can be understood.

The presence of amide functional groups also increased the toxicity of PFAS compounds to fish (Fig. 5A), and to *D. magna* (Fig. 5B), when compared to PFAS compounds with equivalent carbon chain lengths. The effect of amides on the toxicity of PFAS compounds is not unexpected, because such effects were observed when the impact of such amides on mitochondrial energetics of mammals was studied (Langely 1990; Schnellmann and Manning 1990; Starkov and Wallace 2002). In these studies, PFCs such as PFOA and PFOS, as well as a fully saturated amide, *n*-ethyl perfluorooctane sulfonamidoethanol (*n*-EtFOSE), were found to be relatively weak inhibitors of mitochondrial oxidative phosphorylation and appeared to act in a non-selective manner on



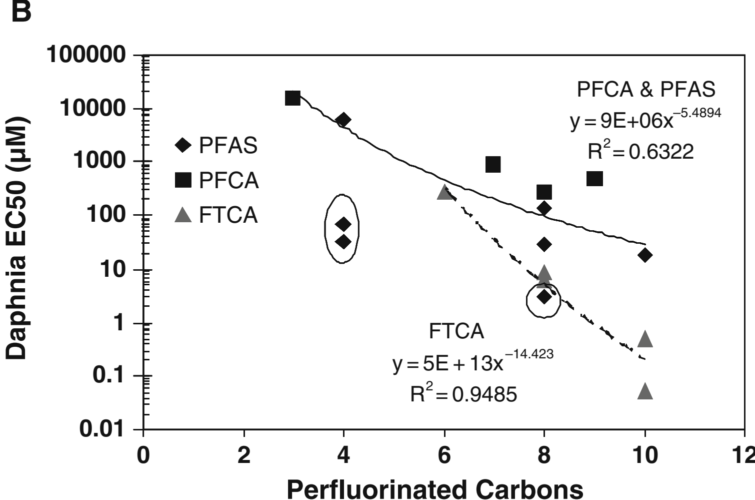


Fig. 5 Acute toxicity of PFAS, PFCA, and fluorotelomer carboxylic acids (FTCA and FTUCA) to aquatic organisms. (**A**) LC_{50} values for bluegill, fathead minnow, and rainbow trout. (**B**). EC_{50} mortality value for the cladoceran, *Daphnia magna*. Fish regression models include both PFAS and PFCA data, while models based on daphnids represent PFAS/PFCA and fluorotelomer data, respectively. Circles identify alcohol and amide sulfonic acids and were not included in the regression analyses

mitochondrial membrane permeability at relatively high concentrations (>100 µM). In contrast, perfluorinated chemicals with secondary amide groups, such as PFOSA and n-EtFOSA, were potent inhibitors (at 5–50 µM levels) of mitochondrial oxidative phosphorylation. The effects of perfluorinated

chemicals on mitochondrial bioenergetics are similar to the protonophoric mechanism of action that is observed in the liver of rats exposed to dinitrophenol. Under this hypothesis, compounds that have ionizable amide groups with favorable p*K*a values can shuttle protons back into the mitochondrial matrix and dissipate the proton motive force generated by the electron transport, thus disrupting oxidative phosphorylation. Therefore, it is not simply the presence of an amide group that impacts the potency of a fluorinated compound to inhibit mitochondrial function. It is also important that the amide group become protonated under prevailing physiological conditions. As such, the substituted amides such as PFOSA, *n*-ethyl perfluorooctane sulfonamidoacetic acid (PFOSAA), *n*-methyl perfluorooctane sulfonamidoethanol (*n*-MeFOSE), and *n*-ethyl perfluorooctane sulfonamide (n-EtFOSA) are potent inhibitors of mitochondrial oxidative phosphorylation, whereas other compounds, such as *n*-EtFOSE and *n*-EtFOSAA that lack the protonated amide, are not effective inhibitors of mitochondrial phosphorylation.

In studies conducted with freshwater algae and macrophytes, the toxicological potency of PFCA was found not to be related to the length of the fluorinated carbon chain, as was observed for aquatic organisms (Fig. 6). For example, in toxicity studies conducted with the green alga *S. capricornutum*, the toxicity of PFCA compounds was not related to carbon chain length, but rather the EC_{50} values were found to vary between 100 and 400 μM for PFCs with chain lengths of 2–9 carbons (Fig. 6A). Because toxicity data for PFAS compounds is limited, the nature of the relationship between chain length and toxicity is difficult to quantify. Notwithstanding, chain length appears to an important determinant of toxicity in that PFBS (C4) was approximately 50-fold less toxic than was PFOS (C8). However, additional study results will be required before the relationship between carbon chain length and toxicity can elucidated. The effect of amide groups on toxicity is also observed for *S. capricornutum,* in that PFBS was significantly less toxic than amide-containing PFBS compounds such as methyl perfluorobutane sulfonamidoethanol and methyl perfluorobutane sulfonamide. The absence of a relationship between PFAS and PFCA chain length and toxicity in aquatic plants was observed in toxicity studies conducted with the aquatic macrophytes, *Lemna* sp. (Fig. 6B; Boudreau et al. 2002; 3M 2003). In these studies, the toxicity of PFCAs and PFASs ranged from approximately 100 to 300 μM, but there was no linear relationship between either carbon chain length or functional head group and toxicity. In contrast, the toxicity of saturated and unsaturated fluorotelomer carboxylic acids was related to carbon chain length for compounds with 4–8 fluorinated carbons (Fig. 6B). The relationship between carbon chain length and toxicity deviated from linearity for fluorotelomers with greater than eight carbons. For 10:2 FTCA and 10:2 FTUCA compounds, toxicity actually decreased from that observed for 8:2 fluorotelomers, in a manner similar to that observed for the mammalian cell line HCT-116, in which cytotoxicity of PFCA compounds with greater than 13 carbons were less toxic than the most toxic PFCA evaluated, PFTeDA (Fig. 4).

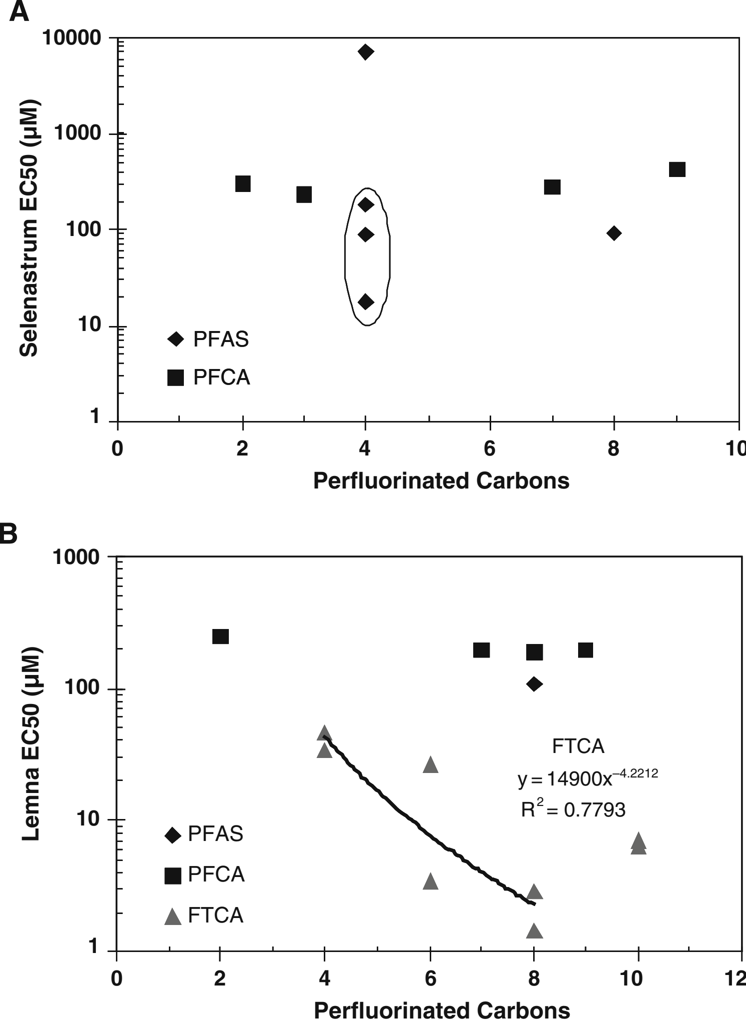


Fig. 6 Inhibition of growth and/or biomass of aquatic plants exposed to fluorinated chemicals. (**A**) Data from studies with *Selenastrum capricornutum* exposed to PFAS acid and PFCA acids. (**B**) Data from studies conducted with duckweed, *Lemna* sp exposed to PFAS, PFCA, FTCA, or FTUCA. Circles identify alcohol and amide sulfonic acids and were not included in the regression analyses

Results available in the literature on the toxicity of PFCs to aquatic organisms indicate that toxicity of fluorinated chemicals is related to length of the fluorinated carbon chain; the nature of functional groups has relatively little effect on the toxic potency of these compounds. Moreover, the addition of amide groups that can be protonated, under environmental conditions,

tends to increase toxic potency of PFCs relative to PFCs of similar chain length. However, additional studies are needed with other fluorinated compounds, as well as with other aquatic species, before we can accept as correct this finding on the potency of fluorinated chemicals to aquatic organisms. Notwithstanding, no such linear relationship between carbon chain length and toxicity has yet been verified for PFCA and PFAS compounds and aquatic plants. The exception to this finding is for saturated and unsaturated fluorotelomer carboxylic acids, wherein chain length was the primary determinant of toxic potency. Additional studies are needed to more fully understand this relationship and also to evaluate the ecological significance of this finding within the context of current environmental concentrations of these compounds. Although the analysis given above indicates that structure–activity relationships can be derived from existing data, there are still numerous data gaps that need to be addressed to quantify the toxicity of different classes of perfluorinated compounds and the relative susceptibility of aquatic organisms and plants. When such data are available it will be feasible to develop more sophisticated models to predict the toxicity of fluorinated compounds to aquatic organisms.

4 Conclusions

From available aquatic organism toxicity data, PFOS concentrations that were protective to selected aquatic species were calculated for surface waters and fish tissues. Using the Great Lakes Initiative, water concentrations of PFOS were calculated to protect aquatic plants and animals. The final plant value was calculated as 8.2 mg PFOS/L; the secondary chronic value for aquatic animals was calculated as 0.46 mg PFOS/L. Based on these calculations, chronic water concentrations less than or equal to 0.46 mg PFOS/L should not pose a significant adverse risk to aquatic organisms, and concentrations of 0.78 mg PFOS/L should be protective of aquatic organisms under acute exposure scenarios. A critical body residue level for PFOS in fish tissues was calculated from a bluegill bioaccumulation study with PFOS. Based on the lower 95% confidence interval of the LC_{01}, a tissue PFOS concentration of 87 mg/kg, wt/wt was calculated as the threshold value below which PFOS is not expected to pose a risk to fish populations. However, results from a toxicity study, wherein PFOS concentrations were measured in freshwater mussels, indicate that significant mussel mortality is associated with tissue concentrations of 88.8 mg PFOS/kg, wt/wt. Thus, it is possible that freshwater mussels are more sensitive to PFOS exposure than are fish. It is also probable that additional studies are needed to more accurately address the tissue residue concentrations of PFOS associated with toxicity in fish.

5 Summary

PFCs are released into the environment via their uses as wetting agents, lubricants, stain resistant treatments, and foam in fire extinguishers. PFOS is the terminal breakdown product of many commercially used perfluorinated compounds and is often the predominant PFC found in the environment. PFOS is resistant to chemical and biological changes and does not significantly degrade under environmental conditions. As a result of its low volatility and strong soil adsorption PFOS has little mobility in the environment. In laboratory and field tests, PFOS has been shown to bioconcentrate in fishes. More information is available about PFOS than for any other PFC. Toxicity studies with plants, invertebrates, and vertebrates from both terrestrial and aquatic habitats have been conducted with PFOS. Therefore, PFOS is used as an example compound in this chapter. Based on available toxicity studies, concentrations of PFOS were calculated that are protective of aquatic plants and organisms in surface waters. A critical body concentration of PFOS was calculated for fish that would be protective of top predators.

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References

3M (2003) Environmental and health assessment of perfluorooctane sulfonic acid and its salts. Prepared by 3M Company with J. Moore (Holly house Inc., J. Rodricks and D. Turnbull (Environ Corp) and W. Warren Hicks (Cadmus Group). August 2003.

Ankley GT, Niemi, GJ, Lodge KB, Harris HJ, Beaver DL, Tillitt DE, Schwartz T, Giesy JP, Jones PD, Hagley C (1993) Uptake of planar polychlorinated biphenyls and 2,3,7, 8-substituted polychlorinated dibenzofurans and dibenzo-p-dioxins by birds nesting in the lower Fox River and Green Bay, Wisconsin, USA. Arch Environ Contam Toxicol 24:332–344.

Ankley GT, Kuehl DW, Kahl MD, Jensen KM, Butterworth BC, Nichols JW (2004) Partial life-cycle toxicity and bioconcentration modeling of perfluorooctanesulfonate in the northern leopard frog (*Rana pipiens*). Environ Toxicol Chem 23:2745–2755.

Barron MG, Hansen JA, Lipton J (2002) Association between contaminant tissue residues and effects in aquatic organisms. Rev Environ Contam Toxicol 173:1–37.

Boudreau T, Sibley P, Mabury SA, Muir DCG, Solomon KR (2002) Toxicity of perfluoroalkyl carboxylic acids of different chain lengths to selected freshwater organisms. Department of Environmental Biology, Masters Thesis, University of Guelph, ON, p. 134.

Boudreau TM, Sibley PK, Mabury SA, Muir DCG, Solomon KR (2003a) Laboratory evaluation of the toxicity of perfluorooctane sulfonate (PFOS) on *Selenastrum*

capricornutum, Chlorella vulgaris, Lemna gibba, Daphnia magna, and *Daphnia pulicaria*. Arch Environ Contam Toxicol 44:307–313.
Boudreau TM, Wilson CJ, Cheong WJ, Sibley PK, Mabury SA, Muir DCG, Solomon KR (2003b) Response of the zooplankton community and environmental fate of perfluorooctane sulfonic acid in aquatic microcosms. Environ Toxicol Chem 22:2739–2745.
Bowerman WW, Best DA, Grubb TG, Zimmerman M, Giesy JP (1998) Trends of contaminants and effects in bald eagles of the Great Lakes Basin. Environ Monitor Assess 53:197–212.
CCME (1999) A protocol for the derivation of water quality guidelines for the protection of aquatic life. Canadian Environmental Quality Guideline. Canadian Council of Ministers of the Environment, Ottawa.
Chapman PM, Fairbrother A, Brown D (1998) Critical evaluation of safety (uncertainty) factors for ecological risk assessment. Environ Toxicol Chem 17:99–108.
Condor JM, Hoke RA, De Wolf W, Russell MH, Buck RC (2008) Are PFCAs bioaccumulative? A critical review and comparison with regulatory criteria and persistent lipophilic compounds. Environ Sci Technol 42:995–1003.
Desjardins D, Sutherland CA, VanHoven RL, Krueger HO (2001a) PFOS: A 96-hr toxicity test with the freshwater alga (*Anabaena flos-aquae*). Wildlife International, Ltd., Project Number 454A-110B, EPA Docket AR226-0186.
Desjardins D, Sutherland CA, VanHoven RL, Krueger HO (2001b) PFOS: A 96-hr toxicity test with the marine diatom (*Skeletonema costatum*). Wildlife International, Ltd., Project Number 454A-113A, EPA Docket AR226-1030a056.
Desjardins D, Sutherland C, VanHoven RL, Krueger HO (2001c) PFOS: A 7-d toxicity test with duckweed (*Lemna gibba* G3). Wildlife International, Ltd. Project Number 454-111, EPA Docket AR226-1030a054.
Di Toro DM, McGarth JA, Hansen DJ (2000) Technical basis for narcotic chemicals and polycyclic aromatic hydrocarbon criteria. I. Water and tissue. Environ Toxicol Chem 19:1951–1970.
Dixon DA (2001) Fluorochemical decomposition process. Theory, modeling, and simulation. WR Wiley Environmental Molecular Sciences Lab., Pacific Northwest National Lab., Richmond, WA.
Drottar KR, Krueger HO (2000a) PFOS: A 96-hr toxicity test with the freshwater alga (*Selenastrum capricornutum*). Wildlife International, Ltd., Project Number 454A-103A, EPA Docket AR226-0085.
Drottar KR, Krueger HO (2000b) PFOS: A 48-hr static acute toxicity test with the cladoceran (*Daphnia magna*). Wildlife International, Ltd., Project No. 454A-104, EPA Docket AR226-0087.
Drottar KR, Krueger HO (2000c) PFOS: A 96-hr static acute toxicity test with the freshwater mussel (*Unio complanatus*). Wildlife International, Ltd., Project No. 454A-105, EPA Docket AR226-0091.
Drottar KR, Krueger HO (2000d) PFOS: A 96-hr static acute toxicity test with the saltwater mysid (*Mysidopsis bahia*). Wildlife International, Ltd. Project No. 454A-101, EPA Docket AR226-0095.
Drottar KR, Krueger HO (2000e) PFOS: A 96-hr shell deposition test with the eastern oyster (*Crassostrea virginica*). Wildlife International, Ltd., Project No. 454A-106, EPA Docket AR226-0089.
Drottar KR, Krueger HO (2000f) PFOS: A semi-static life-cycle toxicity test with the cladoceran (*Daphnia magna*). Wildlife International Ltd., Project No. 454A-109, EPA Docket AR226-0099.
Drottar KR, Krueger HO (2000 g) PFOS: A flow through life-cycle toxicity test with the saltwater mysid (*Mysidopsis bahia*). Wildlife International, Ltd., Project No. 454A-107, EPA Docket AR226-0101.
Drottar KR, Krueger HO (2000 h) PFOS: A 96-hr static acute toxicity test with the fathead minnow (*Pimephales promelas*). Wildlife International, Ltd., Project No. 454-102, EPA Docket AR226-0083.

Drottar KR, Krueger HO (2000i) PFOS: An early life-stage toxicity test with the fathead minnow (*Pimephales promelas*). Wildlife International, Ltd., Project No. 454-108, EPA Docket AR226-0097.

Drottar KR, VanHoven RL, Krueger HO (2001) Perfluorooctanesulfonate, potassium salt (PFOS): A flow-through bioconcentration test with the bluegill (*Lepomis macrochirus*). Wildlife International, Ltd., Project No. 454A-134, EPA Docket AR226-1030a042.

Ellefson M (2001a) Solubility of PFOS in natural seawater and an aqueous solution of 3.5% of sodium chloride. 3M Company, 3M Environmental Laboratory, Laboratory Project No. E00-1716, EPA Docket AR226-1030a026.

Ellefson M (2001b) Solubility of PFOS in octanol. 3M Company, 3M Environmental Laboratory, Laboratory Project No. E00-1716, EPA Docket AR226-1030a027.

Ellefson M (2001c) Solubility of PFOS in water. 3M Company, 3M Environmental Laboratory, Laboratory Project No. E00-1716, EPA Docket AR226-1030a025.

Ellefson M (2001d) Soil adsorption/desorption study of potassium perfluorooctanesulfonate (PFOS). 3M Company, 3M Environmental Laboratory, Laboratory Project No. E00-1311, EPA Docket AR226-1030a030.

Fisk AT, Norstrom RJ, Cymbalisty CD, Muir DCG (1998) Dietary accumulation and depuration of hydrophobic organochlorines: Bioaccumulation parameters and their relationship with the octanol/water partition coefficient. Environ Toxicol Chem 17:951–961.

Giesy JP, Ludwig JP, Tillitt DE (1994) Dioxins, dibenzofurans, PCBs and colonial fish-eating water birds. In: Schecter A (ed) Dioxin and health. New York, NY, Plenum Press, pp. 249–307.

Giesy JP, Kannan K (1998) Dioxin-like and non-dioxin-like toxic effects of polychlorinated biphenyls (PCBs): Implications for risk assessment. Crit Rev Toxicol 28:511–569.

Giesy JP, Kannan K (2001) Global distribution of perfluorooctane sulfonate in wildlife. Environ Sci Technol 35:1339–1342.

Giesy JP, Kannan K (2002) Perfluorochemical surfactants in the environment. Environ Sci Technol 36:146A–152A.

Giesy JP, Newsted JL (2001) Selected fluorochemicals in the Decatur Alabama Area. 3M Report, Project No. 178041. EPA Docket AR226-1030a161.

Gledhill WE, Markley BJ (2000a) Microbial metabolism (biodegradation) studies of perfluorooctane sulfonate (PFOS). I. Activated sludge/sediment. Springborn Laboratories, Inc., Wareham, MA. Lab ID Number 290.6120, EPA Docket AR226-1030a034.

Gledhill WE, Markley BJ (2000b) Microbial metabolism (biodegradation) studies of perfluorooctane sulfonate (PFOS). II. Aerobic soil biodegradation. Springborn Laboratories, Inc., Wareham, MA. Lab ID Number 290.6120, EPA Docket AR226-1030a035.

