Water Air Soil Pollut (2012) 223:2111–2124
DOI 10.1007/s11270-011-1008-1

Pharmaceuticals in Rivers of Two Regions with Contrasted Socio-Economic Conditions: Occurrence, Accumulation, and Comparison for Ukraine and France

Yuliya Vystavna · Frédéric Huneau · Volodymyr Grynenko · Yuri Vergeles · Hélène Celle-Jeanton · Nathalie Tapie · Hélène Budzinski · Philippe Le Coustumer

Received: 13 May 2011 / Accepted: 17 October 2011 / Published online: 19 January 2012

Abstract The goal of our study was to identify pharmaceuticals, their potential sources and consumption level in two different socioeconomic and geographical regions—Bordeaux, France and Kharkiv, Ukraine. These substances were monitored in rivers water during contrasted seasonal conditions with application of passive samplers. The 21 pharmaceuticals (psychiatric drugs: alprazolam, amitriptyline, diazepam, fluoxetine, nordiazepam, carbamazepine, bromazepam; analgesics: aspirin, paracetamol; broncholidator: clenbuterol, salbutamol, terbutaline; non-steroidal anti-inflammatory drug: diclofenac, ibuprofen, ketoprofen, naproxen; lipid regulator: gemfibrozil; stimulants: caffeine, theophylline) were identified in sites upstream and downstream of urban areas and discharge of wastewaters. Caffeine, carbamazepine, and diclofenac were relatively abundant into the surface water and could be considered as potential anthropogenic markers of wastewater discharges into rivers. A mass balance

Capsule abstract This work (comparing two Ukrainian and French rivers) has demonstrated the successful application: (1) of passive samplers to monitor water quality, (2) of mass balance modeling to estimate drug consumption rates, and (3) of pharmaceuticals as potential indicators of wastewater treatment efficiency.

Y. Vystavna · F. Huneau · P. Le Coustumer
UFR des Sciences de la Terre, Université de Bordeaux,
B18, Avenue des Facultés,
33405 Talence, France

Y. Vystavna · F. Huneau · P. Le Coustumer
EA 4592, Géoressources & Environnement,
Institut EGID,
1 Allée F. Daguin,
33607 Pessac, France

Y. Vystavna · V. Grynenko · Y. Vergeles
National Academy of Municipal Economy at Kharkiv,
Department of Environmental Engineering and Management,
vul. Revolutsii 12,
Kharkiv 61002, Ukraine

H. Celle-Jeanton
Clermont Université, Université Blaise Pascal,
Laboratoire Magmas et Volcans,
BP 10448, 63038 Clermont-Ferrand, France

H. Celle-Jeanton
CNRS, UMR 6524, LMV,
63038 Clermont-Ferrand, France

H. Celle-Jeanton
IRD, R 163, LMV,
63038 Clermont-Ferrand, France

N. Tapie · H. Budzinski (✉)
LPTC-EPOC CNRS UMR 5805, Université Bordeaux-1,
351 Cours de la Libération,
33405 Talence, France
e-mail: h.budzinski@ism.u-bordeaux1.fr

modeling has been applied to calculate approximate consumption rates for carbamazepine, diclofenac, and caffeine in both regions to assess socio-economic factors linked with pharmaceuticals behavior.

Keywords Emerging pollutants · Passive sampling · POCIS · Anthropogenic wastewater markers · Mass balance modeling

1 Introduction

Pharmaceutical products (PPs) have been detected in various natural media: fresh surface waters (Bendz et al. 2005), drinking and tap water (Heberer 2002; Kuster et al. 2006), groundwater (Barnes et al. 2008), marine and ocean waters, and some aquatic organisms (Comeau et al. 2008) in different countries. The presence of these compounds in the environment is generally linked to effluents of metabolized and unused pharmaceuticals into natural waters through wastewater treatment facilities (Togola and Budzinski 2007a). All pharmaceuticals and metabolites are bioactive and they can have toxic effect on living organisms (Cleuvers 2003). However, due to recent developments of analytical chemistry techniques, protocols, and growing consumption rate of these substances in the world, PPs are becoming a part of the environmental monitoring.

The water monitoring on pharmaceuticals is processed using standard (Buerge et al. 2003; Kasprzyk-Hordern et al. 2009) and passive sampling techniques (MacLeod et al. 2007; Togola and Budzinski 2007a; Söderström et al. 2009). Standard approach (pump or grab sampling) can only measure the instantaneous concentrations of contaminants in water (Li et al. 2010). Such method is more time and cost efficient for short-term investigations. (Söderström et al. 2009). The main limitation of this technique is that the measured results represent the value of targeted compounds at a specific place and time, while inter- and intra-diurnal variations of pharmaceuticals can be significant (Togola and Budzinski 2007a). The other alternative for the sampling is the biological sampling (e.g. fish), but this procedure brings up other problematic issues: (1) difficulty of complex biological matrixes chemical analysis; (2) different accumulation patterns inherent to each species (e.g. age, size, metabolism rate) which make data interpretation misleading; and (3) unexpected mortality of test organisms.

