19 Pharmaceuticals and Personal Care Products (PPCPs) as Emerging Environmental Pollutants: Toxicity and Risk Assessment

Sunil Chopra and Dharmender Kumar

19.1 Introduction

Pharmaceuticals and personal care products (PPCPs), which include diverse groups of organic chemicals, are a class of compounds considered as emerging organic contaminants (EOCs). These products include nutritional supplements, diagnostic agents, antibiotics, hormones, musk fragrances, and non-steroidal anti-inflammatory drugs (NSAIDs) as well as other drugs that are used for veterinary medicine, human health, agricultural practice, and cosmetic care (Farre et al. 2008; Fent et al. 2006). PPCPs in aquatic environments are considered as some of the most critical environmental pollutants (Al-Odaini et al. 2010). PPCPs enter the ecosystem in a number of ways. Effluents from wastewater treatment plants (WWTPs) or sewage treatment plants (STPs) and large farms with many animals are considered as the main sources responsible for the discharging of PPCPs into the environment. These PPCPs are not completely digested by humans and animals, and undigested PPCPs are excreted as waste and washed off into sink drains. PPCPs, like hormones, are naturally excreted by humans and animals, and this poses potential risks both to the ecosystems into which the PPCPs are discharged and to drinking water resources. Many studies performed worldwide have shown that hundreds of PPCPs and their derivatives are usually detected in various environments. Concentrations of PPCPs in groundwater vary from place to place; in incompletely treated water, concentrations are less than 0.1 μgl, and in drinking water and treated water, concentrations are commonly below 0.05 μg/l. PPCP metabolites are also commonly detected in the environment; the lifespan of PPCPs and their metabolites in the environment varies from months to years, depending on their natural degradation in the environment (US EPA, 2013).

Almost all PPCPs seem to be biologically active in nature. These compounds are designed to act in humans and animals according to specific pathways and processes

S. Chopra · D. Kumar (✉)
Department of Biotechnology, Deenbandhu Chhottu Ram University of Science and Technology, Sonepat, Haryana, India

S. K. Gahlawat et al. (eds.), *Advances in Animal Biotechnology and its Applications*, https://doi.org/10.1007/978-981-10-4702-2_19

to cure diseases. The United States Environmental Protection Agency (US EPA 2013) considers PPCPs as emerging contaminants. There is little knowledge about the impact of these contaminants on human health after they are released into ecosystems. PPCPs are widely detected in many aquatic environments around the world—in rivers, lakes, and groundwater in almost every continent. There is some evidence of PPCPs in groundwater and surface is reported in literature (Table 19.2). PPCPs in aquatic environments have negative effects on aquatic species. Steroid hormones have adverse effects on the environment, and even at μgL^{-1} or ng^{-1}concentrations can inhibit reproduction in aquatic species. The continuous release of huge quantities of PPCPs (including steroid hormones) has led to these compounds being widespread in the environment, and as they exert bio-activity at extremely low concentrations, there is a need to study the possible effects of these compounds in our surroundings on human, aquatic, and ecological environments. PPCPs have unpredictable biochemical interactions with other compounds in the environment, and PPCPs and their metabolites, or the interaction of two or more of these compounds present in the environment, affects both aquatic and terrestrial species. PPCPs are present in water utilized by plants for photosynthesis and photorespiration, and this water is stored in the edible parts of plants. When humans and animals eat the plants, these compounds enter our food cycle. We use water for our daily needs, and wastewater recycled by WWTPs and STPs is often used for irrigation. The use of untreated or treated water obtained from STPs for irrigation will introduce PPCPs into the fields. The uptake of this contaminated water leads to the accumulation of PPCPs that contaminate plants and so these compounds may be further transferred to the food chain (US EPA 2013).

In this chapter the modes of sources of PPCPs that enter the environment and the potential effect of these compounds on the environment and the risks associated with these compounds has been discussed. The biodegradation of PPCPs by microorganisms constitutes an eco-friendly technique to decontaminate the environment and this will also reduce the concentrations of these compounds.

19.1.1 Classification of PPCPs

PPCPs or pharmaceutically active compounds are used to treat various diseases due to their bioactive property. PPCPs consist of two categories: pharmaceuticals and personal care products. The pharmaceuticals include commercially available drugs and agents that are used to treat diseases in both humans and animals. This category includes NSAIDs, other anti-inflammatory agents, antidepressants, tranquilizers, pain killers, antipsychotic agents, anti-cancer drugs, anti-hypertensive medicines, antiseptic agents, lipid regulators, oral contraceptives, antibiotics, synthetic hormones, and many other classes and types of drugs. Personal care products include various compounds; for example, perfumes, deodorants, shampoos, synthetic hair dyes, hair sprays, oral hygiene products, make-up products, sunscreen creams, body lotions, and various other creams (Table 19.1).

Table 19.1 Classification and uses of various pharmaceuticals and personal care products (PPCPs)

Class of PPCP	Generic name	Pharmaceutical use	Scientific name	Chemical formula
A. Pharmaceuticals				
Nonsteroidal anti-inflammatory drugs	Diclofenac	Treat mild to moderate pain, or signs and symptoms of osteoarthritis or rheumatoid arthritis	2-[(2,6-Dichlorophenyl)amino] benzeneacetic acid	$C_{14}H_{11}C_{l2}NO_2$
	Ibuprofen	Reduce fever and treat pain or inflammation caused by many conditions, such as headache, toothache, back pain, arthritis, menstrual cramps, and minor injuries	a-Methyl-4-(isobutyl) phenylacetic acid	$C_{13}H_{18}O_2$
	Naproxen	Treat pain or inflammation caused by conditions such as arthritis, ankylosing spondylitis, tendinitis, bursitis, gout, and menstrual cramps	(S)-(+)-2-(6-Methoxy-2-naphthyl) propionic acid	$C_{14}H_{14}O_3$
Antidepressants	Fluoxetine	Treat major depression, obsessive-compulsive disorder, and panic disorder	(±)-N-methyl-c-[4-(trifluoromethyl) phenoxy] benzenepropanamine	$C_{17}H_{18}F_3NO$
	Citalopram	Helps to restore the balance of serotonin (a natural substance) in the brain	1-[3-(Dimethylamino) propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile	$C_{20}H_{21}FN_2O$
Hormones	Estrone	Manage vaginal menopausal symptoms such as itching, burning, and dryness in or around the vagina, and painful sexual intercourse	1,3,5(10)-Estratrien-3-ol-17-one	$C_{18}H_{22}O_2$
	17b-Estradiol	Progestin therapy, for changes in vaginal bleeding; dysmenorrhea; increases in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; changes in cervical secretion; and cervical ectropion	1,3,5-Estratriene-3,17b-diol	$C_{18}H_{24}O_2$
	17a-Ethinylestradiol	Orally bioactive estrogen used in many formulations of combined oral contraceptive pills	17a-Ethynyl-1,3,5(10)-estratriene-3,17b-diol	$C_{20}H_{24}O_2$