Gledhill WE, Markley BJ (2000c) Microbial metabolism (biodegradation) studies of perfluorooctane sulfonate (PFOS). III. Anaerobic sludge biodegradation. Springborn Laboratories, Inc., Wareham, MA. Lab ID Number 290.6120, EPA Docket AR226-1030a036.

Goecke-Flora CM, Reo NV (1996) Influence of carbon chain length on the hepatic effects of perfluorinated fatty acids. Chem Res Toxicol 9:689–695.

Hanson ML, Sibley PK, Brain RA, Mabury SA, Solomon R (2005) Microcosm evaluation of the toxicity and risk to aquatic macrophytes from perfluorooctane sulfonic acid. Arch Environ Contam Toxicol 48:329–337.

Hatfield T (2001a) Screening studies on the aqueous photolytic degradation of potassium perfluorooctane sulfonate (PFOS). 3M Environmental Laboratory, Lab Request No. W2775, St. Paul, MN, EPA Docket AR226-1030a041.

Hatfield T (2001b) Hydrolysis reactions of perfluorooctane SULFONATE (PFOS). 3M Environmental Laboratory, Lab Request No. W1878. St. Paul, MN, EPA Docket AR226-1030a039.

Hekster FM, Laane RWPM, de Voogt P (2003) Environmental and toxicity effects of perfluoroalkylated substances. Rev Environ Contam Toxicol 179:99–121.

Hu W, Jones PD, Upham BL, Trosko JE, Lau C, Giesy JP (2002) Inhibition of gap junctional intercellular communication by perfluorinated compounds in rat liver and dolphin kidney epithelial cell lines in vitro and Sprague-Dawley rats *in vivo*. Toxicol Sci 68:429–439.

Jacobs RL, Nixon WB (1999) Determination of the melting point/melting range of PFOS. Wildlife International, Ltd., Project No. 454C-106. EPA Docket AR226-0045.

Johnson JD, Gibson SJ, Ober RE (1984) Cholestyramine-enhanced fecal elimination of carbon-14 in rats after administration of ammonium [14-C] perfluorooctanoate and potassium [14-C] perfluorooctane sulfonate. Fund Applied Toxicol 4:972–976.

Jones PD, Hu W, DeCoen W, Newsted JL, Giesy JP (2003) Binding of perfluorinated fatty acids to serum protein. Environ Toxicol Chem 22:2639–2649.

Kannan K, Tao L, Sinclair E, Paskva S, Jude DL, Giesy JP (2005) Perfluorinated compounds in aquatic organisms at various levels in a Great Lakes food chain. Arch Environ Contam Toxicol 48:559–566.

Kannan K, Franson JC, Bowerman WW, Hansen KJ, Jones PD, Giesy JP (2001b) Perfluorooctane sulfonate in fish-eating water birds including bald eagles and albatrosses. Environ Sci Technol 35: 3065–3070.

Kannan K, Koistinen J, Beckmen K, Evans T, Gorzelany JF, Hansen KJ, Jones PD, Helle E, Nyman M, Giesy JP (2001a) Accumulation of perfluorooctane sulfonate in marine mammals. Environ Sci Technol 35:1593–1598.

Kleszczynski K, Gardzielewski P, Mulkiewicz E, Stepnowski P, Skladanowski AC (2007) Analysis of structure-cytotoxicity in vitro relationships (SAR) for perfluorinated carboxylic acids. Toxicol In Vitro 21:1206–1211.

Kurume Laboratory (2001) Final report, Bioconcentration test of 2-perfluoroalkyl (C = 4-14) ethanol [This test was performed using 2-(perfluorooctyl)-ethanol (Test substance number K-1518)] in carp. Kurume Laboratory, Chemicals Evaluation and Research Institute, Japan. EPA Docket AR226-1276.

Kurume Laboratory (2002) Final report, Biodegradation test of salt (Na, K, Li) of perfluoroalkyl (C = 4-12) sulfonic acid, test substance number K-1520 (test number 21520). Kurume Laboratory, Chemicals Evaluation and Research Institute, Japan.

Lange CC (2001) The 35-d aerobic biodegradation study of PFOS. Pace Analytical Services, Minneapolis, MN. 3M Project Number E01-0444. EPA Docket AR226-1030a040.

Langely AE (1990) Effects of perfluoro-n-decanoic acid on respiratory activity of isolated rat liver mitochondria. J Toxicol Environ Health 29:329–336.

Lau C, Anitole K, Hodes C, Lai D, Pfahles-Hutchens A, Seed J (2007) Perfluoroalkyl acids: A review of monitoring and toxicological findings. Toxicol Sci 99:366–394.

Leonards PEG, Zierikzee Y, Brinkman UATh, Cofino WP, van Straalen NM, van Hattum B (1997) The selective dietary accumulation of planar polychlorinated biphenyls in the otter (*Lutra lutra*). Environ Toxicol Chem 16:1807–1815.

MacDonald MM, Warne AL, Stock NL, Mabury SA, Solomon KR, Sibley PK (2004) Toxicity of perfluorooctane sulfonic acid and perfluorooctanoate to *Chironomus tentans*. Environ Toxicol Chem 23:2116–2123.

Martin JW, Mabury SA, O'Brian PJ (2005) Metabolic products and pathways of fluorotelomer alcohols in isolated rat hepatocytes. Chem Biol Interact 155:165–180.

Martin JW, Mabury SA, Solomon KR, Muir DCG (2003a) Dietary accumulation of perfluorinated acids in juvenile rainbow trout (*Oncorhynchus mykiss*). Environ Toxicol Chem 22:189–195.

Martin JW, Mabury SA, Solomon K, Muir DCG (2003b) Bioconcentration and tissue distribution of perfluorinated acids in rainbow (*Oncorhynchus mykiss*). Environ Toxicol Chem 22:196–204.

McCarty LS, Mackay D (1993) Enhancing ecotoxicological modeling and assessment. Environ Sci Technol 27:1719–1728.

Moody CA, Martin JW, Kwan WC, Muir DCG, Mabury SA (2001) Monitoring perfluorinated surfactants in biota and surface water samples following an accidental release of fire-fighting foam into Etobicoke Creek. Environ Sci Technol 36:545–551.

Mulkiewicz E, Jastorff B, Skladanowski AC, Kleszczynski K, Stepnowski P (2007) Evaluation of the acute toxicity of perfluorinated carboxylic acids using eukaryotic cell lines, bacteria and enzymatic assays. Environ Toxicol Pharmacol 23:279–285.

Newsted JL, Beach SA, Gallagher SP, Giesy JP (2008) Acute and chronic effects of perfluorobutane sulfonate (PFBS) on the mallard and northern bobwhite quail. Arch Environ Contam Toxicol 54:535–545.

Newsted JL, Coady KK, Beach SA, Butenhoff JL, Gallagher S, Giesy JP (2007) Effects of perfluorooctane sulfonate on mallard and northern bobwhite quail exposed chronically via the diet. Environ Toxicol Pharmacol 23:1–9.

NICNAS (2005) Potassium perfluorobutane sulfonate. Report to the National Industrial Chemicals Notification and Assessment Scheme, Sydney Australia.

Oakes KD, Sibley PK, Martin JW, MacLean DD, Solomon KR, Mabury SA, Van Der Kraak GJ (2005) Short-term exposures of fish to perfluorooctane sulfonate: Acute effects on fatty acyl-CoA oxidase activity, oxidative stress, and circulating sex steroids. Environ Contam Toxicol 24:1172–1181.

Obourn J, Frame SR, Bell RH, Longnecker DS, Elliott GS, Cook J (1997) Mechanisms for the pancreatic oncogenic effects of the peroxisome proliferator wyeth-14,643.Toxicol Appl Pharmacol 145:425–436.

OECD (Organization for Economic Cooperation and Development) (2002) Hazard assessment of perfluorooctane sulfonate (PFOS) and its salts. ENV/JM/RD 17/Final. 21 November, 2002. Paris, p. 362.

Ohmori K, Kudo N, Katayama K, Kawashima Y (2006) Comparison of the toxicokinetics between perfluorocarboxylic acids with different carbon chain length. Toxicol 184:135–140.

Olson CT, Anderson ME (1983) The acute toxicity of perfluorooctanoic and perfluorodecanoic acids in male rats and effects on tissue fatty acids. Toxicol Appl Pharmacol 70:362–372.

Palmer SJ, Krueger HO (2001) PFOS: A frog embryo teratogenesis assay-*Xenopus*(FETAX). Wildlife International, Ltd., Project No. 454A-116. EPA Docket AR226-1030a057.

Palmer SJ, Van Hoven RL, Krueger HO (2002a) Perfluorooctanesulfonate, potassium salt (PFOS): A 96-hr static acute toxicity test with the rainbow trout (*Oncorhynchus mykiss*). Wildlife International Ltd. Report No. 454A-145. EPA Docket AR226-1030a044.

Palmer SJ, van Hoven RL, Krueger HO (2002b) Perfluorooctanesulfonate, potassium salt (PFOS): A 96-hr static renewal acute toxicity test with the sheepshead minnow (*Cyprinodon variegatus*). Wildlife International Ltd. Report No. 454A-146A.

Phillips MM, Dinglasan-Panlilio MJA, Mabury SA, Solomon KR, Sibley PK (2007) Fluorotelomer acids are more toxic than perfluorinated acids. Environ Sci Technol 41:7159–7163.

RIVM (2001) Guidance document on deriving environmental risk limits in the Netherlands. In: Traas TP (ed) Report No. 601501 012. National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

Robertson JC (1986) Potential for environmental impact of AFA-6 surfactant. Beak Consultants Ltd. Missassauga, Ontario, Canada. EPA Docket AR226-1030a043.

Sargent J, Seffl R (1970) Properties of perfluorinated liquids. Fed Proc 29:1699–1703.

Schaefer EL, Flaggs RS (2000) PFOS: An activated sludge respiration inhibition test. Wildlife International, Ltd., Project No. 454E-101, EPA Docket AR226-0093.

Schnellmann RG, Manning RO (1990) Perfluorooctane sulfonamide: A structurally novel uncoupler of oxidative phosphorylation. Biochem Biophys Acta 1016:344–348.

Sohlenius AK, Andersson K, Bergstrand A, Spydevold O, De Pierre JW (1994) Effects of perfluorooctanoate, a potent peroxisome proliferator in rat, on morris hepatoma 7800C1 cells, a rat cell line. Biochem Biophys 1213:63–74.

Starkov A, Wallace KB (2002) Structural determinants of fluorochemicals-induced mitochondrial dysfunction. Toxicol Sci 66:244–252.

Sutherland CA, Krueger HO (2001) PFOS: A 96-hr toxicity test with the freshwater diatom (*Navicula pelliculosa*). Wildlife International, Ltd., Project Number 454A-112. EPA Docket AR226-1030a055.

Taniyasu S, Kannan K, Horii Y, Hanari N, Yamashita N (2003) A survey of perfluorooctane sulfonate and related perfluorinated organic compounds in water, fish, birds, and humans from Japan. Environ Sci Technol 37:2634–2639.

Tolls J, Haller M, Graaf ID, Thijssen MATC, Sijm DTHM (1997) Bioconcentration of LAS: Experimental determination and extrapolation to environmental mixtures. Environ Sci Technol 31:3426–3431.

Tolls J, Sijm DJHM (1995) A preliminary evaluation of the relationship between bioconcentration and hydrophobicity for surfactants. Environ Toxicol Chem 14:1675–1685.

Trosko JE, Rush RJ (1998) Epigenetic toxicology as toxicant-induced changes in signaling leading to altered gap junctional intercellular communication. Toxicol Lett 102/103:71–78.

Upham BL, Deocampo ND, Wurl B,Trosko JE (1998) Inhibition of gap junctional intercellular communication by perfluorinated fatty acids is dependent on the chain length of the fluorinated tail. Int J Cancer 78:491–495.

US EPA (1985) Guidelines for deriving numerical national water quality criteria for the protection of aquatic organisms and their uses. PB-85-227049. US Environmental Protection Agency, NTIS, Springfield, VA, USA.

US EPA (1995) Final Water Quality Guidance for the Great Lakes System: Final Rule. Federal Register 60: 15366-15425. US EPA, Washington, DC, USA.

US EPA (2001) Perfluorooctyl sulfonates; proposed significant new use rule. Federal Register 65:62319–62333.

Van Hoven RL, Stenzel JI, Nixon WB (1999) Determination of the vapor pressure of PFOS using the spinning rotor gauge method. Wildlife International, Ltd., Project Number 454C-105. EPA Docket AR226-0048.

Wildlife International Ltd (2001a) PFBS: An activated sludge respiration test. Wildlife International Ltd., Project No. 454E-102A.

Wildlife International Ltd. (2001b) Perfluorobutane sulfonate, Potassium salt (PFBS): A 48-hour static acute toxicity test with the cladoceran (*Daphnia magna*). Wildlife International Ltd., Project No. 454A-118A.

Wildlife International Ltd (2001c) Perfluorobutane sulfonate, potassium salt (PFBS): A 96-hour static acute toxicity test with the fathead minnow (*Pimephales promelas*). Wildlife International Ltd., Project No. 454A-115.

Wildlife International Ltd. (2001d) Perfluorobutane sulfonate, Potassium salt (PFBS): A 96-hour static acute toxicity test with bluegill (*Lepomis macrochirus*). Wildlife International Ltd., Project No. 454A-114.

Wildlife International Ltd (2001e) PFBS: A 96-hour static acute toxicity test with the freshwater alga (*Selenastrum capricornutum*). Wildlife International Ltd., Project No. 454A-129.

Wildlife International Ltd (2001f) PFBS: A 96-hour toxicity test with the saltwater mysid (*Mysiodopsis bahia*). Wildlife International Ltd., Project No. 454A-128.

Wildlife International Ltd (2001 g) PFBS: A semi-static life-cycle toxicity test with the cladoceran (*Daphnia magna*). Wildlife International Ltd., Project No. 454A-130.

Yamada T, Taylor PH (2003) Laboratory-scale thermal degradation of perfluoro-octanyl sulfonate and related substances. Environmental Sciences and Engineering Group, University of Dayton, Research Institute, Dayton, OH.

Occurrence and Fate of Human Pharmaceuticals in the Environment

Sara C. Monteiro and Alistair B.A. Boxall

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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= –CH_2–	1.83	2.74	210 (est)
	Penicillin V R= –OCH_2 –	2.09	2.79	101 (est)
	Amoxicillin R= HO– –CH– NH_2	0.87	–	3430 (est)
Sulfonamides	Sulfonylamide R=H	−0.62	10.58	7500
	Sulfamethoxazole R= CH_3 N–O	0.89	–	610

Table 2 (continued)

Therapeutic class/compound chemical structure	Compound/chemical structure or side chains	Log K_{ow}	p*K*a	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_{ow}	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}	p*K*a	Water solubility (mg/L)
Beta-blockers				
R–O–CH₂–CH(OH)–CH₂–NH–CH(CH₃)–CH₃	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, R2 =	4.77 (est)	–	–
	Clofibrate R1=C_2H_5, R2 =	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-Sympathomimethics	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 thiazolidine 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 naphthacene-carboxamide 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 $\beta 1$ receptors, which are located primarily in the heart muscle, and the $\beta 2$ receptors, which are found in the blood vessels. While selective β-adrenergic antagonists only act on the $\beta 1$ 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 $\beta 1$ and $\beta 2$ receptors. Substances such as metoprolol and atenolol are examples of selective $\beta 1$ antagonists as a result of their greater affinity for $\beta 1$ 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 anti-neoplastic 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	$RNHCH_3 \rightarrow RNH_2 + CH_2O$	Diazepam, codeine, erythromycin, tamoxifen, caffeine
Aliphatic hydroxylation	$RCH_2CH_3 \rightarrow RCH(OH)CH_3$	Ibuprofen, meprobamate
N-Oxidation	$R_1R_2NH \rightarrow R_1R_2N\text{-}OH$	Quinidine, acetaminophen
Deamination	$RCH(NH_2)CH_3 \rightarrow R\text{-}C(OH)(NH_2)\text{-}CH_3 \rightarrow R\text{-}C(=O)\text{-}CH_3 + NH_2$	Diazepam
2. Hydrolysis reactions	$R_1C(=O)OR_2 \rightarrow R_1COOH + R_2OH$	Aspirin, clofibrate, enalapril, cocaine
	$R_1C(=O)NR_2 \rightarrow R_1COOH + R_2NH_2$	Lidocaine, indomethacin
Phase II		
3. Conjugation reactions		
Glucuronation	UDP - glucuronic acid + R - OH → glucuronide (O-R) + UDP	Acetaminophen, oxazepam, morphine
Sulfation	ROH + 3' - phosphoadenosine-5'-phosphosulfate (PAPS) → R–O–S(=O)(=O)–OH + 3' - phosphoadenosine-5'- phosphate	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

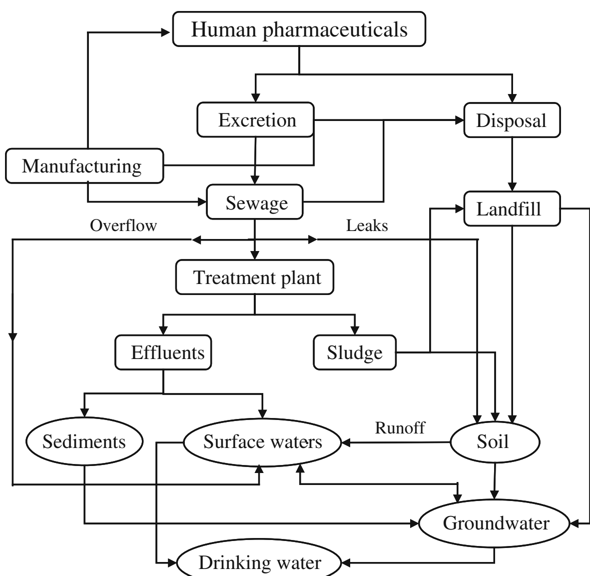

Fig. 1 Major pathways by which human-use pharmaceuticals reach the environment

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	$(0.005^{b}–0.011^{b}) \pm 0.001$	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		0.370[ac]		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		0.068[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		$nd^{d}–15.5 \times 10^{-3}$	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.

