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Occurrence and fate of pharmaceutical products and by-products, from resource to drinking water

S. Mompelat, B. Le Bot, O. Thomas *

School of Public Health (Ecole des Hautes Etudes en Santé Publique), Laboratoire d'Etude et de Recherche en Environnement et Santé (LERES), Avenue Professeur Léon Bernard, 35000 Rennes, France

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ABSTRACT

Among all emerging substances in water, pharmaceutical products (PPs) and residues are a lot of concern. These last two years, the number of studies has increased drastically, however much less for water resources and drinking water than for wastewater. This literature review based on recent works, deals with water resources (surface or groundwater), focusing on characteristics, occurrence and fate of numerous PPs studied, and drinking water including water quality. Through this review, it appears that the pharmaceutical risk must be considered even in drinking water where concentrations are very low. Moreover, there is a lack of research for by-products (metabolites and transformation products) characterization, occurrence and fate in all water types and especially in drinking water.

1. Introduction

In Europe, around 4000 different pharmaceutical active compounds, used as human and veterinary drugs, are susceptible to reach every environmental compartment. The relatively recent awareness of pharmaceutical products (PPs) impact on environment is reflected in literature since the 1990s through the exponentially increasing number of studies concerning this emergent class of water pollutants. For example, only half of papers cited in this review were published before 2007. This rising interest is not only concomitant with the widespread and growing use of human and veterinary PPs consumption, but also with the analytical techniques improvement allowing detecting traces of substances (ng/L or less) in any type of water.

The great majority of studies on pharmaceutical products PPs in water concerns their analysis, occurrence and fate in wastewater (WW) and wastewater treatment plant (WWTP), with an emphasis on processes efficiency with respect to their removal. As the majority of organic micropollutants, the contamination origin is above all anthropogenic and continuously released in wastewater or directly in the environment (via human and animal excretion). As some pesticides and other priority substances, PPs are ubiquitary substances more often persistent and bioaccumulable in the environment mainly in surface water (SW) and sometimes in groundwater (GW). For drinking water (DW), studies are less numerous but the risk is higher. The aim of this literature review is to show the quality and safety issue for water resource and drinking water. It mainly focuses on occurrence and fate of PPs and by-products (BPs), with few considerations on WWTP, the efficiency of which being rather extensively studied.

2. PPs of concern

The literature review shows that about 160 PPs (human and veterinary), and 30 by-products (BPs) have been recently studied. They are presented according to their therapeutic use in Table 1 from studies concerning analytical developments, occurrence in aquatic compartments, fate in the environment, or fate and elimination during wastewater and drinking water treatments. Works exclusively devoted to ecotoxicology studies were not considered.

PPs and BPs are spread into 24 therapeutic classes, among which 4 are dominant in term of references. About 40% of studies concern non-steroidal anti-inflammatory drugs (NSAIDs), the three others being anticonvulsants, antibiotics, and lipid regulators between 25 and 30% of references (a lot of studies involving substances of several PPs classes).

NSAIDs are essentially represented by ibuprophen and diclofenac, and gemfibrozil is the most studied lipid regulator. For anticonvulsants, carbamazepine is targeted in many studies, notably as a spatial trends indicator of PPs at the entire city scale (Reinstorf et al., 2008). Antibiotics are characterized by the great variety of substances (e.g. macrolides, sulfonamides, β-lactams, quinolones, etc.). Kemper (2008) has studied 52 substances, among which sulfamethoxazole for human use and trimethoprim, often associated with sulfonamides. Veterinary drugs are more often antibiotics used prevently, curatively (Kümmerer, 2001) or, also as growth promoters before their EU ban in 2006 (Kemper, 2008). In fact, many human and veterinary antibiotics are analogous as well as the most widely antihelminthic used, i.e.

* Corresponding author. Tel.: +33 2 99 02 29 20; fax: +33 2 99 02 29.
E-mail address: Olivier.Thomas@ehesp.fr (O. Thomas).

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Table 1
Human and veterinary pharmaceuticals and few by-products (metabolites and degradation products) found in literature.

Therapeutic use	Compounds (parent compounds and *metabolites*)	References	Number of ref.
Antiacid; Histamine-2 blockers	Cimetidine, ranitidine	Zuccato et al. (2000), Gibs et al. (2007), Kasprzyk-Hordern et al. (2007), Brown et al. (2006), Kolpin et al. (2002), Buth et al. (2007), Stackelberg et al. (2004), Glassmeyer and Shoemaker, (2005)	8
Antianginal	*Dehydronifedipine* (Nifedipine metabolite)	Stackelberg et al. (2007), Gibs et al. (2007), Kolpin et al. (2002), Stackelberg et al. (2004)	4
Antiasthmatic	Albuterol	Stackelberg et al. (2004)	1
Antibiotic: Beta-lactams – Cyclines – Fluoroquinolones/ Quinolones – Lincosamides – Macrolides – Nitrofurans – Phenicols or Propanediols – Phenols – Pyrimidines – Sulfonamides – other chemical classes	Amoxicillin, Cefuroxime, Ceftriaxone, Penicillin G1/2-benzathine salt, Penicillin V potassium salt – Demeclocycline, Doxycycline, Minocycline Oxytetracycline HCl, Chlortetracycline, Tetracycline – Ciprofloxacin, Danofloxacin, Difloxacin, Enoxacin, Enrofloxacin, Flumequine, Lomefloxacin, Nalidixic acid, Norfloxacin, Ofloxacin, Oxolonic acid, Pipemidic acid, Sarafloxacin – Clindamycin, Lincomycin – Azithromycin, Clarithromycin, Erythromycin, *Erythromycin–H2O* (Erythromycin metabolite), Oleandomycin, Roxithromycin, Spiramycin, Tylosin, Tylosin tartrate – Furaltadone, Furazolidone, Nitrofurantoin – Chloramphenicol – Triclosan – Trimethoprim – Sulfachlorpyridazine, Sulfadiazine, Sulfadimethoxine, Sulfamerazine, Sulfamethazine, Sulfamethizole, Sulfamethoxazole, Sulfapyridine, Sulfathiazole – Carbadox, Cephalexin, Gentamicin sulfate, Imipenem, Metronidazole, Miconazole, Monensin, Nistatin, Ornidazole, Roxarsone, Virginiamycin, Vancomycin hydrochloride	Bones et al. (2006), Zuccato et al. (2000), Kasprzyk-Hordern et al. (2007), Kasprzyk-Hordern et al. (2008), Glassmeyer and Shoemaker (2005), Grung et al. (2007), Brown et al. (2006), Kolpin et al. (2002), Stackelberg et al. (2004), Vieno et al. (2006a), Mitani and Kataoka (2006), Hari et al. (2005), Vieno et al. (2007), Tamtam et al. (2008), Stackelberg et al. (2007), Yoon et al. (2007), Huber et al. (2003), Huber et al. (2005), Ternes et al. (2007), Westerhoff et al. (2005), Loraine and Pettigrove (2006), Gibs et al. (2007), Adams et al. (2002), Vieno et al. (2006b), Canonica et al. (2008), Maskaoui et al. (2007), Vanderford and Snyder (2006), Managaki et al. (2007), Edhlund et al. (2006), Palmer et al. (2008), Alexy et al. (2004), Gartiser et al. (2007), Andreozzi et al. (2003), Boreen et al. (2005), Carrara et al. (2008)	35
Anticoagulant	Warfarin	Bones et al. (2006), Gibs et al. (2007), Kolpin et al. (2002), Stackelberg et al. (2004), Glassmeyer and Shoemaker (2005)	5
Anticonvulsant	Carbamazepine, *10,11-dihydro-10-11-dihydroxycarbamazepine, 10,11-dihydro-10-11-epoxycarbamazepine*, 2-,3-hydroxy*carbamazepine, 10,11-dihydro-10-hydroxycarbamazepine* (carbamazepine metabolites), Dilantin, Gabapentin, Primidone	Verliefde et al. (2007), Reinstorf et al. (2008), Osenbrück et al. (2007), Bones et al. (2006), Stackelberg et al. (2007), Ternes et al. (2002), Togola and Budzinski (2008), Yoon et al. (2007), Vieno et al. (2006a), Gibs et al. (2007), Kasprzyk-Hordern et al. (2007), Kasprzyk-Hordern et al. (2008), Urase and Sato (2007), Quintana et al. (2007), Hari et al. (2005), Vieno et al. (2006b), Heberer et al. (2004), Hua et al. (2006), Huber et al. (2003),Huber et al. (2005), Rabiet et al. (2006), Stackelberg et al. (2004), Ternes et al. (2007), Vieno et al. (2007), Westerhoff et al. (2005), Zühlke et al. (2004a), Maskaoui et al. (2007), Vanderford and Snyder (2006), Miao and Metcalfe (2003), Andreozzi et al. (2003), Chiron et al. (2006)	31
Antidepressant; anti-anxiety – antipsychotic	Amitryptiline, Diazepam, Doxepine, Fluoxetine, Imipramine, Meprobamate, *Nordiazepam* (Diazepam metabolite), *Norfluoxetin* (fluoxetin metabolite), Oxazepam (also a diazepam and nordiazepam metabolite), Thioridazine – Risperidone	Togola and Budzinski (2008), Kasprzyk-Hordern et al. (2007), Yoon et al. (2007), Zuccato et al. (2000), Bones et al. (2006), Stackelberg et al. (2007), Kolpin et al. (2002), Bedner and MacCrehan (2006), Huber et al. (2003), Huber et al. (2005), Löffler et al. (2005), Rabiet et al. (2006), Stackelberg et al. (2004), Westerhoff et al. (2005), Maskaoui et al. (2007), Vanderford and Snyder (2006)	16
Anti-diabetic	Metformin, Glibenclamide	Bones et al. (2006), Kolpin et al. (2002), Huber et al. (2005)	3
Antihelminthic	Ivermectin	Bones et al. (2006), Löffler et al. (2005), Sanderson et al. (2007)	3
Antifungal	Clotrimazole	Bones et al. (2006)	1
Antihistamine	Diphenhydramine	Stackelberg et al. (2007), Stackelberg et al. (2004)	2
Antihypertensive	Diltiazem, Enalapril, *Enalaprilat* (=enalapril maleate metabolite), Valsartan	Kolpin et al. (2002), Stackelberg et al. (2004), Kasprzyk-Hordern et al. (2007), Kasprzyk-Hordern et al. (2008), Glassmeyer and Shoemaker (2005), Vanderford and Snyder (2006)	6
Antineoplastic	5-Fluorouracil, Cyclophosphamide, Epirubicin/Doxorubicin, Ifosfamide, Methotrexate, Tamoxifen	Mitani and Kataoka (2006), Verliefde et al. (2007), Yoon et al. (2007), Zuccato et al. (2000), Huber et al. (2005), Stackelberg et al. (2004), Grung et al. (2007), Maskaoui et al. (2007), Buerge et al. (2006), Kümmerer et al. (1997)	10
Beta blocker	Acebutolol, Atenolol, Celiprolol, Metoprolol, Nadolol, Pindolol, Propanolol, Sotalol	Verliefde et al. (2007), Bones et al. (2006), Vieno et al. (2006a), Zuccato et al. (2000), Kasprzyk-Hordern et al. (2007), Quintana et al. (2007), Bedner and MacCrehan (2006), Pinkston and Sedlak (2004), Ternes et al. (2007), Vieno et al. (2007), Grung et al. (2007), Maskaoui et al. (2007), Vanderford and Snyder (2006), Palmer et al. (2008), Andreozzi et al. (2003)	15