(continued)

Table 19.1 (continued)

Class of PPCP	Generic name	Pharmaceutical use	Scientific name	Chemical formula
Tranquillizers	Diazepam	Treat anxiety disorders, alcohol withdrawal symptoms, and muscle spasms	7-Chloro-1-methyl-5-phenyl-3H-1,4-benzodiazepin-2(1H)-one	$C_{16}H_{13}ClN_2O$
Anti-epileptics	Carbamazepine	Treat seizures and nerve pain such as trigeminal neuralgia and diabetic neuropathy	5H-dibenz[b,f]azepine-5-carboxamide	$C_{15}H_{12}N_2O$
Antibiotics	Sulfamethoxazole	Treat a wide variety of bacterial infections (such as middle ear, urinary, respiratory, and intestinal infections)	4-amino-N-(5-methyl-3-isoxazolyl) benzenesulfonamide	$C_{10}H_{11}N_3O_3S$
	Roxithromycin	Treat respiratory tract, urinary tract, and soft-tissue infections	Erythromycin 9-(-O-[2-methoxyethoxy] methyloxime)	$C_{41}H_{76}N_2O_{15}$
	Erythromycin	Treat bacterial infections, such as bronchitis, diphtheria, legionnaires' disease, pertussis (whooping cough), pneumonia; rheumatic fever; venereal disease (VD); and ear, intestinal, lung, urinary tract, and skin infections	6-(4-Dimethylamino-3-hydroxy-6-methyl-oxan-2-yl)oxy-14-ethyl-7,12,13-trihydroxy-4- (5- hydroxy-4-methoxy-4,6-dimethyl-oxan-2-yl) oxy-3,5,7,9,11,13-hexamethyl-1-oxacyclotetradecane-2,10-dione	$C_{37}H67NO13$
	Trimethoprim	Treat urinary tract infections caused by certain types of bacteria	2,4-Diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine	$C_{14}H_{18}N_4O_3$
Lipid regulators	Clofibrate (active metabolite: clofibric acid)	Reduce high levels of cholesterol (a type of fat) in the blood. Clofibrate is especially good at reducing levels of triglycerides and very-low-density lipoprotein (VLDL; a form of cholesterol)	Ethyl 2-(4-chlorophenoxy)-2-methylpropanoate	$C_{12}H_{15}ClO_3$
	Gemfibrozil	Reduces levels of fats (triglycerides) and raises levels of "good" cholesterol (high-density lipoprotein; HDL) in the blood. It may also help to reduce levels of "bad" cholesterol (LDL)	5-(2,5-Dimethylphenoxy)-2,2-dimethyl-pentanoic acid	$C_{15}H_{22}O_3$
Stimulants	Caffeine	Stimulate the brain	1,3,7-Trimethylpurine-2,6-dione	$C_8H_{10}N_4O_2$

(continued)

B. Personal care products				
Fragrances (musks)	Galaxolide	Synthetic ingredient with a clean sweet musky floral woody odor, used in fragrances	1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta(g)-2-benzopyran	$C_{18}H_{26}O$
	Tonalide		6-Acetyl-1,1,2,4,4,7-hexamethyl tetralin	$C_{18}H_{26}O$
	Celestolide		4-Acetyl-6-tert-butyl-1,1-dimethylindane	$C_{17}H_{24}O$
	2,6-DMN (2,6-Dimethylnaphthalene)	Commercial importance as a starting material for high-performance polyester fibers and films. Polyethylene naphthalate (PEN) is made using the oxidation product of 2,6- DMN	2,6-dimethylnapthalene	$C_{12}H_{12}$
	Isophorone	Solvent in some printing inks, paints, lacquers, adhesives, copolymers, coatings, finishings, and pesticides. It is also used as a chemical intermediate and as an ingredient in wood preservatives and floor sealants	3,5,5-Trimethyl-2-cyclohexene-1-one	$C_9H_{14}O$
	Benzotriazole	Specific corrosion inhibitor for copper and copper alloys. It is now widely used in industry to reduce the corrosion of these alloys under both atmospheric and immersed conditions	5-Methyl-1H-benzotriazole	$C_6H_5N_3$
Fire reagents	Tri (2-chloroethyl) phosphate	Flame retardant, plasticizer, and viscosity regulator in various types of polymers, including polyurethanes, polyester resins, and polyacrylates fire	Tri(2-chloroethyl) phosphate	$C_6H_{12}C_{l3}O_4P$

19.1.2 Sources of PPCPs

Individual households, manufacturing sites, dumping sites, large farms, STPs, and WWTPs are considered to be the main sources of the PPCPs that enter different environmental systems. Studies of these sources have produced information regarding the environmental load of PPCPs. The fate of water coming from STPs and WWTPs also has profound effect in the environment. PPCPs are removed by the treatment processes used in WWTPs ultimately determines the extent of PPCPs still left in the aquatic environment. Various studies have focused on the presence of PPCPs in rivers, lakes, STPs, and WWTPs (Table 19.2). Most of the studies has been conducted on the ways by which these compounds enters into ecological systems and their subsequent fates were carried out in areas having high populations density and with rich ecological resources.