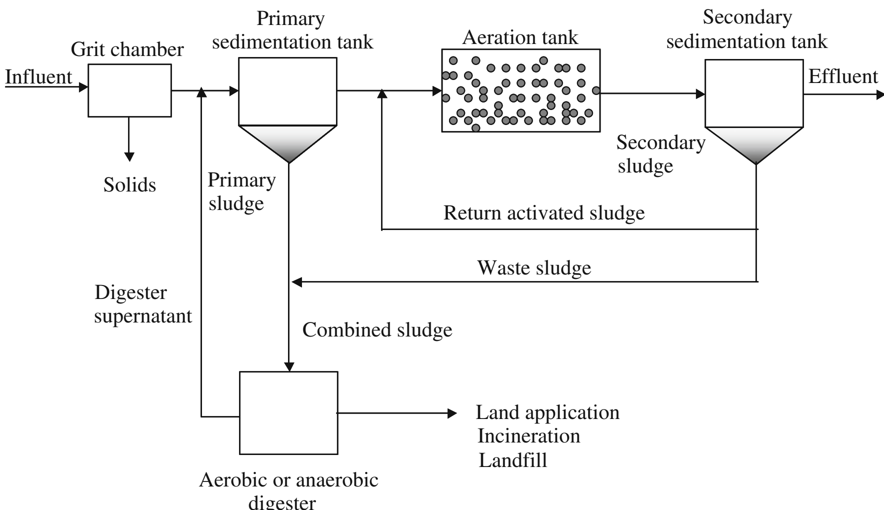

Fig. 2 Schematic of a conventional STP

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)	Atenolol (61)	Diatrizoate (0)		10, 16, 17, 23
		Caffeine (34–>53)	Oestrone (<1)		
	17β-Oestradiol (90–99)	Celiprolol (>82)	Ibuprofen (<1)		
	Azithromycin (90–99)	Clofibric acid[a] (50)	Iomeprol (34)		
	Carbamazepine (>98 –100)	Fenofibric acid (> 62)	Iopadimol (33)		
	Clarithromycin (> 76–99)	Ibuprofen (48–>82)	Iopromide (14–42)		
	Diclofenac (>96–>99)				
Ozone: medium dose (1–5 mg/L; cont.)	Erythromycin[b] (90–99)	Metoprolol (78)			10, 16, 17, 23
	Oestrone (>80–99)	Propranolol (>72)			
	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)				
Ozone: high dose (>5–7.1 mg/L)	Carbamazepine (>99)	Caffeine (>63)	Ibuprofen (>24)		17
	Diclofenac (> 98)	Indomethacin (>50)			
	Erythromycin[b] (>99)	Naproxen (>66)			
	Fluoxetine (>99)				

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 ($\geq$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)	Iopadimol (80)			
	Oestrone (>94)	Iopromide (89)			
	Fluoxetine (>91)				
	Gemfibrozil (>99)				
	Ibuprofen (>93)				
	Naproxen (>98)				
	Sulfamethoxazole (>99)				
	Trimethoprim (>99)				
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
	Outdoor microcosms	82 ± 11	2
	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. 1998b). 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) (adsorption coefficient)	K_{oc}[b] soil (L/kg) (adsorption coefficient corrected for soil organic carbon)	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[c] ± 8/2310 ± 93[2]	459[d] ± 32/16 ± 3[3]	1310[d] ± 180/47 ± 32[3]	0.55–4.66[4]
Ibuprofen			453.79 (predicted)[1] na[d]/7.1 ± 2.0[3]	na[d]/21 ± 4[3]	0.18–1.69[4]
Naproxen	10.13 ± 0.36–252.90 ± 4.77[5]	445.86 ± 47.88–3743.23 ± 184.19[5]	217.20 (predicted)[1] 42.46 ± 2.19[5]	217.20 (predicted)[1] 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] 1192[c] ± 122/3554 ± 194[2]	322162[c] ± 3297/50056 ± 2732[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[c] ± 0.08/37.6 ± 1.2[2]	62.2[c] ± 21.6/530 ± 16.9[2]			
Sulfapyridine	3.47				

Table 14 (continued)

Compound	K_d[a] soil (L/kg) (adsorption coefficient)	K_{oc}[b] soil (L/kg) (adsorption coefficient corrected for soil organic carbon)	K_d sludge (L/kg)	K_{oc} sludge (L/kg)	K_d sediment (L/kg)
Tetracycline antibiotic					
Oxytetracycline	417 ± 97–1026 ± 374[9]	27792 ± 6386–93317 ± 34130[9]	0.02 (predicted)[1]		0.3[10]
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[c] ± 0.01/37 ± 1.6[2]	253.55 ± 9.59 – 584.61 ± 16.45[5] 132[c] ± 2.7/521 ± 23[2]	75.33 ± 0.84[5] 25.52 (predicted)[1] na[d]/1.2 ± 0.5[3]	228.26 ± 2.53[5] na[d]/3.5 ± 1.5[3]	0.21–5.32[4] 1.3[11]
Antiepileptic – metabolite					
CBZ-diol					0.3[2]
Antineoplastic agents					
Cyclophosphamide			55[d] ± 20 / 2.4 ± 0.5[3]	158[d] ± 58/7.1 ± 1.7[3]	
Ifosfamide			22[d] ± 14/1.4 ± 0.4[3]	62[d] ± 40/4.1 ± 1.2[3]	
Beta-blockers					
Atenolol			0.21 (predicted)[1]		
Propranolol	16.3[c] ± 1.4/199 ± 9.6[2]	4405[c] ± 378/2803 ± 135[2]			
Hormones					
17α-Ethinyloestradiol		3.35 (log)[12]	584 ± 136[13] 278[d] ± 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]	

Table 14 (continued)

Compound	K_d[a] soil (L/kg) (adsorption coefficient)	K_{oc}[b] soil (L/kg) (adsorption coefficient corrected for soil organic carbon)	K_d sludge (L/kg)	K_{oc} sludge (L/kg)	K_d sediment (L/kg)
Oestriol					479[14]
Oestrone		3.14 (log)[12]	402 ± 126[13]	3.16 (log)[13]	
Norethindrone					128[14]
Progesterone					204[14]
Iodinated X-ray contrast media					
Iopromide			na[d]/11 ± 1[3]	na[d]/32 ± 5[3]	
Lipid regulators					
Clofibric acid	na[a]/5.38 ± 0.17[2]	na[a]/75.8 ± 2.5[2]	na[d]/4.8 ± 2.5[3]	na[d]/14 ± 7[3]	0.3[11]
Other pharmaceutical					
Diazepam (anxyolitic)			44[d] ± 26/21 ± 8[3]	125[d] ± 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	<	<	–	2, 3
		>Low concent.		
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]
17*β*-Oestradiol	Hormone	50-28-2
17*β*-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

References

Ahel M, Jeličić I (2001) Phenazone Analgesics in Soil and Groundwater below a Municipal Solid Waste Landfill. In: Daughton CG and Jones-Lepp T (eds), American Chemical Society, Symposium series 791, Washington, DC, pp. 100–115.

Ahrer W, Scherwenk E, Buchberger W (2001) Determination of drug residues in water by the combination of liquid chromatography or capillary electrophoresis with electrospray mass spectrometry. J Chromatogr A 910:69–78.

Alder AC, McArdell CS, Golet EM, Ibric S, Molnar E, Nipales NS, Giger W (2001) In: Daughton CG and Jones-Lepp T (eds), American Chemical Society, Symposium series 791, Washington D.C, pp 56–69.

Alexy R, Kümpel T, Kümmerer K (2004) Assessment of degradation of 18 antibiotics in the Closed Bottle Test. Chemosphere 57:505–512.

Analgesics. In: An A-Z of Medicinal Drugs. Oxford University Press 2000. Oxford Reference online. Oxford University Press. York University (accessed 18 January 2007) online http://www.oxfordreference.com/views/ENTRY.html?subview = Main&entry = t61.e207

Andersen H, Siegrist H, Halling-Sørensen B, and Ternes TA (2003) Fate of estrogens in a municipal sewage treatment plant. Environ Sci Technol 37 (18): 4021–4026.

Andersen HR, Hansen M, Kjølhot J, Stuer-Lauridsen F, Ternes TA, Halling-Sørensen B (2005) Assessment of the importance of sorption for steroid estrogens removal during activated sludge treatment. Chemosphere 61:139–146.

Anderson PO, Knoben JE, Troutman WG (2002) Handbook of Clinical Drug Data 10th Ed, McGraw-Hill, USA.

Andreozzi R, Caprio V, Insola A, Marotta R (1999) Advanced oxidation processes (AOP) for water purification and recovery. Catal Today 53 (1): 51–59.

Andreozzi R, Raffaele M, Nicklas P (2003) Pharmaceuticals in STP effluents and their solar photodegradation in the aquatic environment. Chemosphere 50:1319–1330.

Andreozzi R, Caprio V, Ciniglia C, De Champdoré M, Lo Giudice R, Marotta R, Zuccato E (2004) Antibiotics in the environment: occurrence in Italian STPs, fate and preliminary assessment on algal toxicity of amoxicillin. Environ Sci Technol 38 (24): 6832–6838.

Andreozzi R, Canterino M, Giudice RL, Marotta R, Pinto G, Pollio A (2006) Lincomycin solar photodegradation, algal toxicity and removal from wastewaters by means of ozonation. Water Res 40 (3): 630–638.

Arnold W, McNeill K, Latch DE, Boreen AL (2003) Photochemical fate of pharmaceutical compounds discharged and detected in natural waters. National Grants Competition (USGS-WRRI 104G).

Aronson JK (2001)"Antibiotics and anti-infective drugs" In: The Oxford Companion to Medicine. Lock, S, Last, J.M, Dunea G. (eds) Oxford University Press 2001. Oxford Reference Online. Oxford University Press. York University (accessed 18 January 2007), online-http://www.oxfordreference.com/views/ENTRY.html?subview = Main&entry = t185.e29.

Artola-Garicano E, Borkent I, Damen K, Jager T, Vaes WH (2003) Sorption kinetics and microbial biodegradation activity of hydrophobic chemicals in sewage sludge: model and measurements based on free concentrations. Environ Sci Technol 37:116–122.

Ashton D, Hilton M, Thomas KV (2004) Investigating the environmental transport of human pharmaceuticals to streams in the United Kingdom. Sci Tot Environ 333:167–184.

Balcioğlu IA and Ötker M (2003) Treatment of pharmaceutical wastewater containing antibiotics by $O_3$and O_3/ H2O2 processes. Chemosphere 50:85–95.

Baldessarini RJ (2001) Drugs and the treatment of psychiatric disorders: Depression and Anxiety Disorders. In: Hardman JG, Limbird LE (eds) Goodman & Gilman's - The Pharmacological Basis of Therapeutics 10th Ed, McGraw-Hill, New York, USA, pp 447–484.

Beausse J (2004) Selected drugs in solid matrices: a review of environmental occurrence, determination and properties of principal substances. Trends Anal Chem 23 (10–11): 753–761.

Bedner M and MacCrehan WA (2006) Transformation of acetaminophen by chlorination produces the toxicants 1,4-benzoquinone and N-acetyl-p-benzoquinone imine. Environ Sci Technol 40 (2): 516–522.

Belfroid AC, Van der Horst A, Vethaak AD, Schäfer AJ, Rijs GBJ, Wegener J, Cofino WP (1999) Analysis and occurrence of estrogenic hormones and their glucuronides in surface water and waste water in The Netherlands. Sci Tot Environ 225:101–108.

Bendz D, Paxéus N, Ginn TR, Loge FJ (2005) Occurrence and fate of pharmaceutically active compounds in the environment, a case study: Höje River in Sweden. J Hazard Mater 122:195–204.

Bernard S and Gray NF (2000) Aerobic digestion of pharmaceutical and domestic wastewater sludges at ambient temperature. Water Res 34:725–734.

Bernhard M, Müller J, Knepper TP (2006) Biodegradation of persistent polar pollutants in wastewater: comparison of an optimised lab-scale membrane bioreactor and activated sludge treatment. Water Res 40:3419–3428.

Besse J-P, Kausch-Barreto C, Garric J (2008) Exposure assessment of pharmaceuticals and their metabolites in the aquatic environment. Application to the French situation and preliminary prioritization. Hum Ecol Risk Assess 14 (4): 665–695.

Beta-blockers (2000) In: An A-Z of Medicinal Drugs. Oxford University Press 2000. Oxford Reference online. Oxford University Press. York University (accessed 18 January 2007) online-http://www.oxfordreference.com/views/ENTRY.html?subview = Main&entry = t61.e461.

Blackwell PA, Kay P, Boxall ABA (2007) The dissipation and transport of veterinary antibiotics in a sandy loam soil. Chemosphere 62(2):292–299.
Boreen AL, Arnold WA, McNeill K (2003) Photodegradation of pharmaceuticals in the aquatic environment: a review. Aquat Sci 65:320–341.
Boxall ABA, Blackwell PA, Cavallo R, Kay P, Tolls J (2002) The sorption and transport of a sulphonamide antibiotic in soil systems. Toxicol Lett 131:19–28.
Boxall A (2004) The environmental side effects of medication. EMBO J 5:1110–1116.
Boxall A, Fogg LA, Blackwell P, Kay P, Pemberton EJ, Croxford A (2004) Veterinary medicines in the environment. Rev Environ Contam Toxicol 180:1–91.
Boyd GR, Reemstsma H, Grimm DA, Mitra S (2003) Pharmaceuticals and personal care products (PPCPs) in surface and treated waters of Louisiana, USA and Ontario, Canada. Sci Tot Environ 311:135–149.
Boyd GR, Palmeri JM, Zhang S, Grimm DA (2004) Pharmaceuticals and personal care products (PPCPs) and endocrine disrupting chemicals (EDCs) in stormwater canals and Bayou St. John in New Orleans, Louisiana, USA. Sci Tot Environ 333:137–148.
Braga O, Smythe GA, Shäfer AI, Feitz AJ (2005) Steroid Estrogens in ocean sediments. Chemosphere 61 (6):827–833.
Brooks BW, Chambliss CK, Stanley JK, Ramirez A, Banks KE, Johnson RD, Lewis R J (2005) Determination of select antidepressants in fish from an effluent-dominated stream. Environ Toxicol Chem 24:464–469.
Buser H-R, Müller MD, Theobald N (1998a) Occurrence of the pharmaceutical drug clofibric acid and the herbicide mecoprop in various Swiss Lakes and in the North Sea. Environ Sci Technol 32 (1):188–192.
Buser H-R, Poiger T, Müller MD (1998b) Occurrence and fate of the pharmaceutical drug diclofenac in surface waters: rapid photodegradation in a lake. Environ Sci Technol 32 (22):3449–3456.
Buser H-R, Poiger T, Müller MD (1999) Occurrence and environmental behavior of the chiral pharmaceutical drug ibuprofen in surface waters and in wastewater. Environ Sci Technol 33 (15): 2529–2535.
Calamari D, Zuccato E, Castiglioni S, Bagnati R, Fanelli R (2003) Strategic survey of therapeutic drugs in the rivers Po and Lambro in Northern Italy. Environ Sci Technol 37:1241–1248.
Calvet R (1989) Adsorption of organic chemicals in soils. Environ Health Perspect 83:145–177.
Carballa M, Omil F, Lema JM, Llompart M, García-Jares C, Rodríguez I, Gómez, M, Ternes T (2004) Behavior of pharmaceuticals, cosmetics and hormones in a sewage treatment plant. Water Res 38:2918–2926.
Carballa M, Omil F, Lema JM (2005) Removal of cosmetic ingredients and pharmaceuticals in sewage primary treatment. Water Res 39 (19): 4790–4796.
Carballa M, Omil F, Ternes T, Lema JM (2007) Fate of pharmaceutical and personal care products (PPCPs) during anaerobic digestion of sewage sludge. Water Res 41(10): 2139–2150.
Carballa M, Omil F, Lema JM (2008) Comparison of predicted and measured concentrations of selected pharmaceuticals, fragrances and hormones in Spanish sewage. Chemosphere 72 (8): 1118–1123.
Chabner BA, Ryan DP, Paz-Ares L, Garcia-Carbonero R, Calabresi P (2001) Antineoplastic agents. In: Hardman JG, Limbird LE (eds) Goodman & Gilman's - The Pharmacological Basis of Therapeutics 10th Ed, McGraw-Hill, New York, USA, pp 1389–1460.
Chambers HF (2001) Antimicrobial agents - general considerations. In: Hardman JG, Limbird LE (eds) Goodman & Gilman's - The Pharmacological Basis of Therapeutics 10th Ed, McGraw-Hill, New York, USA, pp 1143–1170.
Clara M, Kreuzinger N, Strenn B, Gans O, Kroiss H (2005) The solids retention time - a suitable design parameter to evaluate the capacity of wastewater treatment plants to remove micropollutants. Water Res 39:97–106.

Clara M, Strenn B, Kreuzinger N (2004) Carbamazepine as a possible anthropogenic marker in the aquatic environment: investigations on the behaviour of Carbamazepine in wastewater treatment and during groundwater infiltration. Water Res 38:947–954.

Collucci M, Bork H, Topp E (2001) Persistence of estrogenic hormones in agricultural soils (I - 17-beta estradiol and estrone). J Environ Qual 30:2070–2076.

Contrast medium (2002) In: Concise Medical Dictionary. Oxford University Press 2002. Oxford Reference Online. Oxford University Press.York University (accessed 31 January 2007) online http://www.oxfordreference.com/views/ENTRY.html?subview = Main&entry = t60.e2140.

Daughton C, Ternes T (1999) Pharmaceuticals and personal care products in the environment: agents of subtle change? Environ Health Perspect 107:907–938.

Daughton C (2005) Pharmaceuticals and personal care products in the environment: overarching issues and overview. In: Daughton CG and Jones-Lepp T (eds), American Chemical Society, Symposium series 791, Washington, DC, pp .2–38.

Díaz-Cruz MS, López de Alda MJ, Barceló D (2003) Environmental behavior and analysis of veterinary and human drugs in soil, sediments and sludge. Trends Anal Chem 22:340–351.

Díaz-Cruz S and Barceló D (2004) Occurrence and analysis of selected pharmaceuticals and metabolites as contaminants present in wastewaters, sludge and sediments. Handb Environ Chem 5:227–260.

Doll TE, Frimmel FH (2003) Fate of pharmaceuticals - photodegradation by simulated solar UV-light. Chemosphere 52:1757–1769.

Drillia P, Stamatelatou K, Lyberatos G (2005) Fate and mobility of pharmaceuticals in solid matrices. Chemosphere 60 (8): 1034–1044

Dubus IG, Barriuso E, Calvet R (2001) Sorption of weak organic acids in soils: clofencet 2,4-D and salicylic acid. Chemosphere 45:767–774.

Environment Agency (2008) Prioritisation of pharmaceuticals of possible environmental concern. R&D technical report, UK.

Erickson BE (2002) Analysing the ignored environmental contaminants. Environ Sci Technol 36:140A-145A.

EU Landfill Directive (2003) – Strategy & Legislation: Legislation/Directives. DEFRA online www.defra.gov.uk/environment/waste/topics/landfill-dir/index.htm.

Farré M, Ferrer I, Ginebreda A, Figueras M, Olivella L, Tirapu L, Vilanova M, Barceló D (2001) Determination of drugs in surface water and wastewater samples by liquid chromatography-mass spectrometry: methods and preliminary results including toxicity studies with *Vibrio fischeri*. J Chromat A 938:187–197.

Ferrer I, Heine CE, Thurman EM (2004) Combination of LC/TOF-MS and LC/Ion trap MS/MS for the identification of diphenhydramine in sediment samples. Anal Chem 76:14378–1444.

Forsling ML (2001) Hormones. In: The Oxford Companion of the body. Blakemore C and Jennet S. (eds) Oxford University Press 2001. Oxford Reference online. Oxford University Press. York University (accessed 18 January 2007), online-http://www.oxfordreference.com/views/ENTRY.html?subview = Main&entry = t128.e494.

Galbraith A, Bullock S, Manias S, Hunt B, Richards A (2004) Pharmacokinetics: absorption and distribution. In: Fundamentals of Pharmacology: A Text for Nurses and Health Professionals, 4th Ed. Pearson Education Limited, Essex, England, pp 109–114.

Gibs J, Stackelberg PE, Furlong ET, Meyer M, Zaugg SD, Lippincott RL (2007) Persistence of pharmaceuticals and other organic compounds in chlorinated drinking water as a function of time. Sci Tot Environ 373 (1):240–249.

Golet EM, Alder AC, Hartmann A, Ternes T, Giger W (2001) Trace determination of fluoroquinolone antibacterial agents in urban wastewater by solid-phase extraction and liquid chromatography with fluorescence detection. Anal Chem 73:3632–3638.

Golet EM, Alder AC, Giger W (2002a) Environmental exposure and risk assessment of fluoroquinolone antibacterial agents in wastewater and river water of the Glatt Valley watershed, Switzerland. Environ SciTechnol 36(17): 3645–3651.

Golet EM, Strehler A, Alder AC, Giger W (2002b) Determination of fluoroquinolone antibacterial agents in sewage sludge and sludge-treated soil using accelerated solvent extraction followed by solid-phase extraction. Anal Chem 64 (21): 5455–5462.

Golet EM, Xifra I, Siegrist H, Alder AC, Giger W (2003) Environmental exposure assessment of fluoroquinolone antibacterial agents from sewage to soil. Environ Sci Technol 37(15): 3243–3249.

Gómez MJ, Martínez Bueno MJ, Lacorte S, Fernández-Alba AR, Agüera A (2006) Pilot survey monitoring pharmaceuticals and related compounds in sewage treatment plant located on the Mediterranean coast. Chemosphere 66(6): 993–1002.

Göbel A, McArdell CS, Suter MJF, Giger W (2004) Trace determination of macrolide and sulfonamide antimicrobials, a human sulfonamide metabolite, and trimethoprim in wastewater using liquid chromatography coupled to electrospray tandem mass spectrometry. Anal Chem 76:4756–4764.

Göbel A, Thomsen A, McArdell CS, Joss A, Giger W (2005) Occurrence and sorption behavior of sulfonamides, macrolides, and trimethoprim in activated sludge treatment. Environ Sci Technol 39:3981–3989.

Grayling T (1999) Guidelines for safe disposal of unwanted pharmaceuticals in and after emergencies. World Health Organization. Online http://www.who.int/water_sanitation_health/medicalwaste/unwantpharm.pdf.

Halling-Sørensen B, Nielsen SN, Lanzky PF, Ingerslev F, Lützhøft H-C, Jørgensen SE (1998) Ocurrence, fate and effects of pharmaceutical substances in the environment. Chemosphere 36 (2): 357–393.

Halling-Sørensen B, Sengeløv G, Tjørnelund J (2002) Toxicity of tetracyclines and tetracycline degradation products to environmentally relevant bacteria, including selected tetracycline-resistant bacteria. Arch Environ Contam Toxicol 42:263–271.

Hamscher G, Sczesny S, Höper H, Nau H (2002) Determination of persistent tetracycline residues in soil fertilized with liquid manure by high-performance liquid chromatography with electrospray ionization tandem mass spectrometry. Anal Chem 74:1509–1518.

Harries JE, Sheahan DA, Jobling S, Matthiessen P, Neal P, Sumpter JP, Tylor T, Zaman N (1997) Estrogenic activity in five United Kingdom rivers detected by measurement of vitellogenesis in caged male trout. Environ Toxicol Chem 16(3): 534–542.

Heberer T, Verstraeten IM, Meyer MT, Mechlinski A, Reddersen K (2001a) Occurrence and fate of pharmaceuticals during bank filtration - preliminary results from investigations in Germany and the United States. Water Resour Update 120:4–17.

Heberer T, Fuhrmann B, Schmidt-Bäumler K, Tsipi D, Koutsouba V, Hiskia A (2001b) Occurrence of Pharmaceutical Residues in Sewage, River, Ground and Drinking Water in Greece and Berlin (Germany). In: Daughton CG and Jones-Lepp T (eds), American Chemical Society, Symposium series 791, Washington D.C, pp 70–83.