Birth control	Ethynylestradiol (Synthetic steroid hormone, EE2); 6α-methyl-17α-hydroxyprogesterone acetate	Yoon et al. (2007), Moder et al. (2007), Canonica et al. (2008), Huber et al. (2003), Huber et al. (2005), Westerhoff et al. (2005), Ra et al. (2008), Glassmeyer and Shoemaker (2005), Grung et al. (2007), Palmer et al. (2008)	10
Bronchodilator	Clenbuterol, Salbutamol, Terbutaline	Verliefde et al. (2007), Bones et al. (2006), Togola and Budzinski (2008), Zuccato et al. (2000), Kasprzyk-Hordern et al. (2007), Quintana et al. (2007), Kolpin et al. (2002), Rabiet et al. (2006)	8
Cardiac stimulant	Digoxin, *Digoxigenin* (Digoxin metabolite)	Kasprzyk-Hordern et al. (2008), Kolpin et al. (2002), Stackelberg et al. (2004)	3
Contrast media	Gadolinium (Gd-DTPA:Gd-diethylenetriamine pentaacetic acid), Iopromide X-ray , Iomeprol, Iohexol, Iopamidol, Diatrizoate	Reinstorf et al. (2008), Yoon et al. (2007), Pérez and Barceló (2007b), Canonica et al. (2008), Huber et al. (2003), Huber et al. (2005), Löffler et al. (2005), Ternes et al. (2007), Westerhoff et al. (2005), Haiß and Kümmerer (2006)	10
Diuretic	Bendroflumethiazide, Furosemide	Bones et al. (2006), Zuccato et al. (2000), Kasprzyk-Hordern et al. (2008), Stackelberg et al. (2004)	4
Lipid regulator	Atorvastatin, Bezafibrate, Clofibrate, *Clofibric acid* (active metabolite of clofibrate), Fenofibrate, *Fenofibric acid* (active metabolite of fenofibrate), Gemfibrozil, *o- and p-hydroxyatorvastatin* (atorvastatin metabolites), Pravastain, Simvastatin, *Simvastatin hydroxy acid* (Simvastatin metabolite)	Bones et al. (2006), Ternes et al. (2002), Zuccato et al. (2000), Kasprzyk-Hordern et al. (2007), Kasprzyk-Hordern et al. (2008), Urase and Sato (2007), Quintana et al. (2007), Moder et al. (2007), Togola and Budzinski (2008), Yoon et al. (2007), Gibs et al. (2007), Kolpin et al. (2002), Heberer et al. (2004), Huber et al. (2003), Huber et al. (2005), Jux et al. (2002), Löffler et al. (2005), Loraine and Pettigrove (2006), Pinkston and Sedlak (2004), Rabiet et al. (2006), Stackelberg et al. (2004), Ternes et al. (2007), Vieno et al. (2005), Vieno et al. (2007), Westerhoff et al. (2005), Ra et al. (2008), Glassmeyer and Shoemaker, (2005), Dordio et al. (2007), Vanderford and Snyder (2006), Vanderford and Snyder (2006), Carrara et al. (2008), Andreozzi et al. (2003)	32
Non-steroidal anti-inflammatory drug (NSAID) and analgesic	5-Aminosalicylic acid, Aminopyrine, Aspirin (acetyl salicylic acid or ASA), Diclofenac, DMAA (dimethylaminophenazone), Fenoprofen, Flufenamic acid, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Meclofenamic acid, Mefenamic acid, Naproxen, Nimesulide, Paracetamol (acetaminophen), Phenazone, Propyphenazone, *Salicylic acid* (ASA active metabolite), Sulfapyridine, Sulfasalazine, Tolfenamic acid	Araujo et al. (2008), Kasprzyk-Hordern et al. (2007), Kasprzyk-Hordern et al. (2008), Verliefde et al. (2007), Togola and Budzinski (2008), Bones et al. (2006), Ternes et al. (2002), Yoon et al. (2007), Urase and Sato (2007), Quintana et al. (2007), Moder et al. (2007), Zühlke et al. (2007), Zuccato et al. (2000), Gibs et al. (2007), Stackelberg et al. (2007), Hari et al. (2005), Vieno et al. (2006b), Kolpin et al. (2002), Reddersen et al. (2002), Heberer et al. (2004), Canonica et al. (2008), Huber et al. (2003), Huber et al. (2005), Jux et al. (2002), Löffler et al. (2005), Loraine and Pettigrove (2006), Pinkston and Sedlak (2004), Rabiet et al. (2006), Stackelberg et al. (2004), Ternes et al. (2007), Vieno et al. (2005), Vieno et al. (2007), Westerhoff et al. (2005), Zühlke et al. (2004a,b), Ra et al. (2008), Glassmeyer and Shoemaker (2005), Grung et al. (2007), Maskaoui et al. (2007), Vanderford and Snyder (2006), Palmer et al. (2008), Carrara et al. (2008), Andreozzi et al. (2003), Deng et al. (2003)	44
NSAID: DMAA metabolites and/or *degradation products*	*AAA (acetoaminoantipyrine), AMDOPH (1-acetyl-1-methyl-2-dimethyloxamoyl-2-phenylhydrazide), AMPH (1-acetyl-1-methyl-2-phenylhydrazide), FAA (formylaminoantipyrine)*	Zühlke et al. (2007), Reddersen et al. (2002), Heberer et al. (2004), Zühlke et al. (2004a).	4
NSAID: Phenazone *degradation products*	*DP* (1,5-dimethyl-1,2-dehydro-3-pyrazolone), *DMADP* (4-(*N*,*N*-dimethyl)-amino-1,5-dimethyl-1,2-dehydro-3-pyrazolone)	Zühlke et al. (2007), Zühlke et al. (2004a,b)	3
NSAID: Prophyphenazone *degradation product*	*PDP* (4-(2-methylethyl)-1,5-dimethyl-1,2-dehydro-3-pyrazolone)	Zühlke et al. (2007), Zühlke et al. (2004a,b)	3
Opioidanalgesic	Codeine, Fentanyl (synthetic), Morphine, Methadone (synthetic), Tramadol, *6-Acetylmorphine* (6-AM, morphine metabolite), EDDP, *Norcodeine* (codeine metabolite), *Normorphine* (morphine metabolite)	Boleda et al. (2007), Stackelberg et al. (2007), Gibs et al. (2007), Kasprzyk-Hordern et al. (2007), Kolpin et al. (2002), Stackelberg et al. (2004)	6
Psycho-stimulant	Caffeine, *1,7-dimethylxanthine* (Caffeine metabolite), Amphetamine	Bones et al. (2006), Brown et al. (2006), Togola and Budzinski (2008), Yoon et al. (2007), Gibs et al. (2007), Kolpin et al. (2002), Hua et al. (2006), Huber et al. (2005), Rabiet et al. (2006), Stackelberg et al. (2004), Ternes et al. (2007), Westerhoff et al. (2005), Kasprzyk-Hordern et al. (2007), Glassmeyer and Shoemaker (2005)	14
Vasodilatator	Pentoxyfilline	Verliefde et al. (2007), Yoon et al. (2007), Huber et al. (2005), Westerhoff et al. (2005)	4
Steroid hormone (excepted EE2)	Androstenedione, Estradiol (E2) (can also be a metabolite of EE2), *Estriol* (E3), *Estrone* (E1), Progesterone, Testosterone	Zuccato et al. (2000), Yoon et al. (2007), Huber et al. (2005), Westerhoff et al. (2005), Ra et al. (2008), Palmer et al. (2008)	6