PPCPs enter environmental systems by different pathways, some of which are considered as gateways for the entrance of these compounds to the environment. Examples of gateways are manufacturing sites that release their untreated or less-treated water to surface waters or STPs; domestic waste; STPs and WWTPs; sites of medicine landfills; aquaculture facilities; and biosolids. PPCPs that are present in aquatic systems enter terrestrial systems via the effluent from STPs or WWTPs that is used for irrigation and via river or sewage water and sludge used for agricultural practices. STPs and WWTPs play important roles in the transportation of PPCPs from one place to another. The life cycles of PPCPs and their metabolites can be easily studied in WWTPs and STPs. Owing to the complex structure of PPCPs, traditionally built WWTPs were not able to completely remove these compounds, or else they removed only a fraction of the PPCPs, and transformed them into different metabolites or forms in which two or more compounds were conjugated. The efficiency of STPs in the removal of PPCPs is also affected by the three main types of treatment processes they use; mechanical, chemical, and biological. Advanced processes have been developed to treat these compounds, but in developing countries traditional methods of water treatment have been used. Diverse chemical groups are present in PPCPs, so it is not possible to treat all compounds according to their physicochemical properties. Each compound has different physiochemical properties, such as solubility, absorbance onto sludge, half-life under biotic and abiotic conditions, and tendency to volatilize (Liu et al. 2014). The efficiency of STPs and WWTPs for the removal of PPCPs and their metabolites depends upon the environmental and operational conditions under which they work. Environmental factors such as temperature, redox conditions, and pH affect the degradation kinetics of the compounds. Operational conditions such as hydraulic retention time, biodegradation kinetics, and sludge retention time are important for the degradation of these compounds (Evgenidou et al. 2015). Veterinary pharmaceuticals are an important source of PPCPs, as they are released into the environment directly from the treatment of meadow animals, or indirectly by the application of manure to the land, by the runoff of veterinary medicines from the surfaces of farmyards, by cattle carcasses, and by slurry from livestock facilities. The management and uses of PPCP vary around the world, and the pathways in different geographical areas vary from

Table 19.2 Concentrations of PPCPs in different sources

Name of PPCP	Average concentration	Sample source	References
Diclofenac	29 μg L^{-1}	River Elbe and the mouths of its tributaries (Germany)	Wiegel et al. (2004)
Ibuprofen	35 μg L^{-1}		
Acetaminophen	16 μg L^{-1}		
Bisphenol A	40 μg L^{-1}		
Ibuprofen	28 μg L^{-1}	Han, Nakdong, and Youngsan Rivers (South Korea)	Kim et al. (2007)
Acetaminophen	33 μg L^{-1}		
Diclofenac	3 μg L^{-1}		
Oxybenzone	2 μg L^{-1}		
Acetaminophen	12 μg L^{-1}	Ebro River basin (Spain)	López-Serna (2012)
Triclosan	50 μg L^{-1}	Surface waters of Greenwich Bay (RI, United States)	Katz et al. (2013)
Acetaminophen	5 μg L^{-1}	Near-shore habitats of Lake Michigan	
Ibuprofen	8 μg L^{-1}	River discharges into lakes from predominantly urban watersheds (United States)	Ferguson et al. (2013b)
Carbamazepine	40 μg L^{-1}	Aquifers in the delta area of the Llobregat River (NE Spain)	Teijón et al. (2010)
Ibuprofen	185 μg L^{-1}		
Diclofenac	256 μg L^{-1}		
Acetaminophen	180 μg L^{-1}	Groundwater used for drinking-water supply in California (United States)	Fram and Belitz (2011)
Diclofenac	0.2 μg L^{-1}	Urban groundwater in the district of Poble Sec, Barcelona (Spain)	López-Serna et al. (2012)
Ibuprofen	0.2 μg L^{-1}		
Acetaminophen	<0.1 μg L^{-1}		
Erythromycin	<0.1 μg L^{-1}		
Enrofloxacin	75 μg L^{-1}		
Ibuprofen	23 μg L^{-1}	Groundwater wells in Berlin (Germany)	Heberer (2002)
Diclofenac	34 μg L^{-1}		
Clofibric acid	18 μg L^{-1}		
Antibiotics	360 ng L^{-1}	Mekong Delta (Vietnam)	Managaki et al. (2007)
Antibiotics	544 ng L^{-1}	Seine River (France)	Tamtam et al. (2008)
Antibiotics	183 ng L^{-1}	Taff and Ely Rivers (United Kingdom)	Kasprzyk-Hordern et al. (2009)
Antibiotics	696 ng L^{-1}	Vantaa River (Finland); drinking water sources	Vieno et al. (2007)
Antibiotics	300 ng L^{-1}	Choptank River (United States)	Arikan et al. (2008)
Antibiotics	1900 ng L^{-1}	Streams in Iowa (United States)	Kolpin et al. (2004)

(continued)

Table 19.2 (continued)

Name of PPCP	Average concentration	Sample source	References
Hormones	5 ng L^{-1}	Youngsan River (South Korea)	Kim et al. (2007)
Hormones	5 ng L^{-1}	Llobregat River (NE Spain)	Brix et al. (2009)
Hormones	10 ng L^{-1}	Scheldt estuary (Netherlands)	Arikan et al. (2008
Hormones	18.9 ng L^{-1}	Little River estuary (Victoria, Australia)	Ferguson et al. (2013a)
Pharmaceuticals	749 ng L^{-1}	Tamagawa estuary and 37 rivers in Japan	Nakada et al. (2008)
Pharmaceuticals	500 ng L^{-1}	Rivers in Rio de Janeiro State (Brazil)	Stumpf et al. (1999)
Triclosan	5160 ng L^{-1}	Kaveri, Vellar, and Tamiraparani Rivers (India)	Ramaswamy et al. (2011)

one region to another. Traditional systems of wastewater treatment lead to the incomplete removal of PPCPs from WWTPs. Metabolites produced by pharmaceutical compounds and other PPCPs are designed to resist decomposition and microbial degradation. Newer WWTPs employ specific treatments to remove waste via the degradation of lower-molecular-weight compounds, the physical removal of solids, and the transformation or conjugatation of compounds that are further hydrolyzed when released into the environment.