Hilton MJ, Thomas KV (2003) Determination of selected human pharmaceutical compounds in effluent and surface water samples by high-performance liquid chromatography-electrospray tandem mass spectrometry. J Chromat A 1015:129–141.

Hirsch R, Ternes T, Haberer K, Kratz K-L (1999) Occurrence of antibiotics in the aquatic environment. Sci Tot Environ 225:109–118.

Hoffman BB (2001) Catecholamines, sympathomimetic drugs and adrenergenic receptor antagonists. In: Hardman JG, Limbird LE (eds) Goodman & Gilman's - The Pharmacological Basis of Therapeutics 10th Ed, McGraw-Hill, New York, USA, pp 215–268.

Hohenblum P, Gans O, Moche W, Scharf S, Lorbeer G (2004) Monitoring of selected estrogenic hormones and industrial chemicals in groundwaters and surface waters in Austria. Sci Tot Environ 333:185–193.

Holm JV, Rügge K, Bjerg PL, Christensen TH (1995) Occurrence and distribution of pharmaceutical organic compounds in the groundwater downgradient of a landfill (Grinsted, Denmark). Environ SciTechnol 29(5): 1415–1420.

Huang C-H and Sedlak DL (2001) Analysis of estrogenic hormones in municipal wastewater effluent and surface water using enzyme-linked immunosorbent assay and gas chromatography/ tandem mass spectrometry. Environ Toxicol Chem 20 (1): 133–139.

Huber MM, Ternes TA, Von Gunten U (2004) Removal of estrogenic activity and formation of oxidation products during ozonation of 17a-ethinylestradiol. Environ Sci Technol 38 (19): 5177–5186.

Huber MM, Göbel A, Joss A, Hermann N, Löffler D, McArdell CS, Ried A, Siegrist H, Ternes T, Von Gunten U (2005) Oxidation of pharmaceuticals during ozonation of municipal wastewater effluents: a pilot study. Environ Sci Technol 39(11): 4290–4299.

Ingerslev F and Halling-Sørensen B (2000) Biodegradability properties of sulfonamides in activated sludge. Environ Toxicol Chem 19:2467–2473.

Ingerslev F and Halling-Sørensen B (2001) Biodegradability of metronidazole, olaquindox, and tylosin and formation of tylosin degradation products in aerobic soil-manure slurries. Ecotoxicol Environ Saf 48(3): 311–320.

Jacobsen AM, Halling-Sørensen B, Ingerslev F, Hansen SH (2004) Simultaneous extraction of tetracycline, macrolide and sulfonamide antibiotics from agricultural soils using pressurized liquid extraction, followed by solid-phase extraction and liquid chromatography - tandem mass spectrometry. J Chromat A 1038:157–170.

Jjemba P (2006) Excretion and ecotoxicity of pharmaceutical and personal care products in the environment. Ecotoxicol Environ Saf 63(1): 113–130.

Jones OAH, Voulvoulis N, Lester JN (2002) Aquatic environmental assessment of the top 25 English prescription pharmaceuticals. Water Res 36:5013–5022.

Jones OAH, Voulvoulis N, Lester JN (2007) The occurrence and removal of selected pharmaceutical compounds in a sewage treatment works utilizing activated sludge treatment. Environl Pollut 145(3): 738–744.

Joss A, Andersen H, Ternes T, Richle PR, Siegrist H (2004) Removal of estrogens in municipal wastewater treatment under aerobic and anaerobic conditions: consequences for plant optimization. Environ Sci Technol 38(11): 3047–3055.

Joss A, Keller E, Alder AC, Göbel A, McArdell CS, Ternes T, Siegrist H (2005) Removal of pharmaceuticals and fragrances in biological wastewater treatment. Water Res 39:3139–3152.

Jørgensen SE and Halling-Sørensen B (2000) Drugs in the Environment. Chemosphere 40:691–699.

Kah M, Brown C (2006) Adsorption of ionisable pesticides in soils. Rev Environ Contam Toxicol 188:149–217.

Karthikeyan KG and Bleam WF (2003) Occurrence of antibiotics in wastewater effluents and their mobility in soils: a case study for Wisconsin. Final Project Report submitted to Wisconsin Department of Natural Resources and Wisconsin Department of Agriculture, Trade, and Consumer Protection. Online http://www.dnr.state.wi.us/org/water/dwg/gw/research/reports/169.pdf.

Kay P, Blackwell P, Boxall ABA (2005) Column studies to investigate the fate of veterinary antibiotics in clay soils following slurry application to agricultural land. Chemosphere 60:497–507.

Kim S, Eichhorn P, Jensen JN, Weber AS, Aga DS (2005) Removal of antibiotics in wastewater: effect of hydraulic and solid retention times on the fate of tetracycline in the activated sludge process. Environ Sci Technol 39(15): 5816–5823.

Kinney CA, Furlong ET, Zaugg SD, Burkhardt MR, Werner SL, Cahill JD, Jorgensen GR (2006) Survey of organic wastewater contaminants in biosolids destined for land application. Environ Sci Technol 40 (23):7207–7215.

Kirby MF, Bignell J, Brown E, Craft JA, Davies I, Dyer RA, Feist SW, Joines G, Mathiessen P, Megginson C, Robertson FE, Robinson C (2003) The presence of morphologically intermediate papilla syndrome in United kingdom populations of sand goby (*Pomatoschistus* spp.): endocrine disruption? Environ Toxicol Chem 22:239–251.

Kolpin DW, Furlong ET, Meyer MT, Thurman EM, Zaugg SD, Barber LB, Buxton HT (2002) Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams 1999–2000: a national reconnaissance. Environ Sci Technol 36:1202–1211.

Koutsouba V, Heberer T, Fuhrmann B, Schmidt-Baumler K, Tsipi D, Hiskia A (2003) Determination of polar pharmaceuticals in sewage water of Greece by gas chromatography-mass spectrometry. Chemosphere 51:69–75.

Kühne M, Ihnen D, Möller G, Agthe O (2000) Stability of tetracycline in water and liquid manure. J Vet Med A 47:379–384.

Kümmerer K, Al-Ahmad A, Mersch-Sundermann V (2000) Biodegradability of some antibiotics, elimination of the genotoxicity and affection of wastewater bacteria in a simple test. Chemosphere 40:701–710.

Kümmerer K (2001) Drugs in the environment: emission of drugs, diagnostic aids and disinfectants into wastewater by hospitals in relation to other sources - a review. Chemosphere 45:957–969.

Kümmerer K (2004) Pharmaceuticals in the Environment: Sources, Fate, Effects and Risks 2nd Ed. Springer, New York, pp. 3–23.

La Guardia MJ, Hale RC, Harvey EP, Bush EO, Mainor TM, Gaylor MO (2004) Organic contaminants of emerging concern in land-applied sewage sludge (biosolids). J Residuals Sci Technol 1:111–122.

Lalumera GM, Calamari D, Galli P, Castiglioni S, Crosa G, Fanelli R (2004) Preliminary investigation on the environmental occurrence and effects of antibiotics used in aquaculture in Italy. Chemosphere 54:661–668.

Lam MW, Young C, Brain RA, Johnson DJ, Hanson MA, Wilson CJ, Richards SM, Solomon KR, Mabury SA (2004) Aquatic persistence of eight pharmaceuticals in a microcosm study. Environ Toxicol Chem 23:1431–1440.

Langenkamp H, Part P (2001) Organic contaminants in sewage sludge for agricultural use. Erhardt W, Prüeß A (eds) European Commission. Online http://ec.europa.eu/environment/waste/sludge/pdf/organics_in_sludge.pdf.

Larsen TA, Lienert J, Joss A, Siegrist H (2004) How to avoid pharmaceuticals in the aquatic environment. J Biotechnol 113:295–304.

Larsson J, Pedro C, Paxeus N (2007) Effluent from drug manufactures contains extremely high levels of pharmaceuticals. J Hazard Mater 148:751–755.

Latch DE, Stender BL, Packer JL, Arnold WA, McNeill K (2003) Photochemical fate of pharmaceuticals in the environment: cimetidine and ranitidine. Environ Sci Technol 37:3342–3350.

Lindberg RH, Wennberg P, Johansson MI, Tysklind M, Andersson BAV (2005) Screening of human antibiotic substances and determination of weekly mass flows in five sewage treatment plants in Sweden. Environ Sci Technol 39:3421–3429.

Lindberg RH, Olofsson U, Rendahl P, Johansson MI, Tysklind M, Andersson BAV (2006) Behavior of fluoroquinolones and trimethoprim during mechanical, chemical, and active sludge treatment of sewage water and digestion of sludge. Environ Sci Technol 40:1042–1048.

Lindqvist N, Tuhkanen T, Kronberg L (2005) Occurrence of acidic pharmaceuticals in raw and treated sewage and in receiving waters. Water Res 39:2219–2228.

López de Alda MJ, Gil A, Paz E, Barceló D (2002) Occurrence and analysis of estrogens and progestogens in river sediments by liquid chromatography- electrospray-mass spectrometry. Analyst 127:1299–1304.

Löffler D, Römbke J, Meller M, Ternes T (2005) Environmental fate of pharmaceuticals in water/sediment systems. Environ Sci Technol 39:5209–5218.

Macrolide antibiotics (2000) In: An A-Z of Medicinal Drugs. Oxford University Press 2000. Oxford Reference online. Oxford University Press. York University (accessed 18 January 2007), online-http://www.oxfordreference.com/views/ENTRY.html?subview = Main&entry = t61.e2291.

Mahley RW, Bersot TP (2001) Drug therapy for hypercholesterolemia and dyslipidemia. In: Hardman JG, Limbird LE (eds) Goodman & Gilman's - The Pharmacological Basis of Therapeutics 10th Ed, McGraw-Hill, New York, USA, pp 971–1002.

Martinovic D, Hogarth WT, Jones RE, Sorensen PW (2007) Environmental estrogens suppress hormones, behavior, and reproductive fitness in male fathead minnows. Environ Toxicol Chem 26:271–278.

McGechan MB and Lewis DR (2002) Soil and water: transport of particulate and colloid-sorbed contaminants through soil, part 1: general principles. Biosyst Eng 83:255–273.

McNamara JO (2001) Drugs effective in the therapy of the epilepsies. In: Hardman JG, Limbird LE (eds) Goodman & Gilman's - The Pharmacological Basis of Therapeutics 10th Ed, McGraw-Hill, New York, USA, pp 521–548.

Metcalfe C, Miao X-S, Koenig BG, Struger J (2003) Distribution of acidic and neutral drugs in surface waters near sewage treatment plants in the lower Great Lakes, Canada. Environ Toxicol Chem 22:2881–2889.

Miao X-S, Bishay F, Chen M, Metcalfe C (2004) Occurrence of antimicrobials in the final effluents of wastewater treatment plants in Canada. Environ Sci Technol 38:3533–3541.

Miao X-S, Yang J-J, Metcalfe C (2005) Carbamazepine and its metabolites in wastewater and in biosolids in a municipal wastewater treatment plant. Environ Sci Technol 39:7469–7475.

Nowara A, Burhenne J, Spiteller M (1997) Binding of fluoroquinolone carboxylic acid derivatives to clay minerals. J Agric Food Chem 45:1459–1463.

Oaks JL, Gilbert M, Virani MZ, Watson RT, Meteyer CU, Rideout BA, Shivaprasad HL, Ahmed S, Chaudhry MJ, Arshad M, Mahmood S, Ali A, Khan AA (2004) Diclofenac residues as the cause of vulture population decline in Pakistan. Nature 427:630–633.

Oppel J, Broll G, Löffler D, Römbke J, Meller M, Ternes T (2004) Leaching behaviour of pharmaceuticals in soil-testing-systems: a part of an environmental risk assessment for groundwater protection. Sci Tot Environ 328:265–273.

Öllers S, Singer HP, Fässler P, Müller SR (2001) Simultaneous quantification of neutral and acidic pharmaceuticals and pesticides at the low - ng/L level in surface and waste water. J Chromat A 911:225–234.

Packer JL, Werner J.J, Latch DE, McNeill K, Arnold W (2003) Photochemical fate of pharmaceuticals in the environment: naproxen, diclofenac, clofibric acid, and ibuprofen. Aquat Sci 65:342–351.

Parrot JL, Blunt B (2005) Life-cycle exposure of fathead minnows (*Pimephales promelas*) to an ethinylestradiol concentration below 1 ng/L reduces egg fertilization success and demasculinizes males. Environ Toxicol 20:131–141.

Pascoe D, Karntanut W, Muller CT (2003) Do pharmaceuticals affect freshwater invertebrates? A study with the cnidarian *Hydra vulgaris*. Chemosphere 51:521–528.

Pedersen JA, Soliman M, Suffet IHM (2005) Human pharmaceuticals, hormones and personal care product ingredients in runoff from agricultural fields irrigated with treated wastewater. J Agric Food Chem 53:1625–1632.

Petri WA (2001a) Antimicrobial agents: penicillins, cephalosporins, and other β-lactam antibiotics. In: Hardman JG, Limbird LE (eds) Goodman & Gilman's - The Pharmacological Basis of Therapeutics 10th Ed, McGraw-Hill, New York, USA, pp 1189–1218.

Petri WA (2001b) Antimicrobial agents: sulfonamides, trimethoprim- sulfamethoxazole, quinolones, and agents for urinary tract infections. In: Hardman JG, Limbird LE (eds) Goodman & Gilman's - The Pharmacological Basis of Therapeutics 10th Ed, McGraw-Hill, New York, USA, pp 1171–1188.

Petrovic M, Gonzalez S, Barceló D (2003) Analysis and removal of emerging contaminants in wastewater and drinking water. Trends Anal Chem 22:685–696.

Pignatello JJ (1998) Soil organic matter as a nanoporous sorbent of organic pollutants. Adv Colloid Interface Sci 76–77:445–467.

POSEIDON project (EVK1-CT-2000-00047) 2005. Assessment of technologies for the removal of pharmaceuticals and personal care products in sewage and drinking water facilities to improve the indirect potable water reuse. Final Report, http://grdc.bafg.de/servlet/is/2888/.
Pouliquen H, Le Bris H (1996) Sorption of oxolinic acid and oxytetracycline to marine sediments. Chemosphere 33:801–815.
Quinn B, Gagné F, Blaise C (2008) An investigation into the acute and chronic toxicity of eleven pharmaceuticals (and their solvents) found in wastewater effluent on the cnidarian, Hydra attenuate. Sci Total Environ 389:306–314.
Quinolones (2000) In: An A-Z of Medicinal Drugs. Oxford University Press 2000. Oxford Reference online. Oxford University Press. York University (accessed 18 January 2007), online http://www.oxfordreference.com/views/ENTRY.html?subview = Main&entry = t61.e3196.
Rabølle M and Spliid NH (2000) Sorption and mobility of metronidazole, olaquindox, oxytetracycline and tylosin in soil. Chemosphere 40:715–722.
Reddersen K, Heberer T, Dünnbier U (2002) Identification and significance of phenazone drugs and their metabolism in ground- and drinking water. Chemosphere 49:539–544.
Renew JE, Huang C-H (2004) Simultaneous determination of fluoroquinolone, sulfonamide, and trimethoprim antibiotics in wastewater using tandem solid phase extraction and liquid chromatography-electrospray mass spectrometry. J Chromat A 1042:113–121.
Richardson ML, Bowron JM (1985) The fate of pharmaceutical chemicals in the aquatic environment. J Pharm Pharmacol 37:1–12.
Roberts LJ, Morrow JD (2001) Analgesic-antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In: Hardman JG, Limbird LE (eds) Goodman & Gilman's - The Pharmacological Basis of Therapeutics 10th Ed, McGraw-Hill, New York, USA, pp 687–732.
Rogers HR (1996) Sources, behaviour and fate of organic contaminants during sewage treatment and in sewage sludges. Sci Total Environ 185:3–26.
Sacher F, Lange FT, Brauch H-J, Blankenhorn I (2001) Pharmaceuticals in groundwaters. Analytical methods and results of a monitoring program in Baden-Württemberg, Germany. J Chromat A 938:199–210.
Sanders-Bush E. and Mayer SE (2001) 5-Hydroxytryptamine (serotonin): receptor agonists and antagonists. In: Hardman JG, Limbird LE (eds) Goodman & Gilman's - The Pharmacological Basis of Therapeutics 10th Ed, McGraw-Hill, New York, USA, pp 269–290.
Scheytt T, Grams S, Rejman-Rasinski E, Heberer T, Stan H-J (2001) Pharmaceuticals in groundwater: clofibric acid beneath sewage farms south of Berlin, Germany. In: Daughton CG and Jones-Lepp T (eds), American Chemical Society, Symposium series 791, Washington D.C, pp 84–99.
Scheytt T, Mersmann P, Lindstädt R, Heberer T (2005) Determination of sorption coefficients of pharmaceutically active substances carbamazepine, diclofenac, and ibuprofen, in sandy sediments. Chemosphere 60:245–253.
Schlüsener MP and Bester K (2006) Persistence of antibiotics such as macrolides, tiamulin and salinomycin in soil. Environ Pollut 143:565–571.
Schwab BW, Hayes EP, Fiori JM, Mastrocco FJ, Roden NM, Cragin D, Meyerhoff RD, D'Aco VJ, Anderson PD (2005) Human pharmaceuticals in US surface waters: A human health risk assessment. Regul Toxicol Pharmacol 42(3):296–312.
Sedlak DL and Pinkston KE (2001) Factors affecting the concentrations of pharmaceuticals released to the aquatic environment. Water Resour Update 120:56–64.
Selective serotonin reuptake inhibitor (2006) In: A dictionary of Psychology. Colman, A.M. (ed.) Oxford University Press 2006. Oxford Reference online. Oxford University Press. York University (accessed 18 January 2007) http://www.oxfordreference.com/views/ENTRY.html?subview = Main&entry = t87.e7424.

Servos MR, Bennie DT, Burnison BK, Jurkovic A, McInnis R, Neheli T, Schnell A, Seto P, Smyth SA, Ternes T (2005) Distribution of estrogens 17 beta-estradiol and estrone, in Canadian municipal wastewater treatment plants. Sci Total Environ 336(1–3):155–170.

Skadsen JM, Rice BL, Meyering DJ (2004) The occurrence and fate of pharmaceuticals, personal care products and endocrine disrupting compounds in a municipal water use cycle: a case study in the city of Ann Arbor. Water Utilities and Fleis & VandenBrink Engineering, Inc., City of Ann Arbor.

Snyder S, Wert E, Rexing DJ, Zegers RE, Drury DD (2006) Ozone oxidation of endocrine disruptors and pharmaceuticals in surface water and wastewater. Ozone Sci Eng 28:445–460.

Stackelberg PE, Furlong ET, Meyer MT, Zaugg SD, Henderson AK, Reissman DB (2004) Persistence of pharmaceutical compounds and other organic wastewater contaminants in a conventional drinking-water-treatment plant. Sci Total Environ 329:99–113.

Stackelberg PE, Gibs J, Furlong ET, Meyer M, Zaugg SD, Lippincott RL (2007) Efficiency of conventional drinking-water-treatment processes in removal of pharmaceuticals and other organic compounds. Sci Total Environ 377:255–272.

Stanley JK, Ramirez AJ, Chambliss CK, Brooks BW (2007) Enantiospecific sublethal effects of the antidepressant fluoxetine to a model aquatic vertebrate and invertebrate. Chemosphere 69:9–16.

Steger-Hartmann T, Kümmerer K, Schecker J (1996) Trace analysis of the antineoplastics ifosfamide and cyclophosphamide in sewage water by two-step solid-phase extraction and gas chromatography - mass spectrometry. J Chromat A 726:179–184.

Stumpf M, Ternes T, Wilken R-D, Rodrigues SV, Baumann W (1999) Polar drug residues in sewage and natural waters in the state of Rio de Janeiro, Brazil. Sci Total Environ 225:135–141.

Syracuse Research Corporation, Phys Prop Database (2004) – online www.syrres.com/esc/physdemo.htm.

Tauxe-Wuersch A, De Alencastro LF, Grandjean D, Tarradellas J (2005) Occurrence of several acidic drugs in sewage treatment plants in Switzerland and risk assessment. Water Res 39:1761–1772.

Ter laak TL (2005) Sorption to soil of hydrophobic and ionic organic compounds: measurement and modelling. Ph.D. Dissertation (online), Utrecht University, The Netherlands, September 2005
http://igitur-archive.library.uu.nl/dissertations/2006-0529-200329/index.htm.

Ter Laak TL, Gebbink W, Tolls J (2006) The effect of pH and ionic strength on the sorption of sulfachloropyridizine, tylosin, and oxytetracycline to soil. Environ Toxicol Chem 25:904–911.

Ternes T (1998) Occurrence of drugs in German sewage treatment plants and rivers. Water Res 32:3245–3260.

Ternes T, Stumpf M, Mueller J, Haberer K, Wilken R-D, Servos M. (1999) Behaviour and occurrence of estrogens in municipal sewage treatment plants - I. investigations in Germany, Canada and Brazil. Sci Total Environ 225:81–90.

Ternes T, Hirsch R (2000) Occurrence and behavior of X-ray contrast media in sewage facilities and the aquatic environment. Environ Sci Technol 34:2741–2748.