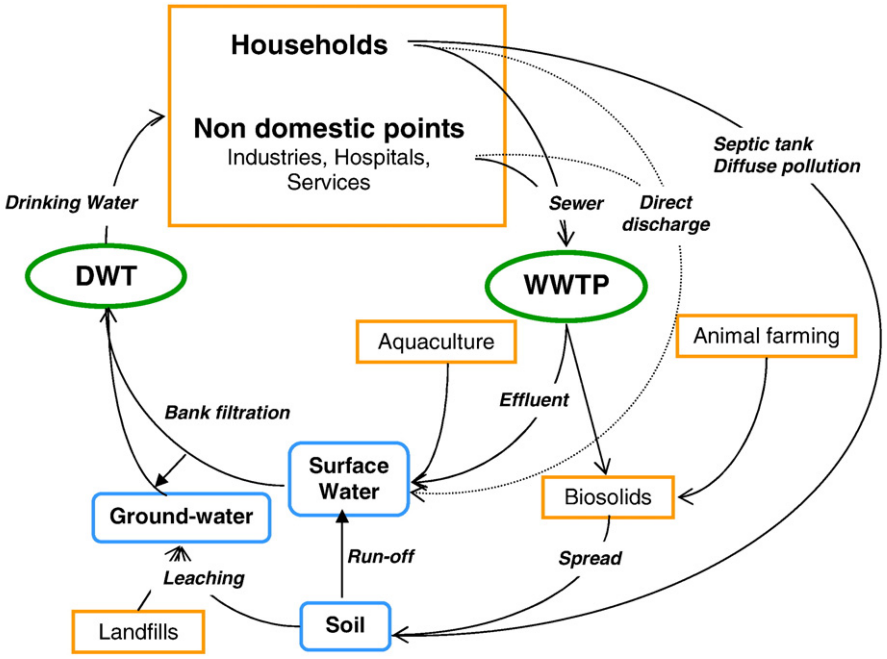

Fig. 1. Origin and routes of PPs (adapted from Petrović et al., 2003).

ivermectin (Sanderson et al., 2007), diclofenac (NSAID) (Fent et al., 2006), etc.

Little is still known about the occurrence and fate of BPs, most of studies being more often limited to parent PPs (Löffler et al., 2005). Clofibric acid, a clofibrate metabolite, is one of the most studied metabolites, probably because of the fact that it is a pro-drug metabolite, the active form on human body being not the ingested molecule (clofibrate) but the metabolized one. Fenofibric acid and salicylic acid are also active metabolites of pro-drugs, respectively fenofibrate and aspirin.

The choice of PPs is principally based on consumption considerations, on their toxicity at trace level (ng/L) for aquatic flora (Fent, 2008; Nentwig, 2008), fauna and/or human beings, and on their persistence in environment. PPs like erythromycin, cyclophosphamide, naproxen, sulfamethoxazole, sulfasalazine, or metabolite such as clofibric acid, are known to be persistent more than one year in all natural waters (Zuccato et al., 2000). Many PPs are candidates to produce acute or chronic adverse effects on ecosystems and humans. For instance, hormones like estrogens are recognized as endocrine disruptors or modulators because they may cause adverse effects on reproductive and sexual development (Robinson et al., 2007; Ingerslev et al., 2003; Lai et al., 2002), like feminization of male fishes at only ng/L range. North America (Canada, USA, and Mexico) is ahead of EU in matter of PPs consumption (Robinson et al., 2007) which continuously arises every year, e.g. near 10% increase per year of antineoplastic administrations (Johnson et al., 2008). For the most common PPs, the

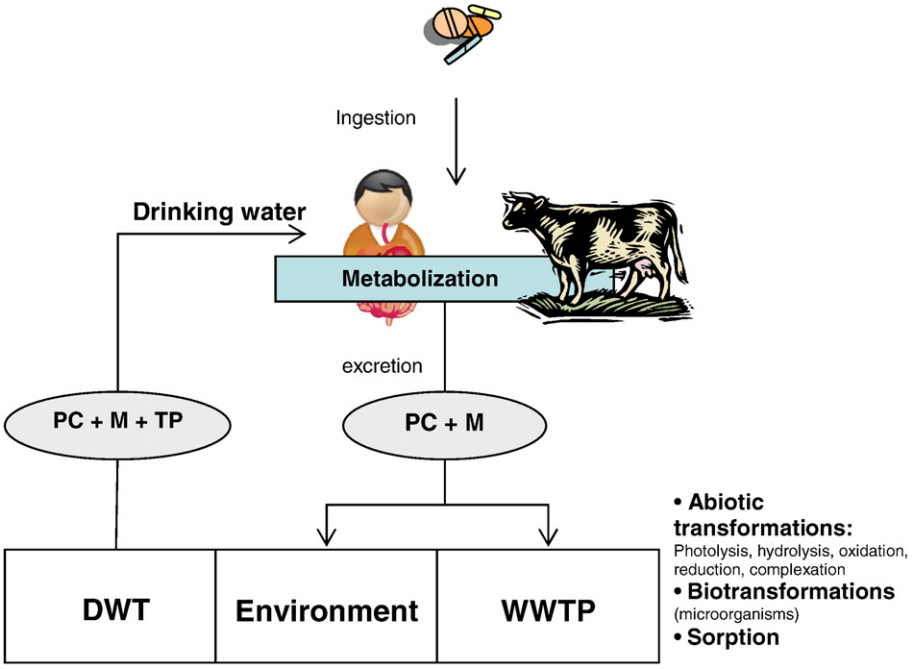

Fig. 2. Transformation pathways of PPs (PC: parent compound, M: Metabolite(s), TP: Transformation Product(s), WWTP: Waste Water Treatment Plant; DWT: Drinking Water Treatments).

annual consumption in Europe is several hundred tons (Fent et al., 2006). For instance, NSAIDs like aspirin (acetylsalicylic acid), paracetamol, ibuprofen, diclofenac were produced in Germany in 2001 at respectively, 836, 622, 345 and 86 t, while metformin (antidiabetic) and carbamazepine (anticonvulsant) were produced at 517 and 88 t (Fent et al., 2006). Moreover, antibiotics consumption can reach up to several thousand tons per year because of their extensive use in farming, aquaculture, and human medicine, e.g. more than 13000 t (65% as human use) in EU and Switzerland in 1999 (Kemper, 2008), with France positioned as the greatest consumer in Europe (Goossens et al., 2005).