19.2 Toxicity of PPCPs: Personal Care Products

The everyday use of personal care products such as toothpaste, shampoo, personal soaps, hair products, lotions, and make-up products leads to the release of compounds that are not naturally present in the environment (Lu et al. 2011). Many personal care products show low volatility in nature, so PPCPs are limited in the atmospheric environment. However, some PPCPs, such as siloxanes, are highly volatile so they are found in indoor dust and air. Indoor dust releases these compounds when electrical appliances are used and smoke is present in the house (Lu et al. 2010). The concentrations of parabens in indoor dust particles were found to be in the order of 2320 ng g^{-1} in Korea, 2300 ng g^{-1} in Japan), and 1390 ng g^{-1} in the United States (Wang et al. 2012).

PPCPs and their metabolites follow the same biological pathways and have modes of action similar to those of their parent molecules. Compounds that have been transformed or conjugated are more toxic than their parent compounds and have adverse effects on our aquatic and terrestrial systems. The transformed compounds exist with their parent molecules in the form of mixtures. The eco-toxicological effect of PPCPs and their transformed and conjugated products cannot be ignored. The toxicity of the transformed products differs from that of their parent molecules in two ways: their toxicokinetics and toxicodynamics (mode of action). Transformation creates new toxicophores that have higher toxicity than their parent molecules or that are similar in mode of action. These chemicals are present in low

concentrations, but they form conjugated products with other compounds, resulting in synergistic mixtures with greater toxicity that strongly affect the environment. Therefore, it is essential to evaluate the ecological risk associated with PPCPs and their conjugated products. High exposure to PPCPs and their metabolites leads to a high probability of risk associated with these compounds (Evgenidou et al. 2015).

19.2.1 Human Risk

Humans use water for their day-to-day activities and for drinking; however, the water contains various PPCPs that cause health-related problems. The major potential routes of exposure to PPCPs that entail risks to human health vary. Consumption of marine or territorial fishes exposed to PPCPs is one of the main causes for interaction to these compounds. At present, the concentrations of PPCPs in the environment in some countries are very high, and so people are exposed to these compounds in their drinking water and in bathing/showering. PPCPs are also present in surface and groundwater, and this may also have adverse effects on human health. In drug development and approval, the toxicological properties of drugs in relation to humans and other mammals are studied, and this information is often available from pharmaceutical companies. This data is very important in the evaluation of risks associated with these drugs during human exposure to the EOCs in the environment. The existing data on drugs used to treat human diseases is very satisfactory, whereas data on the prevalence of PPCPs and their derivatives in the environment is limited. Thus, the human risk associated with the intake of these chemicals from the environment is unknown. Because of the daily use and long lifespan of PPCPs, they are found in environmental water and enter food chains. Healthy water and food are primary priorities for humans. But these unwanted compounds are present in human environments. Compounds such as the antibiotic fluoroquinolone have been identified in tap water for drinking in many countries (Wang et al. 2010). Triclosan, a pharmaceutical compound, has been detected not only in tap water but also in packed bottled water, in varying concentrations (9.7–14.5 ng L^{-1}); the concentration was low but has been increasing steadily. The intake of triclosan in adults and infants was shown to be increasing, and it was detected at concentrations of 10 and 5 ng L^{-1}, respectively, in bottled water for adults and in baby bottles (Li et al. 2010). The agricultural use of water containing PPCPs increases health risks to humans. Antibiotics are now used in non-organic farming and for livestock to increase production. Livestock wastes are used as fertilizers in many developing countries, and concentrations of PPCPs in the environment are increasing because of this practice. The accumulation of antibiotics in vegetables probably arises from the transportation and absorption and distribution of water in the plants, with accumulation in the leaves being more than that in the stems and that in the stems being more than that in the roots (Hu et al. 2010).

Owing to their many exposure pathways, PPCPs have been detected in human breast milk, blood, and urine. In human breast milk, synthetic musks have been detected at concentrations of 1.4–917 ng g^{-1}; the synthetic musks enter the body of

the infant during feeding with breast milk, and high concentrations of these compounds may cause physiological or genetic changes in the infant. The main reason for the detection of such compounds in humans is the frequent use of personal care products (Yin et al. 2012). In human breast milk, the four most commonly found synthetic musks are musk xylene (MX); musk ketone; 1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran (HHCB); and 7-acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene, with HHCB showing the highest concentration. Daily infant intake of milk containing synthetic musks at concentrations of 277–7391 ng g^{-1} increases the potential risk (Zhang et al. 2011). Synthetic musks have been detected in human breast milk in many countries, e.g., in the United States (2–917 ng g^{-1} lipid weight), Denmark (38–422 ng g^{-1} lipid weight), and Sweden (2–268 ng g^{-1} lipid weight) (Duedahl-Olesen et al. 2005; Reiner et al. 2007a, b; Lignell et al. 2008).

Polycyclic compounds contained in musk fragrances and nitro musk fragrances have been commonly detected in human blood (Hu et al. 2010). The synthetic musks HHCB and MX have been reported in human blood plasma. In Austria, HHCB and MX were detected in adult blood at concentrations of 11–450 ng g^{-1} (Hutter et al. 2009). Triclosan wasdetected in urine samples from young children and adults, with the mean concentration in 3- to 24-year-old persons being 3.55 μg g^{-1} (Li et al. 2013). Parabens and their derivatives were detected in urine samples from people in the United States. A pharmacokinetic study reported that PPCPs caused no major risk to human health. However, another study has shown that regular exposure to these compounds in the current environment leads to high risks to human health (Touraud et al. 2011). These studies describe the presence of PPCPs in the environment in various forms as well as describing the accumulation of these compounds in the human body. Regular exposure to PPCPs, whether direct or indirect, and intake of these compounds, are possible reasons for their effect on human health.