Ternes T (2001a) Pharmaceuticals and Metabolites as Contaminants of the Aquatic Environment. In: Daughton CG and Jones-Lepp T (eds), American Chemical Society, Symposium series 791, Washington D.C, pp 39–54.

Ternes T, Bonerz M, Schmidt T (2001b) Determination of neutral pharmaceuticals in wastewater and rivers by liquid chromatography - electrospray tandem mass spectrometry. J Chromat A 938:175–185

Ternes TA, Andersen H, Gilberg D, Bonerz M (2002a) Determination of estrogens in sludge and sediments by liquid extraction and GC/MS/MS. Anal Chem 74:3498–3504.

Ternes T, Meisenheimer M, McDowell D, Sacher F, Brauch H-J, Haist-Gulde B, Preuss G, Wilme U, Zulei-Seibert N (2002b) Removal of pharmaceuticals during drinking water treatment. Environ Sci Technol 36:3855–3863.

Ternes T, Stüber J, Herrmann N, McDowell D, Ried A, Kampmann M, Teiser B (2003) Ozonation: a tool for removal of pharmaceuticals, contrast media and musk fragrances from wastewater? Water Res 37:1976–1982.

Ternes T, Joss A, Siegrist H (2004a) Scrutinizing pharmaceuticals and personal care products in wastewater treatment. Environ Sci Technol 38:393A–398A.

Ternes T, Hermann N, Bonerz M, Knacker T, Siegrist H, Joss A (2004b) A rapid method to measure the solid-water distribution coefficient (Kd) for pharmaceuticals and musk fragrances in sewage sludge. Water Res 38:4075–4084.

Ternes T, Bonerz M, Herrmann N, Teiser B, Andersen HR (2007) Irrigation of treated wastewater in Braunschweig, Germany: an option to remove pharmaceuticals and musk fragrances. Chemosphere 66:894–904.

Tetracyclines (2000) In: An A-Z of Medicinal Drugs. Oxford University Press 2000. Oxford Reference online. Oxford University Press. York University (accessed 18 January 2007), online http://www.oxfordreference.com/views/ENTRY.html?subview=Main&entry=t61.e3673.

Thiele-Bruhn S (2003) Pharmaceutical antibiotic compounds in soils - a review. J Plant Nut Soil Sci 166:145–167.

Thiele-Bruhn S, Seibicke T, Schulten H-R, Leinweber P (2004) Sorption of sulfonamide pharmaceutical antibiotics on whole soils and particle-size fractions. J Environ Qual 33(4):1331–1342.

Thomas KV and Hilton MJ (2004) The occurrence of selected human pharmaceutical compounds in UK estuaries. Mar Pollut Bull 49:436–444.

Tixier C, Singer HP, Oellers S, Müller SR (2003) Occurrence and fate of carbamazepine, clofibric acid, diclofenac, ibuprofen, ketoprofen, and naproxen. Environ Sci Technol 37:1061–1068.

Tolls J (2001) Sorption of veterinary pharmaceuticals in soils: a review. Environ Sci Technol 35:3397–3406.

Topp E, Hendel JG, Lu Z, Chapman R (2006) Biodegradation of caffeine in agricultural soils. Can J Soil Sci 86(2–3): 533–544.

Topp E, Monteiro SC, Beck A, Coelho BB, Boxall ABA, Duenk PW, Kleywegt S, Lapen DR, Payne M, Sabourin L, Li H, Metcalfe CD (2008a) Runoff of pharmaceuticals and personal care products following application of biosolids to an agricultural field. Sci Total Environ 396:52–59.

Topp E, Hendel J, Lapen D, Chapman R (2008b) Fate of the non-steroidal anti-inflammatory drug naproxen in agricultural soil receiving liquid municipal biosolids. Environ Toxicol Chem (in press).

Urase T, Kawaga C, Kikuta T (2005) Factors affecting removal of pharmaceutical substances and estrogens in membrane separation bioreactors. Desalination 178:107–113.

Velagaleti R, Burns PK, Gill M, Prothro J (2002) Impact of current good manufacturing practices and emission regulations and guidances on the discharge of pharmaceutical chemicals into the environment from manufacturing, use, and disposal. Environ Health Perspect 110:213–220.

Vieno NM, Tuhkanen T, Kronberg L (2006) Analysis of neutral and basic pharmaceuticals in sewage treatment plants and in recipient rivers using solid phase extraction and liquid chromatography - tandem mass spectrometry detection. J Chromat A 1134(1–2):101–111.

Webb S, Ternes T, Gibert M, Olejniczak K (2003) Indirect human exposure to pharmaceuticals via drinking water. Toxicol Lett 142:157–167.

Weigel S, Kuhlmann J, Hühnerfuss H (2002) Drugs and personal care products as ubiquitous pollutants: occurrence and distribution of clofibric acid, caffeine and DEET in the North Sea. Sci Total Environ 295:131–141.

Weigel S, Berger U, Jensen E, Kallenborn R, Thoresen H, Hühnerfuss H (2004) Determination of selected pharmaceuticals and caffeine in sewage and seawater from Tromsø/Norway with emphasis on ibuprofen and its metabolites. Chemosphere 56:583–592.

Westerhoff P, Yoon Y, Snyder S, Wert E (2005) Fate of endocrine-disruptor, pharmaceutical, and personal care product chemicals during simulated drinking water treatment. Environ Sci Technol 39:6649–6663.

Wiegel S, Aulinger A, Brockmeyer R, Harms H, Löffler J, Reincke H, Schmidt R, Stachel B, von Tümpling W, Wanke A (2004) Pharmaceuticals in the river Elbe and its tributaries. Chemosphere 57:107–126.

Wilkinson GR (2001) Pharmacokinetics: the dynamic of drug absorption, distribution and elimination. In: Hardman JG, Limbird LE (eds) Goodman & Gilman's - The Pharmacological Basis of Therapeutics 10th Ed, McGraw-Hill, New York, USA, pp 3–30.

Williams RT (2005) Human health pharmaceuticals in the environment: an introduction. In: Williams RT (ed) Human pharmaceuticals: assessing the impacts on aquatic ecosystems, Allen Press/ACG Publishing, pp 1–45.

Xia K, Bhandari A, Das K, Pillar G (2005) Occurrence and fate of pharmaceuticals and personal care products (PPCPs) in biosolids. J Environ Qual 34:91–104.

Yang S, Carlson KH (2004a) Routine monitoring of antibiotics in water and wastewater with a radioimmunoassay technique. Water Res 38:3155–3166.

Yang S and Carlson KH (2004b) Solid-phase extraction-high performance liquid chromatography- ion trap mass spectrometry for analysis of trace concentrations of macrolide antibiotics in natural and waste water matrices. J Chromat A 1038:141–155.

Yu JT, Bouwer EJ, Coelhan M (2006) Occurrence and biodegradability studies of selected pharmaceuticals and personal care products in sewage effluent. Agric Water Manag 86 (1–2): 72–80.

Zepp RG, Baughman GL, Schlotzhauer PF (1981) Comparison of photochemical behavior of various humic substances in water: I. Sunlight induced reactions of aquatic pollutants photosensitized by humic substances. Chemosphere 10:109–117.

Zuccato E, Castiglioni S, Fanelli R (2005a) Identification of the pharmaceuticals for human use contaminating the Italian aquatic environment. J Hazard Mater 122:205–209.

Zuccato E, Chiabrando C, Castiglioni S, Calamari D, Bagnati R, Schiarea S, Fanelli R (2005b) Cocaine in surface waters: a new evidence-based tool to monitor community drug abuse. Environ Health: A Global Access Science Source 4:14

Zwiener C, Frimmel FH (2000) Oxidative treatment of pharmaceuticals in water. Water Res 34:1881–1885.

Chemistry and Environmental Fate of Fenoxycarb

Jonathan J. Sullivan

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1 Introduction

The insecticide fenoxycarb (ethyl [2-(4-phenoxyphenoxy)ethyl]carbamate) is a polycyclic, non-neurotoxic carbamate juvenile hormone agonist (JHA) first developed, tested, and marketed by Hoffman-La Roche (R. Maag) in the 1980 s (Godfrey 1995). Fenoxycarb, defined by its mechanism of action, is classified as an insect growth regulator (IGR). It is a member of the carbamate class of insecticides, but does not function as an acetyl cholinesterase inhibitor as does conventional *N*-methyl and *N*-ethyl carbamates. Structurally, fenoxycarb is an aromatic phenoxy-based compound having a carbamate moiety at its

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polar end. However, in contrast to the early synthetic JHAs such as methoprene (1-methylethyl (2*E*,4*E*)-11-methoxy-3,7, 11-trimethyl-2,4-dodecadien-oate) and hydroprene (ethyl (2*E*,4*E*)-3,7,11-trimethyl-2,4-dodecadien-oate), the overall structural features of current JHAs (e.g., fenoxycarb and pyriproxyfen (2-[1-methyl-2-(4-phenoxyphenoxy)ethoxy] pyridine)) do not resemble the isoprenoid framework of the natural juvenile hormones (JHs). Nonetheless, both fenoxycarb and pyriproxyfen have pervasive JH-like effects as exemplified by their effective suppression of embryogenesis and adult formation in target organisms. The structures of the natural juvenile hormones and their synthetic analogs are shown in Figs. 1 and 2.

Regardless of their structural framework, none of the synthetic JHAs are directly toxic to target organisms as are conventional broad-spectrum insecticides. Rather, exposure leads to developmental abnormality, which in turn impairs the survival of the insect (CCME 2007). JHAs are unique in that they specifically target insects and generally have very low toxicity and reduced risks for non-target organisms. These insecticides have low mammalian and avian toxicity, but some JHAs affect crabs, shrimp, and other non-target aquatic invertebrates that molt, as well as bees and fish (Tatarazako et al. 2003; McKenney et al. 2004; Nates et al. 2000; Templeton et al. 1983; Verslycke et al. 2004; Campiche et al. 2006, Lee and Scott 1989). Fenoxycarb, for example, has been linked to honeybee brood damage at application rates as low as 140 g/ha (Tasei 2001). The compound is also considered moderately to highly toxic to fish with LC_{50s} ranging from 0.66 ppm for rainbow trout to 1.5 ppm for carp (U.S. EPA 2000). Concerns about non-target impacts on these and other aquatic vertebrates and invertebrates, many of which are ecologically and economically important, have led to a number of restrictions on some JHA uses (Hajek 2004).

Fenoxycarb was the first JHA compound introduced to control agricultural pests (Miyamoto et al. 1993) and has shown JHA activities against a variety of insect orders including Lepidoptera, Coleoptera, Homoptera, Dictyoptera, Diptera, and Orthoptera. Because of its high activity and foliar stability, fenoxycarb is especially effective for the control of Lepidopteran pests in orchard and vine crops, e.g., codling moth (*Cydia pornonella* L.) and light brown apple moth (*Epiphyas postvittana* Walker; Grenier and Grenier 1993). Fenoxycarb is very active against fleas (Chamberlain and Becker 1977; Grenier and Grenier 1993), mosquitoes (Schaefer et al. 1987), and cockroaches (Evans et al. 1995, Reid et al. 1990). The LC50 values for the codling moth *Cydia pomonella* L and cat fleas *Ctenocephalides felis* exposed to fenoxycarb, for example, are reported to be 0.05 and 0.031 ppm, respectively (Charmillot and Fabre 2001; Rajapakse et al. 2002). Fenoxycarb has also been marketed for the control of various homopterous pests, particularly certain scale species attacking olive, citrus, and other fruit trees, e.g., the black scale, *Saissetia oleae*, and the Florida wax scale, *Ceroplastes floridensis*, which are major pests of citrus and olive (Eisa et al. 1991; Dhadialla et al. 1998). Fenoxycarb is one of several insecticides being used in California for the control of the Red Imported Fire Ant (*Solenopsis invicta*), a major agricultural, horticultural, and urban pest throughout the Southeastern and Southwestern United States (Eliahu et al. 2007). In some agricultural practices such as sericulture, the propensity of JHAs

JH-0

(2E,6E)-methyl 3,7-diethyl-9-((2S,3R)-3-ethyl-3-methyloxiran-2-yl)nona-2,6-dienoate

JH-I

(2E,6E)-methyl 7-ethyl-9-((2S,3R)-3-ethyl-3-methyloxiran-2-yl)-3-methylnona-2,6-dienoate

JH-II

(2E,6E)-methyl 9-((2S,3R)-3-ethyl-3-methyloxiran-2-yl)-3,7-dimethylnona-2,6-dienoate

JH-III

(2E,6E)-methyl 9-((S)-3,3-dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dienoate

4-Methyl JH-I

(2E,6E)-methyl 7-ethyl-9-((2S,3R)-3-ethyl-3-methyloxiran-2-yl)-3,4-dimethylnona-2,6-dienoate

JHB_3

(E)-methyl 5-(3-(2-(3,3-dimethyloxiran-2-yl)ethyl)-3-methyloxiran-2-yl)-3-methylpent-2-enoate

Fig. 1 Chemical structures of the six natural forms of juvenile hormone (JH-0, JH-I, JH-II, JH-III, JHB_3, 4-methyl-JH-I)

to preserve larval characteristics has been exploited to boost production. For example, the use of fenoxycarb and methoprene in sericulture has been shown to boost good cocoon yield. JHAs are routinely utilized for the improvement of silk production in the silkworm *Bombyx mori* (L) (Mamatha et al. 2008).

a) Fenoxycarb (CAS No. 72490-01-8)

Ethyl 2-(4-phenoxyphenoxy)ethylcarbamate

b) Methoprene (CAS No. 40596-69-8)

Isopropyl (E,E)-(RS)-11-methoxy-3,7,11-trimethyldodeca-2,4-dienoate

c) Hydroprene (CAS No. 41096-46-2)

Ethyl (E,E)-(RS)-3,7,11-trimethyldodeca-2,4-dienoate

d) Pyriproxyfen (CAS No. 95737-68-1)

4-phenoxyphenyl (RS)-2-(2-pyridyloxy)propyl ether

e) Kinoprene (CAS No. 42588-37-4)

Prop-2-ynyl (E,E)-(RS)-3,7,11-trimethyldodeca-2,4-dienoate

f) Triprene (CAS No. 40596-80-3)

S-ethyl(E,E)-(RS)-11-methoxy-3,7,11trimethyldodecadienethioate

g) Epofenonane (CAS No. 57342-02-6)

(±)–6,7-epoxy-3-ethyl-7-methylonyl 4-ethylphenyl ether

Fig. 2 Structure and IUPAC names of some common juvenile hormone agonists (JHAs)

Fenoxycarb is formulated as a general IGR for nurseries and greenhouse, container, and landscape ornamentals (Preclude®, Precision®), fire ant bait (Award®, Logic®, Polyon®), and as a component in mixed-pesticide products such as foggers and carpet sprays to control fleas. Fenoxycarb is a General Use Pesticide (GUP) by the U.S. EPA and labels for products containing it must bear the Signal Word CAUTION. The U.S. EPA has classified fenoxycarb as practically non-toxic (toxicity class IV). However, fenoxycarb is a U.S. EPA class B2 probable human carcinogen (U.S. EPA Office of Pesticide Programs 2007) and the California Office of Environmental Health Hazard Assessment (OEHHA) has included it on the list (Proposition 65) of cancer causing chemicals (California EPA 2008).

There is currently just one registered product containing fenoxycarb in California (Award® Fire Ant Bait), which has been approved for the control of fire ants in landscape maintenance, commercial, recreational, institutional or industrial areas, ornamental uses, and limited agricultural uses (e.g., citrus, apple, plum, cherry, avocado, peach). The product is applied to single mounds (1–3 level tablespoons per mound) and by broadcast (apply uniformly with ground equipment calibrated to give correct dosage [1–1.5 lb/A]). In 2006, less than 8 lb of fenoxycarb was applied in California, approximately 75% of which was applied on outdoor container plants and greenhouse flowers (6 lb). Public health and structural pest control uses each accounted for less than 0.10 lb (CDPR 2006). Because of its overall low toxicity to non-target species, fenoxycarb is considered to be suitable for integrated pest management (IPM) programs (UC Statewide IPM Program 2007). Fenoxycarb is one of several pesticide active ingredients recommended by the World Health Organization (WHO) for the control of such public health pests as cockroaches and fleas (WHO 2006).

2 Chemistry

2.1 Physicochemical and Chemodynamic Properties

Fenoxycarb (CAS No. 72490-01-8) is a colorless to white solid with a melting point of 53–54°C and a density greater than that of water (1.23 g/mL at 20°C). At ambient temperature (25°C) and a pH 7.55, fenoxycarb is sparingly soluble in water (7.9 mg/L), but is highly soluble in organic solvents such as hexane (400 g/L), toluene (630 g/L), and acetone (770 g/L). It is non-corrosive and has no discernible acidic or basic characteristics. Additional physicochemical characteristics are summarized in Table 1.

If discharged into the air, a vapor pressure of 8.67×10^{-4} mPa (25°C) and estimated Henry's law constant of 3.3×10^{-5} Pa m^3/mol indicate that fenoxycarb is only slightly volatile and will not dissipate appreciably into the atmosphere via mass transfer across the air–water or air/soil pore water interface.

Table 1 Physicochemical properties of technical fenoxycarb[a]

Chemical Abstracts Service (CAS) registry number	72490-01-8
Molecular wt (g mol^{-1})	301.3
Molecular formula	$C_{17}H_{19}NO_4$
Chemical name	
IUPAC	ethyl 2-(4-phenoxyphenoxy)ethylcarbamate
CAS	ethyl [2-(4-phenoxyphenoxy)ethyl]carbamate
Color and physical state	Colorless to white crystals
Odor	Faint characteristic odor
Melting point	53–54°C
Density	1.23 g/mL at 20°C
Vapor pressure	8.67×10^{-4} mPa at 25°C
Henry's law constant	3.3×10^{-5} Pa m^3 mol^{-1}
Ultraviolet (UV) – visible spectrum	λ_{max} (in water) = 270 nm
Solubility (g/kg)	
Water	7.9 mg/L at pH 7.55–7.84, 25°C
n-Hexane	400 g/L
n-Octanol	130 g/L
Ethanol	510 g/L
Toluene	630 g/L
Acetone	770 g/L
n-Octanol–water partition coefficient (K_{ow})	log K_{ow} = 4.07 at 25°C

[a]Data from Tomlin (2006)

Estimations based on a gas/particle partition model for semi-volatile compounds suggest that fenoxycarb will exist in the atmosphere primarily as a particulate and that particulate-phase fenoxycarb will be removed from the air by wet and dry deposition (Bidleman 1988). It is predicted that at 25̊C vapor-phase fenoxycarb will degrade rapidly with photochemically produced hydroxyl radical in the atmosphere at a rate of 6.53×10^{-11} cm^3/molecules sec (EPI Suite 2004). The average half-life for this reaction is estimated to be 5.9 hr, based on a mean atmospheric hydroxyl radical concentration of 5×10^5 molecules/cm^3 (Atkinson 1985).Vapor-phase fenoxycarb is thus expected to be a minor exposure hazard and minimally toxic when inhaled; hence, the potential for non-occupational exposure by inhalation is unlikely to be significant.