Finally, the choice of PPs and the difficulties encountered to model PPs contamination in natural waters are related to prescription and non-prescription practices in each country (Zuccato et al., 2006; Goossens et al., 2005) (e.g. vancomycin is one of the most prescribed antibiotics in the USA contrary to European countries (Kümmerer, 2001)) and to the quantification uncertainty of PPs really used (Fent et al., 2006).

3. Origins of PPs

Accurate assessment of PPs impact on the environment is as difficult as there is a multitude of input sources in environment with no evident quantitative data available concerning the relative distribution of PPs from all emission sources (Fig. 1). Although humans and animals treated with PPs constitute the main contamination source of potable water resources (i.e. SW and GW), PPs are qualitatively, quantitatively, spatially and temporally shared out into different routes depending on whether patients are located in private households or in hospitals and other places (e.g. schools, residential facilities like retirement facilities). Indeed, prescribed drugs in hospitals are rather designated to treat heavier pathologies than in households. As an example, antineoplastics (also named cytotoxics) used in cancer chemotherapy were exclusively prescribed and principally (intravenously or orally) administered in hospitals. Thus, they were released mainly in hospital effluents between 5 and 50 µg/L (Kümmerer, 2001), but nowadays, 75% of antineoplastics are given in outpatient departments with a huge trend for oral administration at home (Johnson et al., 2008; Kümmerer and Schuster, 2008).

Improper disposal of unused or expired drugs, which are directly thrown in toilets or end up in landfill, and pharmaceutical residues from manufacture spill accidents (Reddersen et al., 2002) can also be regarded as other significant local points of potential contamination.

Once ingested and metabolized, PPs (i.e. native and/or metabolite compounds) are excreted via urine and faeces and take the sewer network as urban wastewater route until wastewater treatment plant (WWTP) or, for countryside households directly released into septic tanks (Carrara et al., 2008). Both, WWTP and septic system are not designed to eliminate highly polar micropollutants like PPs, but depending on PPs nature and on the process design, the elimination rates cover the whole range between 0 and 100% (Radjenović et al., 2007; Drewes, 2007). Among PPs not retained in WWTP, only 10 to 20% of carbamazepine is removed (Radjenović et al., 2007; Pérez and Barceló, 2007a), and then found with other not removed PPs in treated WW discharges in SW (i.e. rivers, lakes, streams, estuaries). Moreover, combined sewer overflows may release directly raw wastewater with PPs in case of heavy rain (Tamtam et al., 2008). For dispersed households and depending on soil nature, septic tanks are also susceptible to release PPs, but this time, into GW (Carrara et al., 2008).

Differently, direct release of veterinary pharmaceuticals in environment may occur via application in aquaculture (i.e. fish farming), but also indirect release by way of animals topically treated, and mostly via run-off and leaching through fields from manure spreading to agricultural fields and livestock wastes (Sanderson et al., 2007; Boxall et al., 2004; Boxall, 2008; Khan et al., 2007; Sarmah et al., 2006; Kemper, 2008).

GW and SW are physically closely linked, and therefore, these compartments can contaminate one another, e.g. GW pollution from artificial recharge of polluted SW or of treated WW reuse (despite soil or bank filtration) and exfiltration from GW to connected SW (Jux et al., 2002).

The ultimate elimination step of PPs in raw water resources before drinking-water distribution is their passage through water works treatment plants.

4. By-products

By-products (BPs) include both metabolites excreted via urine or faeces, and transformation products which can be formed in environment from PPs and/or metabolites released, under physico-chemical and biological factors as in WWTP or water works (Fig. 2). Concern has been raised regarding the BPs of human and veterinary pharmaceuticals since recently some ecosystem impacts have been shown and effect on human suspected (Table 2).

Once in human/animal body, the parent molecule of a pharmaceutical substance (i.e. the ingested molecule) undergoes a set of biochemical reactions. For example, PPs elimination in urine and/or faeces is driven by the hepatic metabolism (Pérez and Barceló, 2007a; Robinson et al., 2007; Löffler et al., 2004), with a first step including oxidation, reduction, hydrolytic cleavages of PPs leading to more polar molecules than the parent compounds. A second conjugation step consists in transferring polar group on parent compounds or metabolites, such as prominently glucuronidation, and sulphatation, allowing metabolites becoming enough hydrophilic and water soluble to be eliminated through urine and/or faeces. Another notable specificity of metabolization is the induction of the loss of pharmaceutical activity of the native PP. Nevertheless, pro-drugs, by definition, are active only after the metabolic activation by enzymatic system(s) of the parent compound to metabolite(s). It concerns fibrates (lipid regulators, e.g. fenofibrate or clofibrate), antineoplastics like cyclophosphamide, ifosfamide (Buerge et al., 2006), 5-fluorouracil, etc.

Metabolite names and formula, and excretion rates are expected to be found in the market authorization files (according to EMEA in Europe, and FDA in USA) and interesting data for some substances can be found in the Martindale electronic database. PPs may be classified in four excretion rates classes under their unchanged form (Jjemba, 2006), i.e. respectively, low excretion ($\leq$5%), moderately low (6–39%), relatively high (40–69%), and high excretion ($\geq$70%). Table 2 presents some PPs belonging to the different excretion rates classes, and as much as possible, refers to associated metabolites with their own excretion rates. Actually, from very partial data listed in Table 2, it can be observed that parent PPs are, for only a little majority (more exactly 20 compounds), moderately low excreted (i.e. between 6 and 39%). The other PPs are quite homogeneously distributed in the three remaining excretion classes. According to the moderately low excretion of parent compound, it seems legitimate to suspect the presence of metabolites in aquatic compartments after their release in sewage waters. Nevertheless, among the numerous metabolites which can be formed during metabolization, usually a few number is prominently excreted. For instance, carbamazepine can be derived in thirty-three metabolites (Miao and Metcalfe, 2003), whereas only two of them are mostly excreted (i.e. 10,11-dihydro-10-11-dihydroxycarbamazepine and 10,11-dihydro-10-11-epoxycarbamazepine).

PPs elimination rates via urine and/or faeces depend on the pharmaceutical substance, the age and constitution of the patient, the way of application (orally or intravenously for humans), and the time of administration (Kümmerer et al., 2000; Pérez and Barceló, 2007a; Kemper, 2008). Despite the difficulty to define precise and general trends of behavior excretion for the PPs therapeutic classes some tendencies can be noted for antidepressants which are lowly excreted ($\leq$5%), and NSAIDs poorly excreted ($\leq$15%).

The difference between metabolites and transformation products is not so clear as reactions may be very close regarding human metabolism and biodegradation in environment or in treatment

Table 2
Class of pharmaceutical products based on their excretion rates (adapted from Jjemba, 2006).