19.2.2 Toxicity and Risks to Ecosystems

PPCPs in aquatic environments are mainly discharged into STPs and WWTPs. The concentration of PPCPs in aquatic environments depends upon the source. Water sources near highly populated areas contain high concentrations of PPCPs, while marine water contains low concentrations. Aquatic organisms such as fish and invertebrates, or other species, that are present near sources of aquatic systems, are regularly exposed to PPCPs throughout their life cycles. PPCPs are designed to be biologically active and are intended to react with the metabolic systems of living cells. In general, PPCPs are produced to treat human disease and are used in the protection of larger domesticated animals. Various regulatory agencies and academic institutions are now working on evaluations of the adverse effects of these compounds on aquatic life and the wildlife associated with water bodies.

Currently, data is limited regarding the adverse effects of direct exposure to PPCPs and their derivatives on aquatic organisms. Traditional toxicological tests are

not able to evaluate the potential effect of regular exposure to PPCPs and their derivatives on the lives of organisms in surface waters, marine water, and sediments contaminated by these compounds. Fish tissues collected for study have shown that some PPCPs, such as antidepressants, are present in the cells of fish that live in streams near urban effluent. Large concentrations of antidepressants were detected in the brain and liver tissues of the fish (Liu and Wong 2013). Other studies have focused on evaluating the toxic effects of PPCPs on marine organisms. In many studies, concentrations greater than the concentrations detected in the environment were used to investigate the possible adverse effects of PPCPs on aquatic organisms exposed to PPCPs such as anti-inflammatory agents, antidepressants, and antibiotics. The presence of PPCPs in the ecosystem leads to concern about their probable adverse effects on the ecosystem. The regular use of antibiotics may also increase the risk of antibiotic resistance genes (ARGs) in organisms, and also has the potential to cause adverse effects on the ecosystem and on human health (Kemper 2008). ARGs were universally detected in insects and microbes identified in hospitals and in effluents from livestock farming, while some microbes containing AGR genes were also detected in drinking water, municipal wastewater, and ground water (Pruden et al. 2006). Multiple antibiotic-resistant genes with hundreds of ARG cassettes have been identified in wastewater and drinking water worldwide (Kobayashi et al. 2007).

When artificial and natural hormones reach the marine environment through human excreta and via medical use, this leads to endocrine disruptions in marine organisms. Many studies have reported hormonal reproductive and developmental changes in these organisms, such as reduction of fertility; the presence of intersex organisms; and feminization and vitellogenesis in males (Lai et al. 2002; Khanal et al. 2006). It is assumed that these endogenic compounds reached the ecosystems via sewage systems and were also present in sewage effluents (Jobling et al. 2006). Personal care products such as ultraviolet sunscreens (Gomez et al. 2005) may also be considered as having the potential to cause endocrine disruption in some species. Some compounds, such as triclosan, caffeine, triclocarban (Yang et al. 2008), and some lipid regulators (Rosal et al. 2009) inhibit algal growth, cause endocrine disruption in fish (goldfish), and reduce the viability of eggs (Japanese medaka) (Huggett et al. 2002). Oxidation stress was caused by carbamazepine (an antiepileptic drug) and HHCB in rainbow trout in a marine environment and in goldfish in a freshwater environment. Schwaiger et al, in 2004, reported that NSAIDs such as diclofenac caused gill alterations and renal lesions in rainbow trout. The synergistic effects of NSAIDs in the ecosystem are an issue of concern. Mixtures of various NSAIDs were considered to exert the strongest adverse effects by forming complexes in aquatic organisms (Cleuvers 2003). PPCPs and their derivatives enter the aquatic environment, which is the gateway for entry to the whole food web (Brausch and Rand 2011).

Recent studies found that PPCPs were detected in effluents, wastewater, groundwater, and drinking water too. PPCPs are organic compounds that are designed to be biologically active, and so a risk of toxicity is anticipated for many species exposed to PPCPs in the environment, even when the concentrations of these

compounds are low. The risk to humans from exposure to PPCPs in environmental waters is more disputed than the ecological risks of PPCP exposure. Although the presence of pharmaceuticals at parts-per-million levels in water for daily use does not currently appear to cause a direct adverse threat to humans, indirect impacts from some pharmaceuticals are documented and need to be considered. Indirect impacts of PPCPs other than pharmaceuticals on human health are more difficult to determine. Toxicology studies of chronic exposure to anticonvulsants, antidepressants, anti-hypertensives, endocrine-disrupting chemicals, and cytostatic pharmaceuticals are limited (U.S.EPA (U.S. Environmental Protection Agency) 2013; U.S.FDA (U.S. Food, Drug Administration) 2013).

19.3 Biodegradation and PPCP Removal

In natural conditions, organic compounds are degraded mostly by bacteria and some fungi. These organisms have a rapid growth rate, great metabolic activity, and easily adapt to new substrates that enter the environment. Numerous laboratory experiments have shown positive results for the degradation of xenobiotic compounds by microbes, but the microbial degradation of these compounds does not occur on a large scale. It is necessary to identify microorganisms (bacteria, fungi, etc.) from the environment that are capable of degrading EOCs.

19.3.1 Pure Cultures

Many studies have reported that pure cultures isolated from wastewater, activated sludge, wastewater, or river sediments have the capacity to degrade carbamazepine, sulfamethoxazole, iopromide, paracetamol, ibuprofen, diclofenac, and triclosan. Some pure cultures exhibit a capacity for the degradation of various PPCPs. Sulfamethoxazole is the not only compound degraded by *Achromobacter denitrificans*; this bacterium also degrades other sulfonamides (Reis et al. 2014). Many pure cultures use different mechanisms for the degradation of PPCPs. Some PPCPs providing the sole carbon and energy source for microbial metabolism (Murdoch and Hay 2005; De Gusseme et al. 2011; Zhang et al. 2013). Paracetamol can be degraded by *Delftia tsuruhatensis*, *Pseudomonas aeruginosa*, and *Stenotrophomonas*. Biosorption played a negligible role in the degradation of paracetamol by *Delftia tsuruhatensis* and *Pseudomonas aeruginosa*, while biosorption contributed to the degradation of paracetamol by *Stenotrophomonas*. Various enzymes play important roles in these degradation processes. Some PPCPs that provide the sole carbon and energy source for microbes are barely degraded by pure cultures of microbes. In such cases, supplementary substances will provide the carbon and energy required for the metabolic function of the microbes. For example, carbamazepine shows poor biodegradability, owing to its stable structure. But in the presence of glucose, pure cultures of *Basidiomycetes* and *Streptomyces* MIUG (Santosa et al. 2012; Popa et al. 2014) degraded carbamazepine. Liu et al. (2013) proved that iopromide could

be degraded by *Pseudomonas* sp. I-24 using starch as the primary substrate. The NSAID diclofenac showed high resistance to biodegradation by a pure culture isolated from activated sludge (Alvarino et al. 2014). However, in 2010, Hata et al. reported that the white rot fungus *Phanerochaete sordida* YK-624 almost completely degraded diclofenac.