Fenoxycarb has a moderately strong affinity for soil and sediment surfaces and consequently is considered a low risk to contaminate surface and ground waters from agricultural sources. The quantitative assessment of this behavior was determined in a series of laboratory and field studies aimed at defining the mobility of fenoxycarb and its major degradates in the context of its partitioning characteristics. Spare (1995a,b) conducted two batch-equilibrium soil adsorption studies with radiolabeled β-phenyl-^{14}C-fenoxycarb (**1b**) (see Fig. 3

(1a)
[α-Phenyl-^{14}C]-fenoxycarb

(1b)
[β-Phenyl-^{14}C]-fenoxycarb

(2)
ethyl 2-(4-hydroxyphenoxy)ethylcarbamate

(3)
ethyl 2-(4-(4-hydroxyphenoxy)phenoxy)ethylcarbamate

(4)
hydroxymethyl 2-(4(4 hydroxyphenoxy)phenoxy)ethylcarbamate

(5)
4-phenoxyphenol

(6)
benzene-1,2,4-triol

(7)
hydroquinone

(8)
catechol

(9)
phenol

(10)
ethyl 2-(4-(3,4-dihydroxyphenoxy)phenoxy)ethylcarbamate

(11)
2-(4-phenoxyphenoxy)ethanamine

(12)
4-(4-(2-aminoethoxy)phenoxy)phenol

(13)
Substituted phenoxybenzenes

Fig. 3 Structures of fenoxycarb (**1a** = α-label, **1b** = β-label) and its degradation products

for names and structures of major fenoxycarb degradation and metabolic products) and the fenoxycarb aqueous photolysis degradate [β-phenyl-^{14}C]-ethyl 2-(4-hydroxyphenoxy)ethyl-carbamate (**2**) to estimate their potential for soil mobility and aquatic dispersion. Using five representative agricultural soils

Table 2 Characterization of soils used for ^{14}C-fenoxycarb batch equilibrium and column-leaching mobility studies

Texture	Clay	Sand	Sandy loam	Silt loam	Loam
% Sand	21	89	65	25	45
% Silt	32	8	24	60	44
% Clay	47	3	11	15	11
% Organic matter	3.1	0.4	3.1	1.7	3.3
% Organic carbon	1.798	0.232	1.798	0.986	1.914
pH	6.6	6.0	7.7	6.7	6.8
Field capacity	35.9	4.7	15.5	27.1	24.3
Cation exchange capacity	33.4	3.5	14.9	14.1	21.4
Bulk density	1.06	1.54	1.25	1.14	1.15

(Table 2), the organic-carbon-normalized sorption coefficient (K_{OC}), sorption constant (K_D), and the exponent n, using the Freundlich isotherm, were determined. The experiments were continuously monitored by high-performance liquid chromatography (HPLC) and thin layer chromatography (TLC) to verify that no degradation of fenoxycarb and (**2**) transpired during the course of the studies. Based upon the results of these soil adsorption studies (Table 3), fenoxycarb is expected to have slight to low leaching potential if released to the soil; the reported organic carbon-based soil adsorption coefficients (K_{OC}) for fenoxycarb ranged from 1251 in sandy loam to 2599 in silt loam. These results were confirmed by subsequent column leaching studies wherein the mobility of radiolabeled fenoxycarb was determined to be limited and slow, with the majority of the applied radiocarbon (>91% of the applied dose) remaining in the top 12 cm of the sand, sandy loam, silt loam, and loam soils (Shepler 1995). In the clay soil, most of the applied radiocarbon (>92% of the applied dose) remained in the top 6 cm of soil. The leachates from sand, sandy loam, loam, silt loam, and clay columns contained an average of 0.39, 0.17, 0.17, 0.30, and 0.10% of applied radioactivity, respectively. Soil desorption data suggest that adsorption is effectively irreversible and that once bound to soils, fenoxycarb has little tendency to desorb. The fenoxycarb metabolite (**2**) was found to have

Table 3 Adsorption characteristics of the fenoxycarb and its major metabolite ethyl 2-(4-hydroxy-phenoxy)ethylcarbamate in five representative agricultural soils and one sediment[a]

	[β-Phenyl-^{14}C]-fenoxycarb (**1b**)[a]			Metabolite (**2**)[b]		
	K_D	K_{OC}	n	K_{OC}	K_D	n
Mississippi clay	46.7	2599	1.192	6.7	375	1.170
Maryland sand	4.4	1883	1.099	0.1	44	1.583
Maryland sandy loam	16.2	1639	1.040	31.3	3175	1.132
Maryland silt loam	22.5	1251	1.153	12.8	712	1.444
Washington loam	32.7	1710	1.146	7.9	414	1.208

[a]Data from Spare (1995a)
[b]Data from Spare (1995b).

moderate to very high mobility, with K_{OC} values ranging from 44 (sand) to 3175 (silt loam). However, corresponding monitoring tests indicated that (**2**) rapidly degrades microbially and is not a significant contamination risk for groundwater.

Although fenoxycarb has a high octanol/water partitioning coefficient (Log P = 4.07 at 25°C) and a high propensity to bioaccumulate, cumulative toxicological effects resulting from bioaccumulation are unlikely following short-term, intermittent exposures, because of its relatively short elimination half-life. Ellgehausen (1985) and Pryde and von der Muhll (1985) reported that ^{14}C-fenoxycarb residues accumulated in bluegill sunfish that were continuously exposed to fenoxycarb at 23 ± 0.09 mg/L and a mean temperature of 19.8 ± 0.03°C for 28 d under flow-through conditions; the resulting mean bioconcentration factors (BCF) were 138.9× for edible tissues, 439.6× for non-edible tissues, and 277.6× for whole fish. After a 2-wk depuration period, 98.4, 99.0, and 98.1% of accumulated residues had been eliminated from whole fish, edible parts, and non-edible parts, respectively. The depuration half-life of fenoxycarb ranged from 2.6 to 4.1 d. Consequently, considering its affinity for soil and sediment and its rapid biotic degradation and depuration half-lives, fenoxycarb is not expected to bioconcentrate in fish under environmentally relevant conditions. However, because it is toxic to fish and many aquatic invertebrates, commercial fenoxycarb product labels have precautionary statements warning that drift and runoff from treated areas may be hazardous to aquatic organisms and the product should not be applied directly to water.

2.2 Synthesis

The first synthetic juvenoids, e.g., hydroprene, methoprene and epofenonane, were derived from isoprene (2-methylbuta-1,3-diene). Since the early 1980s, in an effort to replace potentially labile moieties of JH with more stable functionalities, commercial juvenoids evolved from the isoprenoids to the polycyclic juvenoids, which were characterized by the presence of the 4-phenoxyphenyl group. The first juvenoid of the 4-phenoxyphenoxy series registered for practical use was fenoxycarb, followed by pyriproxyfen, a fenoxycarb derivative in which part of the aliphatic chain has been replaced by pyridyl oxyethylene (Fig. 2). The 4-phenoxyphenyl group is immediately recognizable as the alcohol moiety common to many synthetic pyrethroids, e.g., cypermethrin, deltamethrin, fenvalerate. Hence, fenoxycarb is composed of a carbamate function on one side of the molecule and a familiar pyrethroid moiety on the opposite side. The commercial preparation of fenoxycarb has been successfully used against various urban and field pests under the name Insegar (against orchard pests), Logic (fire ants), Torus (fleas, cockroaches), Pictyl (mosquitoes), and Varikill for many years (Sláma, 1999; Grenier and Grenier 1993).

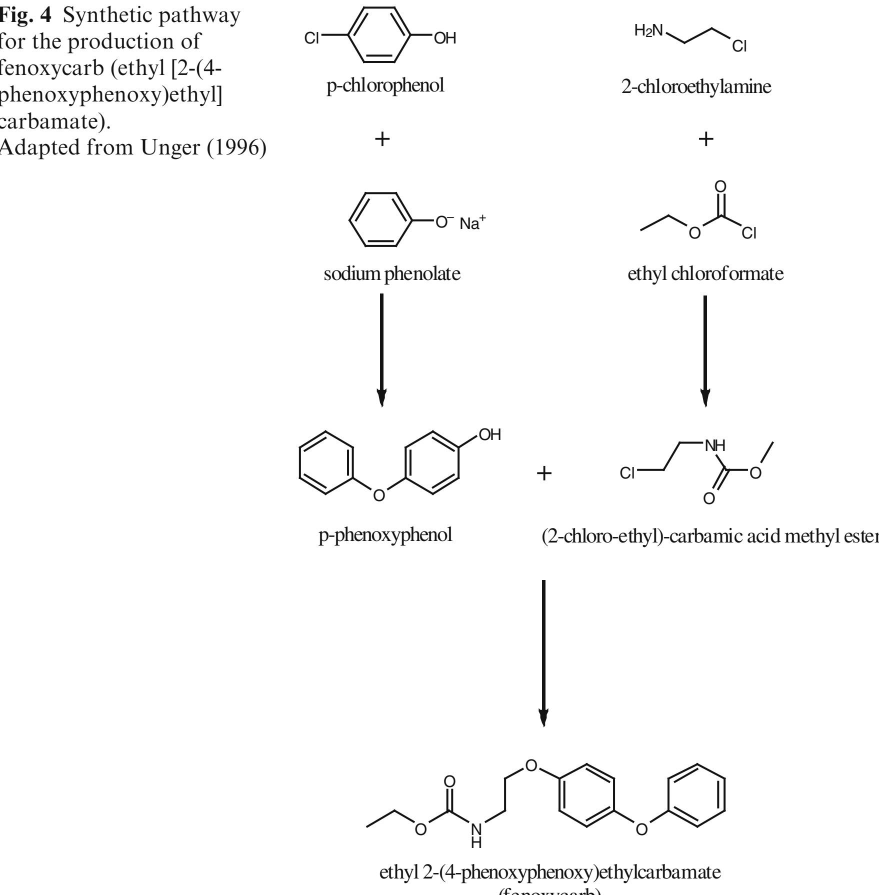

Fig. 4 Synthetic pathway for the production of fenoxycarb (ethyl [2-(4-phenoxyphenoxy)ethyl] carbamate). Adapted from Unger (1996)

Fenoxycarb is synthesized commercially by reacting the potassium salt of 4-phenoxyphenol with 4-phenoxyphenol with excess (2-chloro-ethyl)-carbamic acid methyl ester in toluene at ambient temperatures (Fig. 4). The precursor 4-phenoxyphenol is prepared via oxidative coupling with *p*-chlorophenol and phenolate ion in the presence of a copper catalyst. The electrophile (2-chloro-ethyl)-carbamic acid methyl ester is typically produced via the stoichiometric reaction of ethyl chloroformate and 2-chloroethylamine (Unger 1996). Technical fenoxycarb is typically produced in >97% yield and is a light brown lumpy solid that is stable under normal conditions.

2.3 Mode of Action of JHAs

There are six homologous structural forms of JH (JH-0, JH-I, JH-II, JH-III, JHB_3, 4-methyl-JH-I shown in Fig. 1), all of these forms have one or more

asymmetric (chiral) centers (although only the absolute configurations of JH-I and JH-III have been rigorously established). The morphogenetic activities of synthetic racemic samples of the JHs show that JH-1 has the highest biological activity against most insect species. JH-0, JH-I, JH-II, and 4-methyl JH-I appear to be restricted to the Lepidoptera, while JH-III is the most pervasive and has been found in all insect orders. JH-O and 4-methyl JH-I were isolated from the developing embryos of the tobacco hornworm, *Manduca sexta*, whereas Lepidoptera produce JH-I, JH-II, and JH-III. The bisepoxide JHB_3 is biosynthesized in vitro by the ring gland of third instar fruit fly larvae (*Drosophila melanogaster)*, but it is much less active than JH-III in bioassays on this species. Ordinarily, when sufficient growth has occurred, JH production ceases and triggers the molt to the adult stage (Godfrey 1995).

JHAs such as pyriproxyfen and fenoxycarb act in the same manner as JHs, but are much more chemically stable. Although these active JHAs bear little structural resemblance to JHs, their high stability allows them to compete for JH binding site receptors. Fenoxycarb acts on the endocrine system of insects by mimicking JH, disrupting transformation from egg to larva, larva to pupa, late nymph to reproductive adult, crawler to sessile insect (scale insects), or sucking larva to chewing larva (Hosmer et al. 1998). In insects, ecdysis (molting) and metamorphosis are controlled by two hormones, the steroid ecdysone and a group of acyclic sesquiterpenoids known collectively as JH. JH is produced and discharged by the corpus allatum, a gland at the base of the insect's brain. They are secreted into the hemolymph and transported by binding proteins to tissues, where they enter cells via diffusion. Ecdysone induces and regulates molting, but the character of the molt is mediated by JH. When JH is present, there is no differentiation in form. In its absence, ecdysone initiates the switching in gene expression necessary for metamorphosis, first to the pupa, then to the adult (Riddiford 1994, Zhou and Riddiford 2002). These biologically active components of the insect endocrine system are exclusive to insects (and some arthropods) and control many critical aspects of insect physiology and behavior. Therefore, disrupting these systems has profound and usually lethal effects in individual insects and on insect pest populations. Fenoxycarb kills eggs and larvae of numerous insect species (Masner et al. 1987). Since the egg is not usually exposed to high levels of JH until about halfway through embryonic development, its development is halted and the egg will not hatch. High levels of JHAs, when applied to later instars, cause the adult insect to maintain larval characteristics, and these insects generally cannot reproduce. Compared with conventional insecticides, IGRs do not exhibit quick knockdown in insects or cause mortality, but the long-term exposure to these compounds largely stops the population growth, i.e., they disrupt normal reproductive physiology and act as a method of birth control.

Fenoxycarb disrupts insect development by mimicking the action of JH and maintains the insect in an immature state. It inhibits ecdysone, thereby preventing molting and metamorphosis into adulthood, and involves certain ovicide and delayed larvicide–adulticide effects in various insect species. In some

species, such as the cat flea (*Ctenocephalides felis*), exposure to fenoxycarb has been shown to directly effect oogenesis, embryogenesis, metamorphosis, fecundity, and fertility (Marchiondo et al. 1990). Unlike methoprene, which does not affect 24-hr flea eggs, fenoxycarb is active throughout all stages of embryogenesis (Maddison et al. 2008). With social insects, such as ants and termites, the mode of action of fenoxycarb and other JHAs is more complex and not well understood. It may involve effects on morphogenesis, brood care, fertility and mortality of queens, and especially caste differentiation. These effects can lead to the slow decline and eventual death of the colony (Godfrey 1995). Exposure to fenoxycarb at molting produces deformed insects having mixed larval/pupal or larval/adult morphologies, and they disrupt reproductive physiology in adults to effectively serve as a method of birth control.

2.4 Environmental Endocrine Disruption: An Overview

Recent evidence suggests that numerous natural and synthetic chemicals may interfere with the endocrine system and produce adverse effects in humans, wildlife, fish or birds. Although at this time the evidence linking endocrine-disrupting chemicals to public health is largely putative, such chemicals have been shown to have adverse effects in certain wildlife species and in laboratory animals. Some of these animals serve as indicator species when assessing the environmental impact of endocrine-modulating chemicals. Some pesticides, particularly those designed and synthesized specifically to disrupt insect endocrine systems, i.e., IGRs, are now suspected of being endocrine disruptors. These pesticides include metamorphosis inhibitors (e.g., methoprene), anti-juvenile hormone agonists (e.g., precocene), chitin synthesis inhibitors (e.g., diflubenzuron), ecdysone agonists (e.g., tebufenozide), and molting disruptants (e.g., fenoxycarb). An endocrine disruptor is defined as an exogenous substance or mixture that alters function of the endocrine system and consequentially causes adverse health effects in an intact organism, its progeny, or a population or subpopulation (WHO/IPCS 2002). Endocrine disruption refers to a mechanism of toxicity that impedes normal hormonal communication between cells, tissues, and organs and may lead to a variety of detrimental reproductive, immune, and neurobehavioral health consequences. Recently, scientific concerns and public debate over potential adverse effects resulting from exposure to certain environmental chemicals thought to alter normal endocrine function in wildlife and humans have intensified. Apprehension over these chemical substances has been elicited by a general increase in observed adverse effects in some wildlife and fish populations, the increased incidence of certain endocrine-related human diseases, and laboratory exposure studies (McKinlay et al. 2008). Wildlife researchers have reported a range of effects in terns, gulls, harbor seals, bald eagles, beluga whales, lake trout, panthers, alligators, and other species attributed to exposure to endocrine-disrupting chemicals (Girard

2005). Some of the deleterious effects observed in aquatic organisms and wildlife that may be linked to endocrine-disrupting mechanisms include abnormal thyroid function in birds and fish; decreased fertility in birds, fish, shellfish, and mammals; decreased hatching success in fish, birds, and reptiles; demasculinization and feminization of fish, birds, reptiles, and mammals; defeminization and masculinization of fish and gastropods; and alteration of immune function in birds and mammals (Crisp et al. 1998). In human populations, adverse effects linked to exposure to endocrine disruptors include reproductive abnormalities (Garry 2004), birth defects (Baskin et al. 2001; Schreinemachers 2003), neural and behavioral function (Zala and Penn 2004), immune function, and certain cancers (Mather et al. 2002).

Based on the foregoing and other evidence, the US Congress passed the Food Quality Protection Act (FQPA 1996) and amendments to the Safe Drinking Water Act in 1996 (SDWA 1996); this legislation required EPA to initiate an Endocrine Disruptor Screening Program (EDSP) to screen pesticide chemicals and environmental contaminants for their potential to affect the endocrine systems of humans and wildlife. A short-time later, the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), a federal advisory committee, was formed to make recommendations on how to develop the screening and testing program. In 1998, the EDSTAC recommended that 87,000 chemicals in commercial use be considered for screening, including contaminants of human breast milk, phytoestrogens in soy-based infant formulas, pesticide/fertilizer mixes, disinfectant byproducts, and gasoline (U.S. EPA 1998). Estrogen, androgen, and thyroid effects on humans have also been included in the screening program. In 2007, a draft list of 73 pesticide active ingredients and inert chemicals were selected for Tier 1 screening (U.S. EPA 2007). Operational details regarding the major elements of the EDSP and its implementation were published in two Federal Register Notices (63 Fed. Reg 1998 a and b) in 1998, and the Tier 1 draft list was published in a 2007 Federal Register Notice (72 Fed. Reg 2007).

Internationally, several programs have been implemented to investigate possible adverse effects from exposure to environmental endocrine-disrupting chemicals. In 1996, the Organization for Economic Co-operation and Development (OECD) established a special activity on Endocrine Disrupter Testing and Assessment with the objectives of providing information and coordinating activities, developing new and revised existing Test Guidelines to detect endocrine disrupters, and harmonizing hazard and risk characterization approaches. This effort led to an update of existing toxicity test guidelines to help detect endocrine disruption effects (OECD 2007). In an effort to avoid duplication of effort and coordinate research on this emerging public health concern, the International Programme on Chemical Safety (IPCS), led by WHO, is collaborating with a number of national and regional agencies to establish and maintain an inventory of research activities on endocrine disruption. In Canada, the Toxic Substances Research Initiative (TSRI) subsidizes research

in specific areas of environment and health, including toxic substances that disrupt the hormonal system (Environment Canada 1998). In Europe, a total of 91 pesticides (including fenoxycarb) have been listed as "confirmed" or "possible" endocrine-disrupting chemicals by the Environment Agency of England and Wales, The German Environment Agency, The European Union Community Strategy for Endocrine Disruptors, and the Oslo and Paris Commission (McKinlay et al. 2008).

A large body of evidence has been accumulated that links specific adverse effects with endocrine-disrupting pesticides, particularly in wildlife populations; however, direct causal relationships have generally been difficult to establish. In a recent publication designed to assess the existing level of development and understanding of environmental endocrine disruptors, the WHO/ICPS (2002) completed its review by stating that "*the state-of-the-science assessment indicates that our current understanding of the effects posed by endocrine disrupting chemicals to wildlife and humans is incomplete. The evidence that high-level exposure may impact both humans and wildlife indicates that this potential mechanism of toxicity warrants our attention. Uncertainty over the possible effects of chronic, low-level exposures to a number of chemicals with endocrine disrupting potential and the fundamental roles played by the endocrine system in maintaining homeostasis make understanding the potential effects posed by exposure to these chemicals an obvious international priority. There is a need to identify life stages and species that are more vulnerable to the effects of endocrine disrupting chemicals and to understand how this mechanism of toxicity may affect individual populations and communities.*"

3 Environmental Degradation

3.1 Abiotic Processes

3.1.1 Hydrolysis

Fenoxycarb does not react significantly with water and is neither acid nor alkaline labile, i.e., it is not susceptible to either acid or base catalysis. Consequently, hydrolysis is not an important transformation route of fenoxycarb in the environment. In a representative study, Thomas (1994) found that radiolabeled β-phenyl ^{14}C-fenoxycarb is stable when dissolved in sterile acetate buffer (pH 5.0), phosphate buffer (pH 7), or borate buffer (pH 9.0) at 25°C for 30 d in darkness (see Fig. 3 for position of label). This study yielded hydrolysis half-lives ranging from 1406 d at pH 5.0, 3136 d at pH 7, and 4101 d at pH 9.0. The calculated fenoxycarb hydrolysis rate constants were 4.97×10^{-4} d^{-1}, 2.21×10^{-4} d^{-1}, and -1.69×10^{-4} d^{-1} for pH 5, 7, and 9, respectively. In the 30 d study, no fenoxycarb degradates formed that were greater than 10% of the applied radioactivity under pH 5, 7, or 9 aqueous buffer solutions.

3.1.2 Aqueous Photolysis

Aqueous fenoxycarb readily photodegrades for the reason that it contains photolabile ether linkages that are susceptible to direct and indirect OH-mediated cleavage. Clark (1994) determined that when approximately 1 ppm α-phenyl ^{14}C-fenoxycarb was subjected to artificial sunlight in pH 7 hydrolytically stable aqueous buffer solution at 25°C, and an average intensity of 410 W/m^2 for 30 d, photodegradation was rapid, with a calcuhated half-life of 18 d and a pseudofirst-order rate constant of -0.039 d^{-1}. Only one major degradate, phenol (**9**), which increased to 14.8% of the applied dose by day 14 and stabilized at 17.9% by day 22, was present at greater than 10% of the applied dose. Six other degradation products were observed, each accounting for $\leq$ 9.5% of the applied dose. One of these degradates was identified as ethyl 2-(4-(4-hydroxyphenoxy)phenoxy) ethylcarbamate (**3**), formed from the photo-induced hydroxylation of the parent compound. Another, 4-phenoxyphenol (**5**), is produced during the homolytic cleavage of the phenoxyphenoxy ether linkage. These two degradation products accounted for 3.6 and 5.8% of the initial dose, respectively. A third degradate (4.8%) was characterized as a mixture of the photooxidation products benzene-1,2,4-triol (**6**) and catechol (**8**). A second multicomponent mixture, after partitioning with chloroform, was found to consist of hydroxymethyl 2-(4-(4-hydroxyphenoxy)-phenoxy) ethylcarbamate (**4**), hydroquinone (**7**), and catechol (**8**).