Therapeutic use	Proportion of the parent compound excreted (%)				Metabolites excreted and (% excreted)	References
	Low (≤5%)	Moderately low (6–39%)	Relatively high (40–69%)	High (≥70%)		
Antiacids			Cimetidine (48–75); Ranitidine (30–70)	Cimetidine (48–75);	Cimetidine N-glucuronide (24), cimetidine sulphoxide (7–14), hydroxymethylcimetidine (4); N-oxide (3–6%), S-oxide (1–2) and desmethyl ranitidine (1–2)	Kasprzyk-Hordern et al. (2007)
Antibiotics	Erythromycin (5–10)	Erythromycin (5–10) Norfloxacin (30); Chloramphenicol (5–10 or 8–12); Sulfamethoxazole (15 or 30); Metronidazole (40 or 20) Spiramycin (20); Clarithromycin (25)	Ciprofloxacin (83.7 or 50–70)	Ciprofloxacin (83.7 or 50–70); Amoxicillin (80–90 or 60–80) ; Doxycycline (70) ; Tetracycline (80–90); Trimethoprim (60 or 80); Ceftriaxone (70)	*Amoxicilin:* Penicilloic acid (10–25); *Ciprofloxacin* : Oxociprofloxacin (3) (active) ; *Erythromycin* :**Erythromycin-H_2O**; *Chloramphenicol*: Glucuronide conjugates; *Trimethoprim*: 1,3-oxides; 3′,4-hydroxy derivatives; *Sulfamethoxazole*: **N_4-Acetylsulfamethoxazole**	Jjemba (2006), Kasprzyk-Hordern et al. (2007), Zuccato et al. (2005)
Anticonvulsant	Carbamazepine (1–2)	Primidone (15–40)		Gabapentin (100)	*Carbamazepine*: **10,11-dihydro-10-11-dihydroxycarbamazepine** (most important, no activity**), 10,11-dihydro-10-11-epoxycarbamazepine** (also active)**, 2-hydroxycarbamazepine, 3-hydroxycarbamazepine, 10,11-dihydro-10-hydroxycarbamazepine** and 10,11-dihydro-10-11-dihydroxycarbamazepine glucuronated metabolites; *Gabapentin*: No metabolites	Jjemba (2006), Kasprzyk-Hordern et al. (2007), Miao and Metcalfe (2003)
Antidepressants – anti-anxiety	Diazepam (1); Diltiazem (2–4); Amitryptilline (little)				*Amitryptiline*: Nortriptyline, 10-hydroxyamitriptyline (active), 10-hydroxynortriptyline (active); *Diazepam*: **N-desmethyldiazepam**, **oxazepam**, and temazepam (22–43) ; *Diltiazem*: Desacetyldiltiazem and N-monodemethyldiltiazem (active)	Jjemba (2006), Kasprzyk-Hordern et al. (2007)
Anti-hypertensives		Enalapril (30–36)		Valsartan (80)	*Enalapril*: **Enalaprilate**; *Valsartan*: valeryl 4-hydroxy valsartan (9)	Jjemba (2006), Kasprzyk-Hordern et al. (2007), Zuccato et al. (2005)
Antineoplastics	Cyclophosphamide (≤5–20); Ifosfamide (up to 15)	Cyclophosphamide (≤5–20); Ifosfamide (up to 15); 5-Fluorouracil (11–20); Epirubicin/Doxorubicin (biliary excretion: 9–11 within 48 h)	Epirubicin/ Doxorubicin (40 (biliary excretion within 72 h))		*5-Fluorouracil*: its pro-drug is capecitabine;	Johnson et al. (2008), Kümmerer et al. (1997), Buerge et al. (2006)
Beta-blockers	Propanolol (<0.5) Metoprolol (3–30)	Metoprolol (3–30) Acebutolol (39)	Atenolol (50–90)	Atenolol (50–90) Sotalol (>75)	*Atenolol*: Not active metabolites; Hydroxylated metabolite (3); *Metoprolol*: glucuronide conjugates (20); *Propanolol:* 4-Hydroxypropranolol (active)	Kasprzyk-Hordern et al. (2007), Zuccato et al. (2005), Vieno et al. (2006a)
Bronchodilatators		Salbutamol (30)			Phenolic sulfate (45–60), 4′-o-sulfate ester (inactive)	Kasprzyk-Hordern et al. (2007)
Cardiac stimulants			Digoxin (50–70)		Digoxin metabolite = Digoxigenin	Jjemba (2006)
Diuretics			Furosemide (40–90)	Furosemide (40–90)	–	Jjemba (2006), Zuccato et al. (2005)
Lipid regulators		Simvastatin (10–15)	Bezafibrate (45–50)		*Gemfibrozil*: 70% excreted in urine as a glucuronide conjugates and metabolites; *Clofibrate*(Pro-drug): **clofibric acid**; *Fenofibrate*: fenofibric acid glucuronide conjugates; *Simvastatin(pro-drug):* = **Simvastatin β-hydroxiacid** (active form)	Jjemba (2006), Martindale (1999), Zuccato et al. (2005)
NSAIDs and analgesics	Ibuprofen (1–10) ; Paracetamol (acetaminophen) (<5)	5-Aminosalicylic acid (<12); Diclofenac (15)			*5-Aminosalicylic acid* : N-Acetyl-5-aminosalicylic acid (8–77); *Aspirin*: 2–30% as **salicylic acid**, + ortho-hydroxyhippuric acid + **gentisic acid**; *Ibuprofen*: 2-[4-(2-hydroxy-2 methylpropyl)phenyl]propionic acid (=**hydroxy-ibuprofen**) and 2-[4-(2 carboxypropyl)phenyl]propionic acid (=**carboxy-ibuprofen**); *Paracetamol*: Sulfate conjugate (30%), paracetamol cysteinate and mercapturate (5%)	Kasprzyk-Hordern et al. (2007), Jjemba (2006), Heberer (2002), Jux et al. (2002), Zuccato et al. (2005)
Opioanalgesics		Tramadol (15–35)		Codeine (70 free or as conjugates); Morphine (71.6)	Codeine-6-glucuronide (main); free or conjugated morphine (10–15), and norcodeine (10–20); *Tramadol*: Desmethyltramadol (active)	Kasprzyk-Hordern et al. (2007), Jjemba (2006)
Psycho-stimulants	Amphetamine (1–74)	Amphetamine (1–74)	Amphetamine (1–74)	Amphetamine (1–74)	<25% Phenylacetone, benzoic acid, and hippuric acid; <10% 4-hydroxy-amphetamine, 4-hydroxy-norephedrine, and norephedrine	Kasprzyk-Hordern et al. (2007)
Steroid hormones			Testosterone (60)		–	Jjemba (2006)

Entries in bold indicate metabolites already detected in environment.

plants. Thus, some compounds are both metabolites and residues of two different compounds, as acetoaminopyrine (AAA) and formylaminoantipyrine (FAA) both metamizole (NSAIDs) metabolites, and microbial residues of dimethylaminophenazone (DMAA) products (Zühlke et al., 2007), or hydroxy-ibuprofen and carboxy-ibuprofen both ibuprofen by products of human metabolism and biodegradation in activated sludge WWTP (Pérez and Barceló, 2007a).

In conclusion, as very few PPs by-products are studied or monitored with regard to native PPs, there is a strong need to strengthen the research in this area for environment and human health interest. Moreover, the identification of metabolites being automatically considered during the design of a new drug, the degradation routes and the occurrence and fate of by-products in aquatic compartments must be investigated.

5. Occurrence in water resources

The majority of studies cited in this literature review attest of the general presence of PPs in water bodies from ng/L up to several µg/L, and more rarely but of prime importance for human health, in drinking water. About 90 PPs and BPs are concerned, BPs being less studied than parent compounds, and synthetic data are reported in Fig. 3 for the main therapeutic classes, NSAIDs and antibiotics.

Considering the fate of PPs and BPs (see following section), their concentration obviously decreases from wastewater to the environment. For instance, ofloxacin, a fluoroquinolone antibiotic, were detected up to 35.5 µg/L in Albuquerque (New Mexico, USA) hospital effluents while 410 ng/L, 110 ng/L were found in the Albuquerque WWTP influents and effluents, respectively, corresponding to 77% of WWTP attenuation rate, and finally not been detected in the Rio Grande river (Brown et al., 2006).

NSAIDs have the higher concentrations recorded in SW, ranging between 0.4 ng/L and 15 µg/L, dilofenac, paracetamol and ibuprofen being the most quantitatively found (Jux et al., 2002; Moder et al., 2007). Other main substances are caffeine (not only related to PPs), with a maximum concentration of 6 µg/L and sulfamethoxazole (antibiotic) with 1.9 µg/L in the USA (Kolpin et al., 2002), carbamazepine (anticonvulsant) up to 1.3 µg/L in Germany (Zühlke et al., 2004a) and in Canada (Hua et al., 2006), gemfibrozil (lipid regulator) up to 790 ng/L (Kolpin et al., 2002), ranitidine (anti-acid) up to 580 ng/L (Kolpin et al., 2002), atenolol (beta bloker) with 241 ng/L in Italy (Zuccato et al., 2000) or less in UK (Kasprzyk-Hordern et al., 2007) and metformin (antidiabetic) up to 150 ng/L (Kolpin et al., 2002).