19.3.2 Mixed Cultures

Mixed cultures are an easier method of degrading PPCPs than pure cultures, because pure cultures are not easily identified. Mixed cultures have a greater capacity than pure cultures for degrading wider ranges of PPCPs, because a mixed culture is a consortium of various strains. 17a-Ethinylestradiol was degraded by a mixed culture of heterotrophic bacteria in mixed media, demonstrating the degradation capacity of mixed strains (Khunjar et al. 2011). Mixed cultures are used most widely in biological activated sludge treatment processes in WWTPs, depending on various strategies for the removal of the PPCPs. However, in some cases, mixed cultures show low removal efficiency for specific PPCPs.

19.3.3 Activated Sludge Process

The removal of PPCPs by biological treatment in WWTPs conventionally uses an activated sludge process. The biological treatment has a mixed effect, causing the adsorption, volatilization, and biodegradation of PPCPs, with the main mechanism of PPCP removal by activated sludge being biodegradation. The limitations of biological treatment can be conquered by the use of bioaccumulation and bioaugmentation (Wang et al. 2002). The modeling framework for xenobiotic trace chemicals developed by Plosz et al. (2012) is used to identify the factors that enhance the efficiency of xenobiotic removal by activated sludge.

19.4 Conclusions

PPCPs are a group of compounds used in medicines and other preparations. Their entry to the environment is mediated by different routes and they enter the environment through different water bodies. In this chapter we have outlined the available information on the adverse effects of PPCPs present in the environment. WWTPs are the major gateway by which PPCPs enter the environment, although there are other sources for PPCP entry to the environment, such as agricultural and veterinary runoff, household waste, dumping sites, and aquaculture. This suggests that WWTPs cannot completely remove PPCPs. So there is a need to develop WWTP technologies that will remove PPCPs efficiently. There is also a need for more studies to be conducted on the persistence of PPCPs and the effects of PPCPs and their metabolites on the environment in developing countries, because the availability of

information about PPCPs in the environment is far behind that in developed countries. Further, there are few studies on the adverse effects of PPCPs and their residues on fish, birds, and mammals. At present, advanced research on the removal of such compounds from the environment is playing the major role in PPCP studies. Biodegradation is one technology that may be used for the removal of PPCPs, with pure cultures, mixed cultures, and activated sludge processes being available for this purpose. Biodegradation is a cost-effective and natural technique for the removal of PPCPs. More studies are needed to enhance these techniques. Toxicity and risk assessment studies employed in environmental management systems may reduce the ecological risks and toxicity of these compounds. New and indigenous technologies can be employed for waste reduction and minimization of the toxicity of different agents that enter the environment. The use of efficient microbial systems and biological treatments will lead to a reduction of the effects of PPCPs on living systems.

References

Al-Odaini NA, Zakaria MP, Yaziz MI, Surif S (2010) Multi-residue analytical method for human pharmaceuticals and synthetic hormones in river water and sewage effluents by solid-phase extraction and liquid chromatography–tandem mass spectrometry. J Chromatogr A 1217:6791–6806

Alvarino T, Suarez S, Lema JM, Omil F (2014) Understanding the removal mechanisms of PPCPs and the influence of main technological parameters in anaerobic UASB and aerobic CAS reactors. J Hazard Mater 278:506–513

Arikan OA, Rice C, Codling E (2008) Occurrence of antibiotics and hormones in a major agricultural watershed. Desalination 226:121–133

Brausch JM, Rand GM (2011) A review of personal care products in the aquatic environment: environmental concentrations and toxicity. Chemosphere 82:1518–1532

Brix R, Postigo C, González S, Villagrasa M, Navarro A, Kuster M (2009) Analysis and occurrence of alkylphenolic compounds and estrogens in a European river basin and an evaluation of their importance as priority pollutants. Anal Bioanal Chem 396:1301–1309

Cleuvers M (2003) Aquatic ecotoxicity of pharmaceuticals including the assessment of combination effects. Toxicol Lett 142:185–194

De Gusseme B, Lynn V, Willy V, Nico B (2011) Degradation of acetaminophen by Delftia tsuruhatensis and Pseudomonas aeruginosa in a membrane bioreactor. Water Res 45:1829–1837

Duedahl-Olesen L, Cederberg T, Pedersen KH, Højgård A (2005) Synthetic musk fragrances in trout from Danish fish farms and human milk. Chemosphere 61:422–431

Evgenidou EN, Konstantinou IK, Lambropoulou DA (2015) Occurrence and removal of transformation products of PPCPs and illicit drugs in wastewaters: a review. Sci Total Environ 505:905–926

Farre M, Perez S, Kantiani L, Barcelo D (2008) Fate and toxicity of emerging pollutants, their metabolites and transformafarretion products in the aquatic environment. Trends Anal Chem 27:991–1007

Fent K, Weston AA, Caminada D (2006) Ecotoxicology of human pharmaceuticals. Aquat Toxicol 76(2):122–159

Ferguson EM, Allinson M, Allinson G, Swearer SE, Hassell KL (2013a) Fluctuations in natural and synthetic estrogen concentrations in a tidal estuary in south-eastern Australia. Water Res 47:1604–1615