When the β-labeled test substance was subjected to artificial sunlight under conditions that were analogous to those used to evaluate α-labeled fenoxycarb, comparable results were observed (Clark 1995). In this study, β-phenyl ^{14}C-fenoxycarb was found to photodegrade at a rate of 0.03 d^{-1}, with a calculated half-life of 23 d. Only one photodegradation product, ethyl 2-(4-hydroxyphenoxy)ethylcarbamate (**2**), was observed at $\geq$10% of the applied radioactive dose. Photoproduct (**2**) increased to 10.4% on day 14 and reached 16.9% by day 30. The presence of (**2**) demonstrated ether bridge cleavage, which corroborates the presence of (**9**) in the α-phenyl-labeled study. As in the earlier study, degradates (**3**) and (**5**) were also produced, but at slightly higher levels ($\geq$6.7 and $\leq$7.1%, respectively). From these results, an aqueous photodegradation pathway was proposed and is shown in Fig. 5.

3.1.3 Soil Photolysis

Although fenoxycarb is predisposed to degrade quickly in the presence of sunlight in water, it is very stable to photodegradation in most viable soil types. Sparrow (1995) investigated the photodegradation of radiolabeled β-phenyl ^{14}C-fenoxycarb in two studies conducted with uncharacterized soils in artificial sunlight artificially irradiated for 12 hr per day at 25°C, and an average intensity of 410 W/m^2 for 36 and 40 d. In both artificial sunlight systems, degradation followed biphasic kinetics, wherein rapid initial degradation was promptly followed by an extended lag period during which degradation neared

Fig. 5 Photodegradation pathway for fenoxycarb in aqueous buffer at pH 7 and 25°C. Adapted from Burnett and Thede (1995)

a stable plateau. The biphasic character of the decay curve implies that photolysis and adsorption are in direct competition, resulting in a diminished rate of photodegradation as adsorption processes prevail. The calculated primary half-lives in the 36-d study were 10.4 d for the irradiated incubations and 7.38 d non-irradiated incubations, respectively. The slower secondary half-lives were 104.3 and 73.1 d for the irradiated and non-irradiated incubations, respectively. The calculated primary half-lives in the 40-d study were 13.65 d for the irradiated incubations and 6.2 d non-irradiated incubations, while the secondary half-lives

were 158 d for the irradiated and 1351 d for the non-irradiated incubations. The only major degradate, which accounted for 8.4% of the total applied dose, was identified as the monohydroxylated derivative of fenoxycarb, ethyl 2-(4-(4-hydroxyphenoxy)phenoxy)ethyl-carbamate (**3**).

3.2 Biotic Processes in Soils

3.2.1 Field Dissipation

In 1995, several field dissipation studies were conducted to evaluate the mobility and persistence of fenoxycarb when applied to cropped (squash) and bare ground. A representative study was performed in California on a sandy loam soil composed of an average of 67.4% sand, 26.2% silt, 6.4% clay, and 0.47% organic matter (Shuster and Goff 1995). A more detailed analysis of the characteristics of this soil is shown in Table 4. Fenoxycarb was applied using one (bare soil plot) or two (cropped plot) broadcast applications of a 25% wettable powder formulation at an application rate of 1.0 lb of active ingredient per A (2×0.5 lb of active ingredient per A for the cropped plot). Soil core samples were taken to 60-in. deep at specified intervals immediately before and after application. Core composites were analyzed for fenoxycarb only. Fenoxycarb was found to be stable in soil for up to a year under the storage conditions of the field samples. On the bare ground plot, average fenoxycarb concentrations found in the 0–6 in. soil layer were 0.59 ppm on day 0 and 0.037 ppm on day 121. In the 6–12 in. layer, average residue concentrations were determined to be 0.010 ppm on day 0 and below the 0.01 ppm limit of quantitation (LOQ), thereafter. No fenoxycarb residues were found above the LOQ at any depth below 6 in. from day 3 onward. The half-life of fenoxycarb in the 0–6 in. soil layer was 36.5 d (after 120 d). On the squash cropped plot, average fenoxycarb concentrations found in the 0–6 in. soil layer were 0.40 ppm on day 0 and 0.024 ppm on day 121. In the 6–12 in. layer, average residue concentrations were determined to be below the LOQ from day 0 and thereafter. No fenoxycarb residues were found above the level of quantitation at any depth below 6 in. The half-life of fenoxycarb in the 0–6 in. soil layer was 34.4 d (after 120 d).

A similar study was performed on bare ground only for 528 d in Washington and generated comparable results, yielding fenoxycarb half-lives after 91 d of 28.3 d (Rice et al. 1995). It was reported that soil cores taken to a depth of 48-in. contained no fenoxycarb residues at or above the LOQ in the treated plot over the length of the study period. The average concentration of fenoxycarb in the surface (0–6 in.) layer ranged from 0.017 to 0.46 ppm from day 0 through day 528. As in the previous study, residues were found above the LOQ only in the top 6 in. soil layer, indicating that fenoxycarb residues are not likely to migrate down the soil profile.

McDonald (1995) conducted supplemental field dissipation studies on bare sandy loam plots near Fresno, California, using radiolabeled α-phenyl-^{14}C-

Table 4 Soil characteristics for the terrestrial field dissipation of fenoxycarb in cropped (squash) and bare California sandy loam soil. Adapted from Schuster and Goff (1995)

	Soil depth (in.)									
Measured parameter	0–6	6–12	12–18	18–24	24–30	30–36	36–42	42–48	48–54	54–60
% Organic matter	0.9	0.6	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
pH	7.9	8.1	8.2	8.2	8.3	8.3	8.4	8.4	8.4	8.3
% Sand	66	64	68	66	66	68	68	70	70	68
% Silt	26	28	24	26	26	26	26	26	26	28
% Clay	8	8	8	8	8	6	6	4	4	4
CEC[a]	9.0	8.8	9.1	11.4	16.8	17.7	18.6	17.2	17.3	16.6
Bulk density	1.22	1.21	1.23	1.21	1.24	1.24	1.27	1.27	1.230	1.27
FMC[b]	12.9	14.1	12.2	11.7	11.9	11.9	11.7	10.8	11.1	11.4

[a]Cation exchange capacity in meq/100 g
[b]Field moisture capacity at 1/3 bar/

fenoxycarb and β-phenyl-^{14}C-fenoxycarb to investigate the fate and distribution of fenoxycarb and track possible degradates. The α-labeled and β-labeled test substances were applied to separate plots using single broadcast applications of a 25% wettable powder formulation at an application rate of 0.25 lb of active ingredient per A (equivalent to 123 ppb/A). Soil core samples were taken to a maximum of 12 in. and were collected at regular intervals up to 56 d. Soil characterization data is shown in Table 5. As in the previous studies, residues were restricted to the upper 0–3 in. soil layer beyond the initial phase of the study. Post-application residues were quantitated by TLC to determine the percent of total dose represented by undegraded fenoxycarb. Both α-phenyl-^{14}C-fenoxycarb and β-phenyl-^{14}C-fenoxycarb exhibited biphasic kinetics. The initial rapid degradation was characterized by mean primary half-lives of 4.29 and 4.10 d for the α- and β-labeled test substances, respectively. The slower secondary degradation process exhibited mean half-lives of 18 d (α-label) and 29.3 d (β-label). The only major degradate recovered from extracts of both radiolabeled test substances was the α-ring oxidation product ethyl 2-(4-(4-hydroxyphenoxy)phenoxy)ethylcarbamate (**3**), which accounted for a maximum of 12.54% of the total applied dose. The aqueous photolysis product ethyl 2-(4-hydroxyphenoxy)ethylcarbamate (**2**) was present in several of the β-labeled fenoxycarb samples as a minor component ($\leq$1.52% of the total dose). No other degradates were characterized in this study, and an overall degradation pathway for the dissipation of fenoxycarb was not proposed.

Each of the above dissipation trials were performed using a commercial wettable powder formulation (25 WP) applied at a rate of 0.25–1.0 lb active ingredient/A under conditions conductive to leaching (flat terrain, course textured, highly permeable sandy loam/loamy sand soil with low organic matter, above average moisture input) and support the results of earlier laboratory mobility studies, which suggested that fenoxycarb is neither persistent nor mobile in representative agricultural soils.

Table 5 Soil characteristics for the terrestrial field dissipation of radiolabeled fenoxycarb in bare California sandy loam soil

	Soil depth (in.)			
Measured parameter	0–3	3–6	6–9	9–12
% Organic matter	0.5	0.4	0.4	0.2
pH	6.9	6.1	5.7	6.0
% Sand	65	63	61	63
% Silt	27	29	31	27
% Clay	8	8	8	10
CEC[a]	7.2	5.7	6.6	5.8
Bulk density	1.38	1.32	1.37	1.38
FMC[b]	10.4	9.9	10.0	9.9

Adapted from McDonald (1995)
[a]Cation exchange capacity in meq/100 g
[b]Field moisture capacity at 1/3 bar/

3.2.2 Soil Metabolism

Fenoxycarb degrades initially very rapidly in soil under both aerobic and anaerobic conditions, but after several days the rate of metabolic degradation plateaus and becomes stable. Over time, fenoxycarb residues are slowly converted to CO_2 and unextractable residues. When 0.122 ppm of radiolabeled α-phenyl-^{14}C-fenoxycarb was added to a Maryland sandy loam soil (74% sand, 16% silt, 10% clay, 2.6% organic content, pH 7.8) and incubated under aerobic conditions for 12 mon in darkness at 25°C, the parent compound followed biphasic kinetics with a primary half-life of 6.7 d and a secondary half-life of 246 d. Fenoxycarb also declined via a biphasic mechanism under flooded anaerobic conditions when evaluated using the same soil and experimental parameters. Primary and secondary anaerobic half-lives of 16 and 255 d, respectively, were reported (Dixon 1995). Similar studies conducted with the β-labeled test substance yielded comparable results. In these experiments, aerobic degradation was found to follow biphasic kinetics and gave a primary half-life of 7.37 d and a secondary half-life of 80.12 d. Anaerobic incubations generated a linear decline with a pseudo-first-order half-life of 113.6 d (Schwartz 1995).

Fenoxycarb is highly resistant to hydrolytic and photolytic breakdown in soils but is susceptible to biological catalysis, serving as a carbon source for soil microorganisms. Hence, the major terminal metabolite was carbon dioxide, which accounted for approximately 33 and 26% of the applied radioactive dose in the aerobic and anaerobic studies, respectively, after 12 mon. A large proportion of the radioactivity that was extractable under alkaline refluxing conditions was associated with entities having molecular weights greater than 10,000, suggesting that many intermediates had been incorporated into microbial biosynthetic pathways. A significant fraction of the ^{14}C also quickly became bound in the soil organic matter. The degradation patterns that emerged from α- and β-labeled soil metabolism studies were very similar, with each producing comparable degradation intermediates and terminal products. The pattern of degradation was quickly; each study generated 11 polar intermediate products, of which eight were isolated and identified using size exclusion HPLC, TLC, and liquid scintillation counting (LSC). From these analytical observations, a general aerobic and anaerobic metabolic degradation pathway leading to mineralization and the production of polar and unextractable bound residues was proposed (Fig. 6). Hydroxylation of the α-phenyl ring of the parent (**1**) led to the formation of the metabolite ethyl 2-(4-(4-hydroxyphenoxy)phenoxy)ethylcarbamate (**3**) and ethyl 2-(4-(3,4-dihydroxyphenoxy)phenoxy)ethylcarbamate (**10**), while the loss of the carbamate moiety yielded the uncharacterized substituted phenoxybenzene (**13**). Enzymatic cleavage of the aromatic rings of degradates (**10**) and (**13**) generated polar degradates with free carboxylic acid groups, which formed by way of a series of transient bicyclic alcohols. Cleavage of the diphenyl ether bridge of fenoxycarb produced the hydroxyphenoxy intermediate ethyl 2-(4-hydroxyphenoxy)ethylcarbamate (**2**) and the decarboxylation of fenoxycarb gave carbon dioxide and the phenoxy ethylamines (**11**)

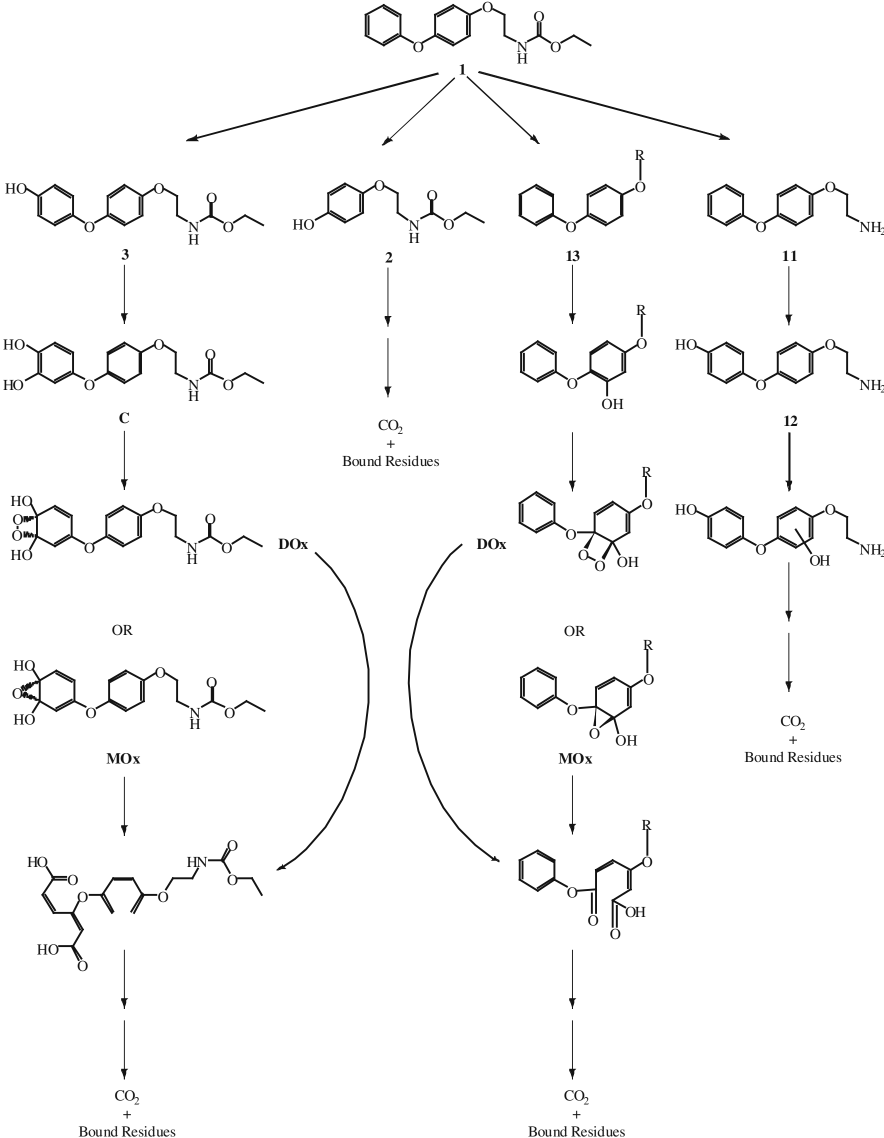

Fig. 6 General aerobic and aerobic/anaerobic metabolic degradation pathways in sandy loam soil leading to mineralization and the production of polar and unextractable bound residues. After aromatic hydroxylation, microbial degradation may progress from either the dioxygenase cleavage intermediate (*DOx*) or the monooxygenase cleavage intermediate (*MOx*). Adapted from Schwartz (1995)

and (**12**). At the conclusion of the year-long studies, all intermediates had mineralized to carbon dioxide and/or were incorporated into the carbon cycles of the soil and microbes.

3.3 Biotic Processes in Water and Sediment

Burton (1995) conducted aerobic aquatic kinetic/degradation studies with β-phenyl-^{14}C-fenoxycarb in natural pond sediment and water at a dose rate of 0.015 ppm (wt/vol) for kinetic samples and 2.02 ppm (wt/vol) for degradation samples. Thirty-two samples were prepared by adding 66 mL of lake water to 20 g (dry-wt equivalent) of natural pond sediment, an approximate 1:3.3 sediment:water ratio. Twenty-two pond sediment/water samples were fortified with β-phenyl-^{14}C-fenoxycarb for kinetic experiments, and 14 were fortified for degradate analyses. Test samples were incubated in the dark at a mean maximum temperature of 26.1 ± 0.43°C for 30 d. Duplicate aliquots were collected from the water layer at regular intervals throughout the study period. After extraction and elutriation, the radioactivity in the water layer and sediment extracts was radioassayed by LSC. The water layer and sediment extracts were analyzed by TLC for fenoxycarb and its metabolites, and identification was verified by HPLC. Physical and chemical characteristics of the aqueous and sediment test systems are summarized in Table 6.

After 30 d, the radioactivity in the aqueous layer was found to have dissipated from an initial mean value of 92.28% of the applied dose at day 0 to a final mean value of 10.26%. Radioactivity in the sediment layer coincidently increased from 10.6% at day 0 to 82.39% by day 30. The non-extractable radioactivity reached a maximum of 19.34% of the applied dose after 30 d. Approximately 3% of the applied dose was cumulative volatiles and was shown to be carbon dioxide. The mean parent concentration in the aqueous layer declined from a preliminary mean value of 84.12% (day 0) to a final mean of 0.54% (day 30). The decline of radiolabeled fenoxycarb corresponded to the simultaneous generation of the monohydroxylated fenoxycarb metabolite ethyl 2-(4-(4-hydroxyphenoxy)phenoxy)ethylcarbamate (**3**) and (TLC) origin material, which reached a maximum of 0.94 and 19.30%, respectively, at day 6. Additional chromatography demonstrated that the origin material was probably multiple polar components. The metabolite (**3**) and uncharacterized polar components declined after day 6 to mean values of 0.01 and 3.79% of the applied dose by the conclusion of the study. The decline of β-phenyl-^{14}C-fenoxycarb appeared biphasic, although a single calculated half-life of 3.89 d was determined from a linear decline curve. For the overall (sediment plus aqueous layer) results, a similar trend was observed. The labeled parent compound was determined to be the major component in the combined sediment extracts and water layers, ranging from 91.64% (day 0) to 28.55% (day 30). The monohydroxylated compound (**3**) was again the only significant residue, increasing concurrently from an initial value of 0.35% to a maximum of

Table 6 Characteristics of natural pond water and sediment used in the assessment of the aerobic aquatic metabolism of fenoxycarb. Data from Burton (1995)

Pond water	
pH	8.0
Conductivity	0.59 mmhos
Total dissolved solids	452 ppm
Calcium	25 mg/L
Magnesium	16 mg/L
Sodium	28 mg/L
Hardness (mg equivalent $CaCO_3$/L)	129 mg/L
Sodium adsorption ratio (SAR)	1.08
Turbidity	0.33 NTU[a]
Sediment	
% Sand	78
% Silt	18
% Clay	4
Textural class (USDA)	Loamy sand
Clay mineralogy	Chlorite, Kaolite, Illite
Bulk density	1.22 (g/cc)
CEC	9.9 (meq/100 g)
% Moisture at 1/3 bar	15.7
% Moisture at 15 bar	6.6
% Organic matter	1.1[b]
% Organic carbon	0.64
pH	7.0
Phosphorus	16 ppm
Total nitrogen	0.057%
Soluble salts	0.19 mmhos/cm

[a]Nephelometric turbidity units
[b]Percent organic carbon = percent organic matter/1.724

3.55% of the dose. The uncharacterized polar components increased from a value of 0.59% of the applied dose at day 0 to a maximum of 33.40% at day 14, followed by a sharp decline to 9.70% by day 30. The half-life of β-phenyl-^{14}C-fenoxycarb was 18.80 d. The decline curve of β-phenyl-^{14}C-fenoxycarb again appeared non-linear, whereas the calculated half-life was linear. The formation of polar residues and the concomitant formation of 14CO2 in both the aqueous and overall studies suggest that the aquatic dissipation pathway is governed by biological catalysis. Metabolism in aerobic aquatic media proceeds through enzyme-mediated hydroxylation followed by oxidative cleavage of the ether linkages. The phenolic scission fragments are further metabolized to form various polar carboxy compounds, polymers, oligomers, and additional products. Fenoxycarb quickly dissipates from the aqueous layer and is transferred to the sediment under aerobic conditions, where it continues to degrade.

A synopsis of fenoxycarb environmental residence times, shown in Table 7, indicates that it is stable to hydrolysis at pH 3–9, and to photolysis when on soil.