PPs contamination in GW is much less reported. Reddersen et al. (2002) studied the impact of a former pharmaceutical plant near Berlin giving high concentrations of phenazone and propyphenazone (up to 4 µg/L) and a BP of DMAA, i.e. AMDOPH (up to 1 µg/L). Other few PPs were found in GW, like paracetamol at 211 ng/L in French wells (Rabiet et al., 2006), carbamazepine in bank filtration transects (up to 465 ng/L between 5 and 10 m below ground, Heberer et al. (2004)), and clofibric acid in Germany with 125 ng/L (Heberer et al., 2004). The presence of ibuprofen, salicylic acid, gemfibrozil, naproxen, indomethacin, and bezafibrate were detected in effluents of septic tanks located in Ontario, Canada, up to 2150, 480, 430, 300, 4 and 12 ng/L, respectively, some of them being still detected at 10 to 20 m in soil downstream up to few µg/L (Carrara et al., 2008).

Metabolites are often detected in WWTP influents and effluents but not systematically in natural waters. Among all PPs, carbamazepine is of great interest as it can be used as a tracer in order to emphasize the anthropogenic contribution to the persistent PPs distribution and fate in urban waters (Reinstorf et al., 2008; Osenbrück et al., 2007). A study of the concentration of five carbamazepine by-products (10,11-dihydro-10,11-epoxycarbamazepine, 10,11-dihydro-10,11-dihydroxycarbamazepine, 2 hydroxycarbamazepine, 3-hydroxycarbamazepine, and 10,11-dihydro-10-hydroxycarbamazepine), in WWTP effluents of Peterborough, Canada, has given respectively 426, 52, 1325, 132,101 and, 9 ng/L, although only carbamazepine and 10,11-dihydro-10,11-dihydroxycarbamazepine were detected in receiving SW at 0.7 and 2.2 ng/L (Miao and Metcalfe, 2003). It should be noted that these results are in agreement with the very low excretion rate of carbamazepine (Table 2). Despite its low excretion rate, several studies concerning carbamazepine, show concentrations reaching the µg/L range in SW (Zühlke et al., 2004a). Hence, persistence of carbamazepine may be the result of cleavages by micro-organisms (Pérez and Barceló, 2007a) or occurring in environment on its conjugated metabolites (Lai et al., 2002).

Even if occurrence studies in SW begin to be consistent, some specific improvements have to be considered. The first one is the interest of an integrated mass balance approach (spatially and temporally, dissolved and solids bounded PPs), complementary to punctual PPs environmental measurements (Beausse, 2004). Another one is the difficulty to discriminate between natural and anthropogenic sources for some PPs, like hormones coming from the excretion of ingested drugs (e.g. estrogens as contraceptives, with the exception of ethynylestradiol which is exclusively synthetic PP) or from natural hormone excretion after organisms synthesis and metabolization. In the same way, antibiotics are not even naturally-occurring but also semi-synthetic and synthetic chemical substances (Khan et al., 2007) and acetylsalicylic acid (i.e. aspirin) is not the exclusive source of salicylic acid molecule which also may comes from keratolytic, dermatice, food preservative, or its natural occurring in environment (Heberer, 2002). Finally, considering, the lack of knowledge about PPs consumption, metabolization, biodegradation, added to the cross variability depending on the geographical (consumption) and temporal (seasons) contexts, occurrence studies of PPs and BPs must be completed with recognized (reference) protocols for field investigations and data processing in order to make relevant comparisons possible.

6. Fate in environment

The presence of PPs and BPs from the main sources of contamination, i.e. discharge of WWTP effluents (human drugs), and animal farming or aquaculture (veterinary substances), is firstly attenuated by dilution in surface water up to trace level (µg/L to ng/L). The other potential attenuation factor of PPs and BPs in receiving waters is the adsorption on suspended solids (and sediments), colloids and natural dissolved organic matter (DOM) (Osenbrück et al., 2007). PPs and BPs may also undergo biotic, chemical and physico-chemical transformations in water, although PPs are designed to resist to microbial degradations and to be chemically stable (Sammartino et al., 2008; Löffler et al., 2004; Khetan and Collins, 2007). However, abiotic PPs and residues elimination is the most likely reaction occurring in SW with predominantly direct and indirect photodegradation (Sammartino et al., 2008; Löffler et al., 2004; Khetan and Collins, 2007; Nikolaou et al., 2007).

The photodegradation of numerous PPs can be direct by the solar absorption or indirect through radicals (e.g. OH.) generated by the solar irradiation of photosensitizers like nitrate, humic acids, etc (Khetan and Collins, 2007; Nikolaou et al., 2007; Sammartino et al., 2008; Buerge et al., 2006). Photodegradation depends also on the intensity of solar irradiation, eutrophic conditions, depth of water course, composition of organic matter, latitude and season (Fent et al., 2006; Heberer, 2002). The indirect photodegradation enhancement of carbamazepine through interaction with Fe (III) colloids and Cl^- ions has been highlighted in artificial conditions, and one of its direct photodegradation BP, acridine, has shown toxicity, mutagenicity and carcinogenicity (Chiron et al., 2006). Boreen et al. (2005) emphasized the effect of DOM on the direct photodegradation sulfa drugs (sulfamethazine, sulfamerazine, sulfadiazine, sulfachloropyridazine, sulfadimethoxine) in natural waters and proposed BPs structures. Tetracycline cannot be photodegraded, mostly because its adsorption onto sediments (Tolls, 2001; Boreen et al., 2003). In a laboratory scale, cyclophosphamide and ifosfamide (antineoplastics) are not degraded