Ferguson PJ, Bernot MJ, Doll JC, Lauer TE (2013b) Detection of pharmaceuticals and personal care products (PPCPs) in near-shore habitats of southern Lake Michigan. Sci Total Environ 458–460:187–196

Fram MS, Belitz K (2011) Occurrence and concentrations of pharmaceutical compounds in groundwater used for public drinking-water supply in California. Sci Total Environ 409:3409–3417

Gomez E, Pillon A, Fenet H, Rosain D, Duchesne MJ, Nicolas JC (2005) Estrogenic activity of cosmetic components in reporter cell lines: parabens, UV screens, and musks. J Toxicol Environ Health 68:239–251

Hata T, Kawai S, Okamura H, Nishida T (2010) Removal of diclofenac and mefenamic acid by the white rot fungus Phanerochaete sordida YK-624 and identification of their metabolites after fungal transformation. Biodegradation 21(5):681–689

Heberer T (2002) Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. Toxicol Lett 131(1–2):5–17

Hu XG, Zhou QX, Luo Y (2010) Occurrence and source analysis of typical veterinary antibiotics in manure, soil, vegetables and groundwater from organic vegetable bases, northern China. Environ Pollut 158:2992–2998

Huggett DB, Brooks BW, Peterson B, Foran CM, Schlenk D (2002) Toxicity of select beta adrenergic receptor-blocking pharmaceuticals (β-blockers) on aquatic organisms. Arch Environ Contam Toxicol 43:229–235

Hutter HP, Wallner P, Moshammer H, Hartl W, Sattelberger R, Lorbeer G (2009) Synthetic musks in blood of healthy young adults: relationship to cosmetics use. Sci Total Environ 407:4821–4825

Jobling S, Williams R, Johnson A, Taylor A, Gross-Sorokin M (2006) Predicted exposures to steroid estrogens in UK rivers correlate with widespread sexual disruption in wild fish populations. Environ Health Perspect 114:32–39

Kasprzyk-Hordern B, Dinsdale RM, Guwy AJ (2009) The removal of pharmaceuticals, personal care products, endocrine disruptors and illicit drugs during wastewater treatment and its impact on the quality of receiving waters. Water Res 43:363–380

Katz K, Inoue T, Ietsugu H, Koba T, Sasaki H, Miyaji N, Kitagawa K, Sharma PK, Nagasawa T (2013) Performance of six multi-stage hybrid wetland systems for treating high-content wastewater in the cold climate of Hokkaido, Japan. Ecol Eng 51:256–263

Kemper N (2008) Veterinary antibiotics in the aquatic and terrestrial environment. Ecol Indic 8:1–13

Khanal SK, Xie B, Thompson ML, Sung S, Ong SK, van Leeuwen JH (2006) Fate, transport, and biodegradation of natural estrogens in the environment and engineered systems. Environ Sci Technol 40:6537–6546

Khunjar W, Mackintosh S, Skotnicka-Pitak J, Baik S, Aga D, Love N (2011) Elucidating the relative roles of ammonia oxidizing and heterotrophic bacteria during the biotransformation of 17a-ethinylestradiol and trimethoprim. Environ Sci Technol 45(8):3605–3612

Kim SD, Cho J, Kim IS, Vanderford BJ, Snyder SA (2007) Occurrence and removal of pharmaceuticals and endocrine disruptors in South Korean surface, drinking, and waste waters. Water Res 41:1013–1021

Kobayashi T, Suehiro F, Tuyen BC, Suzuki S (2007) Distribution and diversity of tetracycline resistance genes encoding ribosomal protection proteins in Mekong river sediments in Vietnam. FEMS Microbiol Ecol 59:729–737

Kolpin D, Skopec M, Meyer M, Furlong E, Zaugg S (2004) Urban contribution of pharmaceuticals and other organic wastewater contaminants to streams during differing flow conditions. Sci Total Environ 328:119–130

Lai KM, Scrimshaw MD, Lester JN (2002) The effects of natural and synthetic steroid estrogens in relation to their environmental occurrence. Crit Rev Toxicol 32:113–132

Li X, Ying GG, Su HC, Yang XB, Wang L (2010) Simultaneous determination and assessment of 4-nonylphenol, bisphenol A and triclosan in tap water, bottled water and baby bottles. Environ Int 36:557–562

Li X, Ying GG, Zhao JL, Chen ZF, Lai HJ, Su HC (2013) 4-Nonylphenol, bisphenol-A and triclosan levels in human urine of children and students in China, and the effects of drinking these bottled materials on the levels. Environ Int 52:81–86

Lignell S, Darnerud PO, Aune M, Cnattingius S, Hajslova J, Setkova L (2008) Temporal trends of synthetic musk compounds in mother's milk and associations with personal use of perfumed products. Environ Sci Technol 42:6743–6748

Liu, LL and Wong, MH (2013) Pharmaceuticals and personal care products (PPCPs): A review on environmental contamination in China. Environ Int 59:208–224

Liu L, Liu C, Zheng J, Huang X, Wang Z, Liu Y, Zhu G (2013) Elimination of veterinary antibiotics and antibiotic resistance genes from swine wastewater in the vertical flow constructed wetlands. Chemosphere 91:1088–1093

Liu L, Liu Y, Wang Z, Liu C, Huang X, Zhu G (2014) Behavior of tetracycline and sulfamethazine with corresponding resistance genes from swine wastewater in pilot-scale constructed wetlands. J Hazard Mater 278:304–310

López-Serna R, Petrović M, Barceló D (2012) Occurrence and distribution of multi-class pharmaceuticals and their active metabolites and transformation products in the Ebro River basin (NE Spain). Sci Total Environ 440:280–289

Lu Y, Yuan T, Yun SH, Wang WH, Kannan K (2010) Occurrence of synthetic musks in indoor dust from China and implications for human exposure. Arch Environ Contam Toxicol 60:182–189

Lu Y, Yuan T, Wang WH, Kannan K (2011) Concentrations and assessment of exposure to siloxanes and synthetic musks in personal care products from China. Environ Pollut 159:3522–3528