Table 7 Fenoxycarb half-lives from field and laboratory studies

Hydrolysis	Stable
Photolysis	
Air	5.9 hr
Water	6.4 d (α-label), 23 d (β-label)
Soil	10.4 d (primary); 104.3 d (secondary)
Bluegill depuration	2.6–4.1 d
Soil dissipation	
0–6-in. soil layer	36.5 d
Cropped	34.4 d
Soil metabolism	
Aerobic	6.7 d (primary, α-label)
	7.4 d (primary, β-label)
	246 d (secondary, α-label)
	80.2 d (secondary, β-label)
Anaerobic	113.6 d
Aerobic aquatic metabolism	
Aqueous layer	3.89 d
Aqueous layer + sediment layer	18.80 d

However, fenoxycarb is expected to photodegrade rapidly in natural waters and dissipate in the atmosphere within several hours. Field studies show that under exaggerated and normal use conditions, dissipation of fenoxycarb in soil is rapid, and adsorption/desorption studies indicate it has a low potential for leaching because of a moderate to strong propensity to bind to soil. It initially metabolizes quickly in soil, but the rate of degradation slows considerably after the first week. Fish exposed to fenoxycarb in water will bioaccumulate fenoxycarb to concentrations 300X greater than the concentration in the water. However, the fish will release 99% of the residues within 2 wk when placed in fenoxycarb-free water.

4 Summary

Fenoxycarb is a phenoxyphenyl-based juvenile hormone agonist containing a non-neurotoxic carbamate side-chain that competes for juvenile hormone binding site receptors in insects, mimicking the action of juvenile hormone and thus maintaining an immature state. Compared with the conventional insecticides, fenoxycarb does not exhibit quick knockdown or cause mortality in insects, but long-term exposure largely inhibits population growth as a result of its effects on the insect endocrine system. Fenoxycarb acts by ingestion, disrupting transformation from egg to larva, larva to pupa, late nymph to reproductive adult, crawler to sessile insect (scale insects), or sucking larva to chewing larva. It has insecticidal activity against public health insect pests such as fire ants, mosquitoes and cockroaches. In agriculture and horticulture, fenoxycarb has been

registered for the control of fire ant, fleas, black scale, mosquitoes and codling moth. It is particularly efficacious against Lepidopteran pests and the cat flea, exhibiting LC_{50} values ≤ 0.05 ppm, and having no effect on predator populations. Although it has low mammalian toxicity, it is a U.S. EPA class B2 probable human carcinogen and is included on the list of cancer-causing chemicals in the State of California. Because fenoxycarb is designed and synthesized specifically to target insect endocrine systems, exposure to it is of concern because of the potential for adverse effects than could alter normal endocrine function in wildlife and humans.

Technical fenoxycarb is a light brown powder, and is stable under normal conditions. It is very soluble (up to 770 g/L solvent) in most organic solvents, but only slightly soluble (7.9 mg/L) in water. The use of fenoxycarb as an agricultural and ornamental insecticide will result in its direct release to the environment. If released into the air, fenoxycarb will not readily disperse into the atmosphere because of its low vapor pressure and Henry's law constant. Particulate-phase fenoxycarb is dissipated via dry deposition, while vapor-phase fenoxycarb will be degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals. Because of low water solubility and relatively high K_{OC} values, fenoxycarb has a propensity to adsorb onto soil surfaces, particularly those having high clay content and organic matter. If released into water, fenoxycarb adsorbs onto suspended solids and organic matter and retains biological activity for up to 2 mon. Its persistence in water in the absence of organic matter declines with increasing temperature and sunlight exposure. Fenoxycarb is hydrologically stable at environmental pH ranges because it lacks hydrolysable functional groups. Hydrolysis half-lives ranged from 1406–4101 d at pH 5, 7, and 9 and 25°C. However, it is susceptible to photodegradation in water, with photolysis half-lives ranging from 18 to 23 d in aqueous buffer solution. In soils, photodegradation proceeds much slower, with half-lives in the range of 10–22 wk. If released to soil, both the parent compound and its major degradation metabolite ethyl 2-(4-(4-hydroxyphenoxy) phenoxy)ethylcarbamate are stable in soil for up to a year but are not mobile beyond the soil surface layer. Fenoxycarb degrades rapidly in aerobic water and soils via biological catalysis, in which it serves as a carbon source for soil microorganisms. The initial rate of degradation in aerobic media proceeds relatively quickly (~7 d) via a biphasic mechanism, and then becomes stable. Secondary aerobic metabolic half-lives ranged from 80 to 246 d. Anaerobic metabolism proceeded at a similar rate, progressing via a biphasic mechanism with half-lives ranging from 80 to 255 d.

The low solubility, moderately high partition coefficients, and hydrophobicity of fenoxycarb are consistent with chemicals that are known to be environmentally persistent. However, its susceptibility to aquatic photodegradation, metabolic breakdown in aerobic soils and waters, and its apparent short depuration half lives in aquatic fauna lead to rapid dissipation in biotic and environmental matrices. In anaerobic conditions, such as brackish waters or sediments, fenoxycarb is somewhat more stable and highly toxic to aquatic

invertebrates. Given its potential to persist, prudence should be used when applying fenoxycarb to or near water bodies and precautions must be taken to avoid or mitigate drift and runoff to surface waters.

References

63 Fed. Reg. 42852 (1998a) Endocrine Disruptor Screening Program. Available at http://www.epa.gov/endo/pubs/081198frnotice.pdf (verified 25 October 2008).

63 Fed. Reg. 71541 (1998b) Endocrine Disruptor Screening Program; Proposed Statement of Policy.

72 Fed. Reg. 33486 (2007) Draft List of Initial Pesticide Active Ingredients and Pesticide Inerts to be Considered for Screening under the Federal Food, Drug, and Cosmetic Act.

Atkinson R (1985) Kinetics and mechanisms of the gas-phase reactions of hydroxyl radical with organic compounds under atmospheric conditions. Chem Rev 85:60–201.

Baskin LS, Himes K, Colborn T (2001) Hypospadias and endocrine disruption: Is there a connection? Environ Health Perspect 109(11): 1175–1183.

Bidleman TF (1988) Atmospheric Processes: Wet and dry deposition of organic compounds are controlled by their vapor-particle partitioning. Environ Sci Technol 22:361–367.

Burnett G, Thede BM (1995) Summary of environmental fate studies for fenoxycarb, Ciby-Geigy Crop Protection (Syngenta Crop Protection, Inc), Laboratory Project Identification ABR-95036, DPR Document No. 51317-0077. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

Burton SD (1995) Aerobic aquatic metabolism of ^{14}C-fenoxycarb, Ciby-Geigy Crop Protection (Syngenta Crop Protection, Inc), Study No. 287-93, DPR Document No. 51317-0077. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

California EPA (2008) Office of Environmental Health Hazard Assessment, Safe Drinking Water and Toxic Enforcement Act of 1986, Chemicals Known To The State To Cause Cancer Or Reproductive Toxicity, September 12, 2008. Sacramento (CA), USA. Available at http://www.oehha.org/Prop65/prop65_list/files/P65single 091208.pdf(verified 23 September 2008).

Campiche S, Becker-van Slooten K, Ridreau C, Tarradellas J (2006) Effects of insect growth regulators on the nontarget soil arthropod *Folsomia candida* (Collembola). Ecotox Environ Saf 63:216–225.

CCME (Canadian Council of Ministers of the Environment) (2007) Canadian water quality guidelines for the protection of aquatic life: Methoprene. In: Canadian Environmental Quality Guidelines, 1999. Canadian Council of Ministers of the Environment, Winnipeg.

CDPR (California Department of Pesticide Regulation) (2006) Summary of Pesticide Use Report Data Indexed By Chemical. California Environmental Protection Agency, Sacramento, CA, p. 171. http://www.cdpr.ca.gov/docs/pur/pur06rep/chmrpt06.pdf

Chamberlain WF, Becker JD (1977) Inhibition of cocoon formation and adult emergence of oriental rat fleas, *Xenopsylla cheopis* (Rothschild), by insect growth regulators. Southwestern Entomol 2:179–182.

Charmillot G, Fabre P (2001) Ovicidal and larvicidal effectiveness of several insect growth inhibitors and regulators on the codling moth *Cydia pomonella* L. (Lep., Tortricidae). J Appl Entomol 125:147–153.

Clark A (1994) Photodegradation of ^{14}C-fenoxycarb (α-phenyl ^{14}C-CGA-114597) in pH 7 buffered solution under artificial sunlight, Ciby-Geigy Crop Protection (Syngenta Crop Protection, Inc), Study No. 259-94, DPR Document No. 51317-0080. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

Clark A (1995) Photodegradation of ^{14}C-fenoxycarb (β-phenyl ^{14}C-CGA-114597) in pH 7 buffered solution under artificial sunlight, Ciby-Geigy Crop Protection (Syngenta Crop Protection, Inc), Study No. 283-93, DPR Document No. 51317-0079. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

Crisp TM, Clegg ED, Cooper RL, Wood WP, Anderson DG, Baetcke KP, Hoffmann JL, Morrow MS, Rodier DJ, Schaeffer JE, Touart LW, Zeeman MG, Patel YM (1998) Environmental endocrine disruption: An effects assessment and analysis. Environ Health Perspect 106(Suppl 1):11–56.

Dhadialla TS, Carlson GR, Le DP (1998) New insecticides with ecdysteroidal and juvenile hormone activity. Ann Rev Entomol 43:545–569.

Dixon B (1995) Aerobic and aerobic/anaerobic metabolism of "A" label ^{14}C-Fenoxycarb in a sandy loam soil, Ciby-Geigy Crop Protection (Syngenta Crop Protection, Inc), Study No. 76-94, DPR Document No. 51317-0082. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

Eisa AA, El-Fatah MA, El-Nabawi A, El-Dash AA (1991) Inhibitory effects of some insect growth regulators on developmental stages, fecundity and fertility of the Florida Wax Scale, Ceroplastes floridensis. Phytoparasitica. 19:49.

Eliahu M, Blumberg D, Horowitz AR, Ishaaya I (2007) Effect of pyriproxyfen on developing stages and embryogenesis of California red scale (CRS), *Aonidiella aurantii*. Pest Manag Sci 63:743–746.

Ellgehausen H (1985) Accumulation and elimination of ^{14}C-RO 13-5223/024 by bluegill sunfish in a dynamic flow through system, Ciby-Geigy Crop Protection (Syngenta Crop Protection, Inc), Study No. 034841, DPR Document No. 51317-0086. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

Environment Canada (1998) Federal Ministers Announce that $40 million will be allocated to research on health and environment in Canada. *Communiqué*, 7 December 1998.

EPI Suite (Estimation Programs Interface Suite) (2004) U.S. EPA Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC), v. 2.20 (Feb. 2007) Available at http://www.epa.gov/oppt/exposure/pubs/episuite.htm (verified 20 November 2008).

Evans RG, Sunley A, Bradford C, Patmore RI (1995) Effects of fenoxycarb on development and reproduction of the oriental cockroach, Blatta orientalis. Med Vet Entomol 9(3):235–240.

FQPA (Food Quality Protection Act of 1996) (1996) Available at http://www.epa.gov/pesticides/regulating/laws/fqpa/ (verified 25 October 2008).

Garry VV (2004) Pesticides and children. Toxicol Appl Pharmacol 198(2): 152–163.

Girard J (2005) Principles of environmental chemistry. Jones & Bartlett Publishers, Sudbury, MA, p. 494.

Godfrey CRA (1995) Agrochemicals from natural products. Marcel Dekker, Inc., New York, NY, p. 161.

Grenier S, Grenier AM (1993) Fenoxycarb, a fairly new insect growth regulator: a review of its effects on insects. Ann Appl Biol 122:369–403.

Hajek A (2004) Natural enemies: An introduction to biological control. Cambridge University Press, UK, p. 327.

Hosmer AJ, Warren LW, Ward TJ (1998) Chronic toxicity of pulse-dosed fenoxycarb to *daphnia magna* exposed to environmentally realistic concentrations. Environ Toxicol Chem 17:1860–1866.

Lee BM, Scott GI (1989) Acute toxicity of temephos, fenoxycarb, diflubenzuron, and methoprene and *Bacillus thuringiensis* var. *israelensis* to the mummichog (*Fundulus heteroclitus*). Bull Environ Contam Toxicol 43(6):827–832.

Maddison JE, Page SW, Church D (2008) Small animal clinical pharmacology, 2nd ed. Elsevier Health Sciences, New York, NY, p. 187.

Mamatha DM, Kanji VK, Cohly HHP, Rao MR (2008) Juvenile hormone analogues, methoprene and fenoxycarb dose-dependently enhance certain enzyme activities in the silkworm *Bombyx Mori* (L). Int J Environ Res Pub Health 5(2):120–124.

Marchiondo AA, Riner JL, Sonenshine DE, Rowe KF Slusser JH (1990) Ovicidal and larvicidal modes of action of fenoxycarb against the cat flea (*Siphonaptera*: *Pulicidae*). J Med Entomol 27(5):913–921.

Masner P, Angst M, Dorn S (1987) Fenoxycarb, an insect growth regulator with juvenile hormone activity: A candidate for *Heliothis virescens* (F.) control on cotton. Pest Sci 18: 89–94.

Mather V, Bhatnagar P, Sharma RG, Acharya V, Sexana R (2002) Breast cancer incidence and exposure to pesticides among women originating from Jaipur. Environ Int 28(5): 331–336.

McDonald J (1995) Terrestrial Dissipation of ^{14}C-Fenoxycarb 25 WP on bare ground soil in California, Ciby-Geigy Crop Protection (Syngenta Crop Protection, Inc), Study No. 279-94, DPR Document No. 51317-0092. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

McKenney CL Jr., Gripe GM, Foss SS, Tuberty SR, Hoglund M (2004) Comparative embryonic and larval developmental responses of an estuarine shrimp (*Palaemonetes pugio*) to the juvenile hormone agonist, fenoxycarb. Arch Environ Contam Toxicol 47:463–470.

McKinlay R, Plant JA, Bell JNB, Voulvoulis N (2008) Endocrine disrupting pesticides: Implications for risk assessment. Environ Int 34:168–183.

Miyamoto J, Hirano M, Takimoto Y, Hatakoshi M (1993) Insect growth regulators for pest control with emphasis on juvenile hormone analogue: Present status and future prospects. Pest Cont Enhance Environ Saf 524: 144–168.

Nates SF, McKenney CL Jr. (2000) Growth, lipid class and fatty acid composition in juvenile mud crabs (*Rhithropanopeus harrisii*) following larval exposure to fenoxycarb, insect juvenile hormone agonist. *Comp Biochem Physiol C Toxicol Pharmacol* 127:317–325.

OECD (2007) Organisation for Economic Co-operation and Development: Draft updated test guideline 407. Available at http://www.oecd.org/dataoecd/22/27/39791889.pdf (verified 25 October 2008).

Pryde A, Von der Muhll A (1985) Nature of radioactive residues in ^{14}C-RO 13-5223/024-treated bluegill sunfish, Dr. R. Maag AG (Syngenta Crop Protection, Inc), Maag Project No. 041/5369, DPR Document No. 51317-0086. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

Rajapakse CNK, Meola R, Readio J (2002) Comparative evaluation of juvenoids for control of cat fleas (*Siphonaptera*: *Pulicidae*) in topsoil. J Med Entomol 39:889–894.

Reid BL, Bennett GW, Yonker JW (1990) Influence of fenoxycarb on German cockroach (*Dictyoptera*: Blattellidae) populations in public housing. J Econ Entomol 83(2):444–450.

Rice F, Fieser J, Speth RM (1995) Terrestrial dissipation of fenoxycarb 25 WP on bare ground in Washington, Ciby-Geigy Crop Protection (Syngenta Crop Protection, Inc), Study No. 188-93, DPR Document No. 51317-0093. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

Riddiford LM (1994) Cellular and molecular actions of juvenile hormone I. General considerations and premetamorphic actions. Adv Insect Physiol 24:213–274.

Schaefer CH, Wilder WH, Mulligan FS, and Dupras EE (1987) Efficacy of fenoxycarb against mosquitoes (Diptera: Culicidae) and its persistence in the laboratory and field. J Econ Entomol 80(1): 126–130.

Schreinemachers DD (2003) Birth malformations and other adverse perinatal outcomes in four U.S. wheat producing states. Environ Health Perspect 111(9):1259–1264.

Schwartz B (1995) Aerobic and anaerobic metabolism of ^{14}C-fenoxycarb in a sandy loam soil, Ciby-Geigy Crop Protection (Syngenta Crop Protection, Inc), Study No. 228-92, DPR Document No. 51317-0083. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

SDWA (1996) Safe Drinking Water Act. Available at http://www.epa.gov/safewater/sdwa/ (verified 25 October 2008).

Shepler K (1995) Column leaching of ^{14}C-CGA-294847 in five soil types, Ciby-Geigy Crop Protection (Syngenta Crop Protection, Inc), Project No. 504W, DPR Document No. 51317-0086. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

Shuster LL, Goff KE (1995) Dissipation of Fenoxycarb in Soil under field conditions with and without crop (squash) in California, Ciby-Geigy Crop Protection (Syngenta Crop Protection, Inc), Study No. 181-93, DPR Document No. 51317-0090. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

Sláma, K (1999) The history and current status of juvenoids. In: WH Robinson, F. Rettich and GW Rambo (eds.) Proceedings of the 3rd International Conference on Urban Pests, pp 9–24.

Spare WC (1995a) The adsorption and desorption of ^{14}C-fenoxycarb by the batch equilibrium method on representative agricultural soils, Ciby-Geigy Crop Protection (Syngenta Crop Protection, Inc), Study No. 12213, DPR Document No. 51317-0088. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

Spare WC (1995b) The adsorption and desorption of ^{14}C-CGA-294847 by the batch equilibrium method on representative agricultural soils, Ciby-Geigy Crop Protection (Syngenta Crop Protection, Inc), Study No. 12214, DPR Document No. 51317-0087. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

Sparrow K (1995) Photodegradation of ^{14}C-fenoxycarb on soil under artificial sunlight, Ciby-Geigy Crop Protection (Syngenta Crop Protection, Inc), Study No. 250-94, DPR Document No. 51317-0081. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

Tasei JN (2001) Effects of insect growth regulators on honey bees and non-*Apis* bees. A review. Apidologie 32:527–545.

Tatarazako N, Oda S, Watanabe H, Morita M, Iguchi T (2003) Juvenile hormone agonists affect the occurrence of male Daphnia. Chemosphere 53:827–833.

Templeton NS, Laufer H (1983) The effects of a juvenile hormone analogue (Altosid ZR-515) on the reproduction and development of *Daphnla magna* (Crustacea: Cladocera). Int J Invert Reprod 6:99–110.

Testing Advisory Committee (EDSTAC), final report (1998). Available at http://www.epa.gov/endo/pubs/edstac/exesum14.pdf (verified 25 October 2008).

Thomas B (1994) Hydrolysis of 14C-Fenoxycarb at pH 5, 7, and 9 Ciba-Geigy Corporation (Syngenta Crop Protection), Ciba Study No. 348-92, DPR Document No. 51317-0078. This unpublished study is proprietary data cited with the authorization of Syngenta Crop Protection, Inc.

Tomlin C (2006) The pesticide manual, 14th ed. BCPC Publications, Berkshire, UK, pp 923–924.

U.S. EPA (1998) U.S. Environmental Protection Agency. Endocrine Disruptor Screening Testing Advisory Committee (EDSTAC), final report (1998). Available at http://www.epa.gov/endo/pubs/edstac/exesum14.pdf (verified 25 October 2008).

U.S. EPA (2000) Pesticide ecotoxicity database. Office of Pesticide Programs, Environmental Fate and Effects Division, U.S. EPA, Washington, DC.

U.S. EPA (2007) June 2007 Draft List of Chemicals for Initial Tier 1 Screening. Available at http://www.epa.gov/endo/pubs/prioritysetting/draftlist.htm (verified 25 October 2008).

U.S. EPA Office of Pesticide Programs (2007) Chemicals evaluated for carcinogenic potential. Available at http://www.epa.gov/pesticides/carlist/(verified 25 October 2008).

UC Statewide IPM Program. (Feb. 2007) Pest Notes: Ants. Oakland: Univ. Calif. Agric. Nat. Res. Publ. 7411.

Unger TA (1996) Pesticide synthesis handbook. William Andrew, Inc. Norwish, NY, p. 82.

Verslycke TA, Fockedey N, McKenney CL Jr., Roast SD, Jones MB, Mees J, Janssen CR (2004) Mysids crustaceans as potential test organisms for the evaluation of environmental endocrine disruption: A review. Environ Toxicol Chem 23:1219–1234.

WHO (2006) Pesticides and their application for the control of vectors and pests of public health importance, 6th ed. World Health Organization, Geneva. Available at http://whqlibdoc.who.int/hq/2006/WHO_CDS_NTD_WHOPES_GCDPP_2006.1_eng.pdf
WHO/IPCS (World Health Organization/International Petroleum Chemical Society) (2002) Global Assessment of the State-of-the-Science of Endocrine Disruptors. Damstra T, Barlow S, Bergman A, Kavlock R, Van Der Kraak G (eds) WHO/IPCS/EDC/02.2 World Health Organization, Geneva, Switzerland, http://ehp.niehs.nih.gov/who/ (verified 23 September 2008).
Zala S, Penn DJ (2004) Abnormal behaviors induced by chemical pollution: A review of the evidence and new challenges. Anim Behav 68:649–664.
Zhou X, Riddiford LM (2002) Broad specifies pupal development and mediates the 'status quo' action of juvenile hormone on the pupal-adult transformation in *Drosophila* and *Manduca*. Development 129:2259–2269.

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