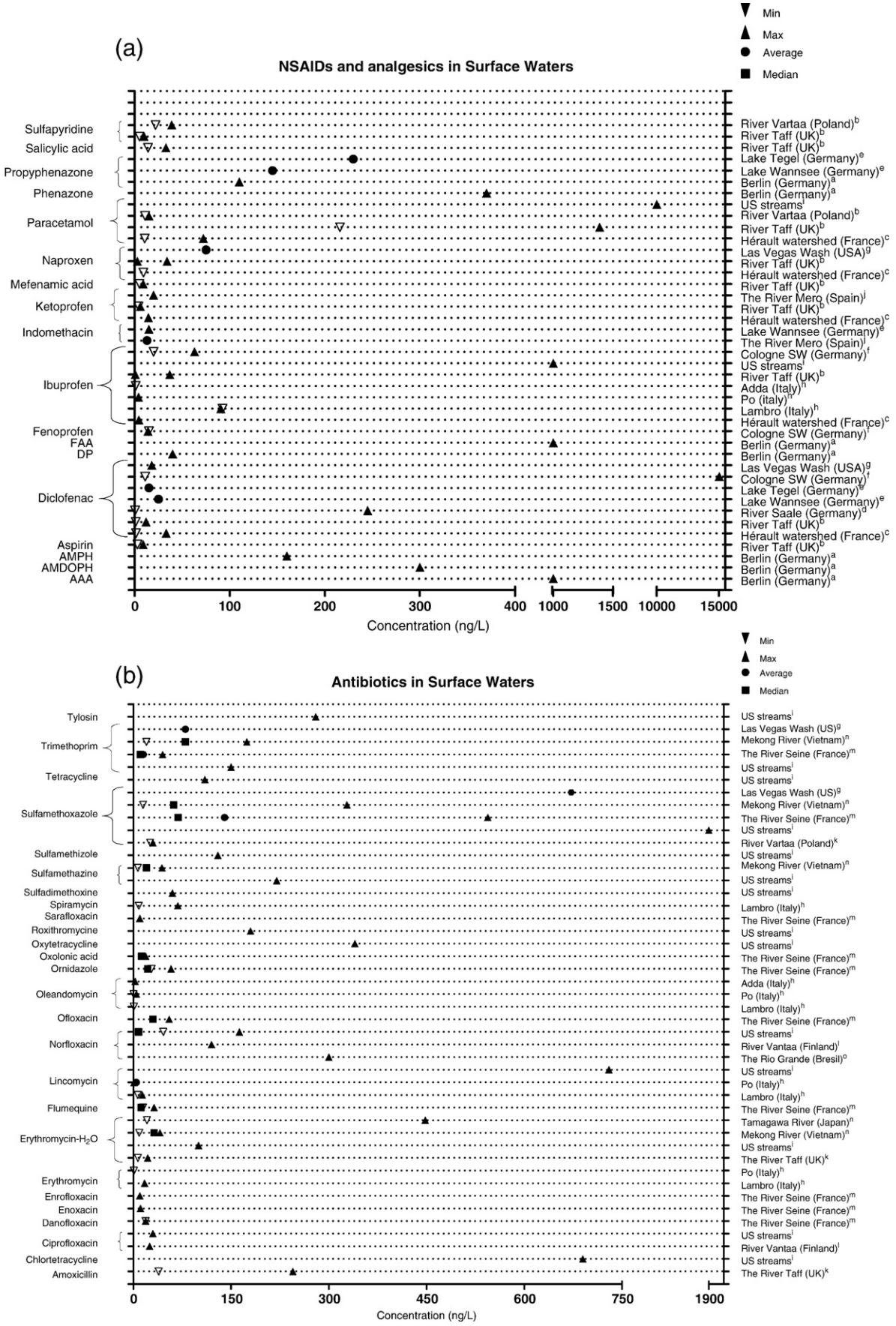

Fig. 3. Occurrence (ng/L) of PPs in SW : (a) NSAIDs and analgesics, (b) Antibiotics. [a] Zühlke et al. (2004a), [b] Kasprzyk-Hordern et al. (2008), [c] Togola and Budzinski (2008), [d] Moder et al. (2007), [e] Heberer et al. (2004), [f] Jux et al. (2002), [g] Vanderford and Snyder (2006), [h] Zuccato et al. (2000), [i] Kolpin et al. (2002), [j] Quintana et al. (2007), [k] Kasprzyk-Hordern et al. (2007), [l] Vieno et al. (2006a), [m] Tamtam et al. (2008), [n] Managaki et al., (2007), [o] Brown et al. (2006).

Table 3
PPs repartition according to log K_{ow}.

Therapeutic use	Log K_{ow}		
	≤2.5	Between 2.5 and 4	>4
Antiacids	Cimetidine, Ranitidine		
Antibiotic classes	Beta-lactams, Cyclines Fluoroquinolones, Quinolones, Lincosamide, Phenicol, Pyrimidines, Sulfonamides, Others	Macrolides	Phenol (triclosan)
Anticoagulants		Warfarin	
Anticonvulsants	Gabapentin , Dilantin	Carbamazepine	
Antidepressants	Meprobamate , Oxazepam	Diazepam	Amitryptiline, Fluoxetine
Antihelminthics		Ivermectin	
Antihistamines		Diphenydramine	
Antihypertensives		Diltiazem	Valsartan
Antineoplastics	5-Fluorouracil, Cyclophosphamide, Doxorubicin		
β-blockers	Acebutolol, Atenolol, Metoprolol, Pindolol, Sotalol	Propanolol	
Contraceptives		Ethynylestradiol	
Bronchodilatators	Clenbuterol, Salbutamol, Terbutaline		
Cardiac stimulants	Digoxin		
Contrast media	Iopromide X-ray, Iomeprol, Iopamidol		
Diuretics	Bendroflumethiazide, Furosemide		
Lipid regulators		Clofibric acid	Bezafibrate, Gemfibrozil, Simvastatin
NSAIDs and analgesics	5-aminosalicicylic acid, Aminopyrine, Aspirin, Paracetamol, Phenazone, Propyphenazone, Sulfapyridine, Salicylic acid	Ketoprofen, Naproxen, Diclofenac, Fenoprofen, Ibuprofen	Indomethacin, Tolfenamic acid
Opioanalgesics	Codeine, Caffeine, Amphetamine	Tramadol	
Vasodilatators	Pentoxyfilline		
Steroid hormones	Estriol	Androstenedione, Estrone, Testosterone	Estradiol, Progesterone

References: software EPISUITE™ 2000 (from EPA's office of pollution and prevention toxics and Syracuse research corporation (SRC)); worldwide website ChemIDplus (http://chem.sis.nlm.nih.gov/chemidplus/).

by UV solar light, even if they are subjected to indirect photodegradation by OH. radicals (Buerge et al., 2006). Fluoxetine, diclofenac, triclosan, albuterol, diazepam, fenofibrate, iodoarene, fluoroquinolones are reviewed to be photoreactive substances (Petrović and Barceló, 2007; Boreen et al., 2003).

Transport in soil of PPs has been suspected to be affected by oxido-reduction properties of soil, probably promoting their degradation (Holm et al., 1995; Carrara et al., 2008).

Although there is very few studies in literature, biodegradation of PPs is supposed to be insignificant in natural waters like SW and GW (Buerge et al., 2006; Pérez and Barceló, 2007b). However, specific microorganisms from biosolids and WWTP activated sludges spread onto the soil may be the centre of biodegradation reactions. For example, biodegradation and postulated biodegradation products of ICM (iodinated contrast media) in WWTP sludges have been reviewed in Pérez and Barceló (2007b). Yet, iopromide has shown low sorption and totally metabolization by microbial flora in water/sediment system (Löffler et al., 2005). Biodegradation tests of antibiotics using OECD standards have shown that the biodegradation rate is low except for penicillin G (Alexy et al., 2004; Gartiser et al., 2007). Biodegradation during water treatment processing of other PPs have been studied, like the metabolic pathway of phenazone which may occur in sand filters (Zühlke et al., 2007).

Actually, photodegradation, and also biodegradation may be limited by the adsorption of PPs in water sediments, the complexation with DOM, sorption into the shallow layer of the soil, or during bank filtration. Sorption depends on PPs physico-chemical properties and also geology, soil texture (sand, clay ...), sediment and DOM nature. In the whole, PPs are generally polar, water soluble, and low volatile molecules authorizing noticeable mobility in environment and moderate retention onto sediments and sludges (Sarmah et al., 2006). Rogers (1996) proposed to characterize the mobility of organic compounds by their classification in 3 log classes of the n-octanol water distribution coefficient (log K_{ow}<2.5 low sorption, log K_{ow} between 2.5 and 4 medium sorption, and log K_{ow}>4.0 high sorption). Table 3 presents the classification of some PPs according to their K_{ow}. Among the majority of hydrophilic substances, iodinated contrast media (ICM), with log K_{ow} between −2.1 and −2.42 (e.g. log K_{ow} iopromide = −2.33), are not retained to organic matter, and hence are likely to be encountered in DW (Pérez and Barceló, 2007b). Intermediate mobility substances have the ability to be attenuated in SW by adsorption to sediments and DOM. PPs with log K_{ow}>4 are not expected in natural waters, despite bezafibrate (log K_{ow} = 4.25) has been found around 100 ng/L in both German SW and GW (Heberer et al., 2004) and in Italian SW (Zuccato et al., 2000). Moreover, Löffler et al. (2005) pointed out in water/sediment systems the low degradability and strong sorption of ivermectin, diazepam, oxazepam and carbamazepine. Thus, log K_{ow} seems to be an excessive restrictive model of PPs distribution in environment because sorption is not only a matter of hydrophobicity.

Electrostatic interactions, chemical bounding and non specific forces between ionised molecules and OM are neglected through exclusive log K_{ow}, K_d and K_{oc} approaches (Tolls, 2001; Maskaoui et al., 2007). Some studies have illustrated that water pH influence could play an important role in the interactions between OM and pH depending PPs (Hari et al., 2005; Maskaoui et al., 2007; Lorphensri et al., 2007). There is a great variability between PPs as regards to their p*K*a. NSAIDs, lipid regulators are in majority acidic compounds, whereas beta-blockers, bronchodilatators, hormones, psycho-stimulants, opioanalgesic, paracetamol, antibiotic phenols and macrolides are mostly basic compounds (Kasprzyk-Hordern et al., 2007, 2008). Besides, numerous antibiotics are amphoteric with ofloxacin, ciprofloxacin, norfloxacin, etc. (Tamtam et al., 2008). Hence, repulsive or attractive interactions may occur between PPs and OM. It has been observed that PPs have more affinity with cationic OM of a clay soil than anionic OM from a sandy soil (Dordio et al., 2007), and complexation between cationic species (e.g. Ca^{2+}) from aquatic OM and tetracycline has been reviewed (Kemper, 2008).