Managaki S, Murata A, Takada H, Tuyen BC, Chiem NH (2007) Distribution of macrolides, sulfonamides, and trimethoprim in tropical waters: ubiquitous occurrence of veterinary antibiotics in the Mekong Delta. Environ Sci Technol 41:8004–8010

Murdoch RW, Hay AG (2005) Formation of catechols via removal of acid side chains from ibuprofen and related aromatic acids. Appl Environ Microbiol 71(10):6121–6125

Nakada N, Kiri K, Shinohara H, Harada A, Kuroda K, Takizawa S (2008) Evaluation of pharmaceuticals and personal care products as water-soluble molecular markers of sewage. Environ Sci Technol 42:6347–6353

Plosz BG, Langford KH, Thomas KV (2012) An activated sludge modeling framework for xenobiotic trace chemicals (ASM-X): assessment of diclofenac and carbamazepine. Biotechnol Bioeng 109:2757–2769

Popa C, Favier L, Dinica R, Semrany S, Djelal H, Amrane A, Bahrim G (2014) Potential of newly isolated wild Streptomyces strains as agents for the biodegradation of a recalcitrant pharmaceutical, carbamazepine. Environ Technol 35(24):3082–3091

Pruden A, Pei RT, Storteboom H, Carlson KH (2006) Antibiotic resistance genes as emerging contaminants: studies in Northern Colorado. Environ Sci Technol 40:7445–7450

Ramaswamy BR, Shanmugam G, Velu G, Rengarajan B, Larsson DGJ (2011) GC–MS analysis and ecotoxicological risk assessment of triclosan, carbamazepine and parabens in Indian rivers. J Hazard Mater 186:1586–1593

Reiner JL, Berset JD, Kannan K (2007a) Mass flow of polycyclic musks in two wastewater treatment plants. Arch Environ Contam Toxicol 52:451–457

Reiner JL, Wong CM, Arcaro KF, Kannan K (2007b) Synthetic musk fragrances in human milk from the United States. Environ Sci Technol 41:3815–3820

Reis PJ, Reis AC, Ricken B, Kolvenbach BA, Manaia CM, Corvini PF, Nunes OC (2014) Biodegradation of sulfamethoxazole and other sulfonamides by Achromobacter denitrificans PR1. J Hazard Mater 280:741–749

Rosal R, Rodea-Palomares I, Boltes K, Fernández-Piñas F, Leganés F, Gonzalo S (2009) Ecotoxicity assessment of lipid regulators in water and biologically treated wastewater using three aquatic organisms. Environ Sci Pollut Res 17:135–144

Santosa IJ, Grossmana MJ, Sartorattob A, Ponezib AN, Durranta LR (2012) Degradation of the recalcitrant pharmaceuticals carbamazepine and 17a-ethinylestradiol by ligninolytic fungi. Chem Eng 27:169–174

Schwaiger J, Ferling H, Mallow U, Wintermayr H, Negele RD (2004) Toxic effects of the non-steroidal anti-inflammatory drug diclofenac: part I: histopathological alterations and bioaccumulation in rainbow trout. Aquat Toxicol 68:141–150

Stumpf M, Ternes TA, Wilken RD, 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

Tamtam F, Mercier F, Le Bot B, Eurin J, Tuc Dinh Q, Clément M (2008) Occurrence and fate of antibiotics in the Seine River in various hydrological conditions. Sci Total Environ 393:84–95

Teijón G, Candela L, Tamoh K, Molina-Díaz A, Fernández-Alba AR (2010) Occurrence of emerging contaminants, priority substances (2008/105/CE) and heavy metals in treated wastewater and groundwater at Depurbaix facility (Barcelona, Spain). Sci Total Environ 408:3584–3595

Touraud E, Roig B, Sumpter JP, Coetsier C (2011) Drug residues and endocrine disruptors in drinking water: risk for humans? Int J Hyg Environ Health 214:437–441

U.S. EPA (U.S. Environmental Protection Agency) (2013) Effluent guidelines—pharmaceutical manufacturing point source category—permit guidance document

U.S. FDA (U.S. Food and Drug Administration) (2013) Code of Federal Regulations Title 21, Part 25 Environmental Impact Considerations

Vieno NM, Härkki H, Tuhkanen T, Kronberg L (2007) Occurrence of pharmaceuticals in river water and their elimination in a pilot-scale drinking water treatment plant. Environ Sci Technol 41:5077–5084

Wang JL, Quan XC, Wu LB, Qian Y, Werner H (2002) Bioaugmentation as a tool to enhance the removal of refractory compound in coke plant wastewater. Process Biochem 38(5):777–781

Wang QJ, Mo CH, Li YW, Gao P, Tai YP, Zhang Y (2010) Determination of four fluoroquinolone antibiotics in tap water in Guangzhou and Macao. Environ Pollut 158:2350–2358

Wang L, Liao CY, Liu F, Wu Q, Guo Y, Moon HB (2012) Occurrence and human exposure of p-hydroxybenzoic acid esters (parabens), mbisphenol A diglycidyl Ether (BADGE), and their hydrolysis products in indoor dust from the United States and three East Asian countries. Environ Sci Technol 46:11584–11593

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

Yang LH, Ying GG, Su HC, Stauber JL, Adams MS (2008) Growth-inhibiting effects of 12 antibacterial agents and their mixtures on the freshwater microalga Pseudokirchneriella subcapitata. Environ Toxicol Chem 27:1201–1208

Yin J, Wang H, Zhang J, Zhou NY, Gao FD, Wu YN (2012) The occurrence of synthetic musks in human breast milk in Sichuan, China. Chemosphere 87:1018–1023

Zhang Y, He C, Sharma V, Li X, Tian S, Xiong Y (2011) A new reactor coupling heterogeneous Fenton-like catalytic oxidation with membrane separation for degradation of organic pollutants. J Chem Technol Biotechnol 86:1488–1494

Zhang L, Hu J, Zhu R, Zhou Q, Chen J (2013) Degradation of paracetamol by pure bacterial cultures and their microbial consortium. Appl Microbiol Biotechnol 97(8):3687–3698