The adsorption (based on the log K_d measurement) to natural aquifer materials and sediments of 4 selected PPs was studied (i.e. acetaminophen, carbamazepine, nalidixic acid, and norfloxacin) by Hari et al. (2005). Carbamazepine, which has higher log K_{ow} (i.e. 2.45) than norfloxacin and nalidixic acid was poorly adsorbed at pH 7.6 on natural OM comparatively to nalidixic acid and norfloxacin, although the lipophilicity and molecular weight seem to prevail over the other interactions between PPs and colloids (Maskaoui et al., 2007). Very few studies concerning PPs behaviour with suspended aquatic matter are carried out in realistic concentration of PPs like in Ra et al. (2008), showing the negligible sorption of PPs with suspended OM in aquatic environment. However, the constant increase of dissolved organic matter (DOM) in worldwide natural waters with climate change observed through the last 15 years (e.g. about 91% in UK SW) may probably have an influence on PPs photodegradation, sorption, and by extension their behavior and fate in the environment (Evans et al., 2005). Thus, this issue needs more future investigations.

7. Occurrence and fate in drinking water

The apparent weak persistence of a PP does not necessary mean the absence of drinking water contamination. However, only very few data

Table 4
Overview of pharmaceutical (and *metabolites*) concentrations detected in worldwide tap water (adapted from Jones et al. (2005)).

Therapeutic use	Compound	Maximal concentration detected (ng/L)	Country	Refs.
Antibiotics	Triclosan	734	USA	Loraine and Pettigrove (2006)
Anticonvulsants	Carbamazepine	24	Canada	[f]
		140–258	USA	Stackelberg et al. (2004), Stackelberg et al. (2007)
		43.2	France	Togola and Budzinski (2008)
		60	Germany	Heberer et al. (2004)
	Dilantin	1.3	USA	Vanderford and Snyder (2006)
	Primidone	40	Germany	Heberer et al. (2004)
Antidepressants, anti-anxiety	Amitryptilline	1.4	France	Togola and Budzinski (2008)
	Diazepam	10	UK	[g]
		23.5	Italy	Zuccato et al. (2000)
	Meprobamate	5.9	USA	Vanderford and Snyder (2006)
Antineoplastics	Bleomycin	13	UK	[b]
Iodinated X-ray contrast media	Diatrizoate	1200	Germany	Pérez et Barceló (2007b)
	Iopromide	<50	Germany	Pérez et Barceló (2007b)
Lipid regulators	Bezafibrate	27	Germany	[a]
	Clofibric acid	50–270	Germany	[a], [c], [d], [e], Heberer et al. (2004)
		5.3	Italy	Zuccato et al. (2000)
NSAIDs and analgesics	Gemfibrozil	70	Canada	[f]
	Acetaminophen	210.1	France	Togola and Budzinski (2008)
	AMDOPH	900–1250	Germany	Heberer et al. (2004), Reddersen et al. (2002)
	Diclofenac	6–35	Germany	[a], Heberer et al. (2004)
		2.5	France	Togola and Budzinski (2008)
	DP	1.10	Germany	Zühlke et al. (2004b)
	Ibuprofen	3	Germany	[a]
		0.6	France	Togola and Budzinski (2008)
		8.5	Finland	Vieno et al. (2005)
		1350	USA	Loraine and Pettigrove (2006)
	Ketoprofen	8.0	Finland	Vieno et al., 2005
		3.0	France	Togola and Budzinski (2008)
	PDP	0.24	Germany	Zühlke et al. (2004b)
	Phenazone	250–400	Germany	Zühlke et al. (2004b), Reddersen et al. (2002)
	Propyphenazone	80–240	Germany	Zühlke et al. (2004b), Reddersen et al. (2002), Heberer et al. (2004)
Opioidanalgesics	Codein	30	USA	Stackelberg et al. (2007)
Psycho-stimulants	Caffeine	60–119	USA	Stackelberg et al. (2007), Stackelberg et al. (2004)
		22.9	France	Togola and Budzinski (2008)

Cited from Jones et al. (2005):
[a] Stumpf, M. et al. (1996) Determination of drugs in sewage treatment plants and river water (in German). Vom Wasser 86, 291–303.
[b] Aherne, G.W. et al. (1990) Cytotoxic drugs and the aquatic environment – estimation of Bleomycin in river and water samples. J. Pharm. Pharmacol. 42, 741–742.
[c] Stan, H.J. et al. (1994) Occurrence of clofibric acid in the aquatic system – does the medical application cause contamination of surface, ground and drinking water (in German)? Vom Wasser 83, 57–68.
[d] Heberer, T. et al. (1997) Detection of drugs and drug metabolites in ground water samples of a drinking water treatment plant. Fresenius Environ. Bull. 6, 438–443.
[e] Heberer, T. and Stan, H.J. (1996) Occurrence of polar organic contaminants in Berlin drinking water (in German). Vom Wasser 86, 19–31.
[f] Tauber, R. (2003) Quantitative Analysis of Pharmaceuticals in Drinking Water from Ten Canadian Cities, Enviro-Test Laboratories, Xenos Division, Ontario, Canada.
[g] Waggot, A. (1981) Trace organic substances in the River Lee (Great Britain). In Chemistry in Water Reuse (1st edn) (Cooper, W.J., ed.), pp. 55–99, Ann Arbour Science.
Cited from Pérez et Barceló (2007b): Putschew A, Wischnack S, Jekel M (2000) Sci Total Environ 255:129–134.

are available on the occurrence of PPs in tap water (Table 4). It can be explained by the analytical difficulties to quantify ultra-trace level (ng/L) of such compounds, and hopefully by concentrations below the quantification limit. Thus, only 17 PPs and 5 BPs have been found in DW between 1.4 and 1250 ng/L. NSAIDs and in a slight less extent anticonvulsants are the mainly detected in Europe (Germany, France, Finland) and in the USA. DW occurrence of NSAIDs can directly be linked with their first worldwide PPs consumption rates. Otherwise, the presence of carbamazepine is related to its high resistance to transformation during its whole environmental, WWTP and water work course. Besides, iodinated contrast media (ICM) are the most susceptible to be encountered in DW because their very low lipophilicity (Pérez and Barceló, 2007b). Thus, the most concentrated PP found in DW is diatrizoate ranging at 1.2 µg/L (Pérez and Barceló, 2007b).

From water resource to drinking water network, the removal efficiency of PPs in drinking water treatment plant is rather known. However, even if some processes are efficient such as nanofiltration, ozonation, chlorination or photodegradation,…, degradation BPs may also be potentially toxic and some PPs cannot be totally removed in DWT (Glassmeyer and Shoemaker, 2005; Stackelberg et al., 2004, 2007; Ternes et al., 2002; Yoon et al., 2007; Verliefde et al., 2007; Vieno et al., 2006b, 2007). For example, the removal rate for a classical DWT (clarification/filtration/disinfection) is 98% for acetaminophen, 88%, for caffeine and 85% for carbamazepine (Stackelberg et al., 2007).

PPs behavior in distribution system is not well-known. However, a recent study (Gibs et al., 2007) has shown the influence of residual free chlorine on PP's fate in distribution network according to time. PPs of initial concentration of 5 µg/L were added to finished drinking water samples with free chlorine concentration of 1.2 mg/L. Concentration of PPs were followed according to time, during 10 days, which represent common progress time of water through the distribution system up to tap. Acetaminophen, codein, warfarin, and 1,7-dimethylxanthine appeared to totally react with free chlorine in only one day, whereas persistence of caffeine, carbamazepine, cotinine and dehydronifedipine were confirmed: after 10 days these 4 PPs remained entirely in DW samples. This study which does not focus on chlorination BPs of the degraded PPs, confirms that human health risk assessment studies must be considered for PPs and BPs in drinking water.

8. Conclusion

This literature review, shows however that relatively few works are available for BPs in general and drinking water contamination in particular. For this last point, it is important to check the absence of the most widespread PPs such as carbamazepine, NSAIDs or ICM in the main drinking water networks. Furthermore there is a real need for complementary studies such as the comparison on PPs consumption and occurrence in water based on a reference methodology, the

climate change influence on PPs and BPs occurrence, or the identification and toxicity assessment on the degradation BPs formed during DWT. Finally, data human health risk assessment and ecotoxicological risk assessment related to PPs and BPs must also be developed.

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