In order to avoid these limitations, the passive sampling technique can be chosen instead for the pilot identification of targeted chemicals in the rivers. Since, this technique can greatly simplify sample collection (both in handling and long time maintenance) ensuring simultaneously the obtaining of representative time-integrated samples for the identification of studied compounds (Vrana et al. 2005; Togola and Budzinski 2007a; Arditsoglou and Voutsa 2008).

Polar organic chemical integrative sampler (POCIS) is one of the types of time-integrated sampler was developed for assessing the presence and potential toxicological significance of a broad spectrum of environmental contaminants (Petty et al. 2004; MacLeod et al. 2007). These sampling devices have the capacity to record large volumes of water fluxes over a period from several days to weeks. They have the ability to integrate episodic changes in distribution of environmental contaminants and their membrane is fitted for the selective sampling of polar molecules from the dissolved phase. POCISs were successfully applied in the water of various countries, e.g. Czech Republic (Grabic et al. 2010), Greece (Arditsoglou and Voutsa 2008), France (Togola and Budzinski 2007b), USA (Jones-Lepp et al. 2004). The only complexity of the use of POCISs is an estimation of the sampling rate and calculation of water concentration of targeted compounds (Togola and Budzinski 2007a). The sampling rate (Zhang et al. 2008; Arditsoglou and Voutsa 2008) can be affected by field conditions (water temperature, UV light, pH, flow rate, turbulence, suspended solids, organic carbon, salt content, algal growth, biofouling, degradation), but still independent from the presence of analytes in the water (Vrana et al. 2005; Togola and Budzinski 2007a).

Monitoring of pharmaceuticals in water gives us a possibility to (1) detect these emerging pollutants, (2) measure their concentration, and (3) use these environmental data for the further research. For example, due to specific properties (degradation, solubility, accumulation, etc), pharmaceuticals have been found to be efficient markers of wastewaters (Glassmeyer et al. 2005; Nakada et al. 2008). Previous studies report the application of carbamazepine as a conservative marker of treated sewage (Clara et al. 2004; Fenz et al. 2005; Nakada et al. 2008) and caffeine as a labile indicator of untreated wastewater (Buerge et al. 2003;

Benotti and Brownawell 2007) for coastal and freshwater systems.

Additionally, in perspective, the data on pharmaceuticals in the water can be used for the approximate estimation of drug consumption rates in communities. Usually, data on medicaments consumption are scarce or unavailable due to the use of a large amount of non-prescription drugs. In this case, the application of mass balance modeling provides a possible means to obtain these data (Khan and Ongerth 2004; Kasprzyk-Hordern et al. 2009; ter Laak et al. 2010).

The objective of the study was (1) identify, quantify, and compare the presence of targeted pharmaceuticals in two small rivers influenced by municipal wastewater discharges: the Jalle River, Bordeaux (France) and the Lopan River, Kharkiv region (Ukraine), (2) determine time–spatial distribution of PPs compounds in water in order to access potential pollution sources and (3) estimate drug consumption rates in two different socio-economic regions (France and Ukraine) using the mass balance modeling.

2 Site Selection and Sampling

The Jalle River, Bordeaux agglomeration (France), and the Lopan River, Kharkiv region (Ukraine) have been selected to introduce pollution status of river basins with similar hydrological characteristics (length, width, depth, water flow, etc.) and water usage (wastewaters discharge, irrigation, etc), representing however different socio-economic characteristics of watersheds in terms of population density, economic activities, incomes, lifestyles, etc. Surface water in both rivers was sampled in sites located upstream and downstream of the major cities and wastewater treatment plants (WWTPs). Average flow rates were obtained from annual reports of the regional Environmental Agencies.

The alluvial Jalle River is a right tributary of the Garonne River with 34 km of length, with depth from 0.8 to 2.5 m, and 3 $m^3\ s^{-1}$ of average water debit, located on the north from Bordeaux city (Fig. 1). The subsurface geological structures of the area are dated from Oligocene and consist mainly of sedimentary rocks like sand and marl. The river has mostly pluvial feeding, runs through residential suburban and rural areas and receives effluents from two major municipal wastewater treatment facilities of the Bordeaux suburbs, serving greater than 100,000 people. The treated effluent accounted up to 33% of the river flow and heavily impacted on the quality of the river's water (Labadie 2004; Othoniel 2006).

The Lopan River is an alluvial transboundary river, which flows through Russia and Ukraine (Vystavna et al. 2011) and is used for the recreation, drinking water supply, irrigation, and fishing in the Kharkiv region of Ukraine (c.a. 2,700,000 inhabitants; 2010). The total length of the river is about 98 km, depth ranges from 0.4 to 2.3 m and several dams constructed along the watercourses regulate the flow. The mean annual discharge of the Lopan River is 1.4 $m^3\ s^{-1}$ in winter and 0.9 $m^3\ s^{-1}$ in summer in the site located upstream of the Kharkiv city (Vasenko et al. 2006). River is partly covered by ice from the end of November to the end of March. The subsurface geological structures of the area are dated from Palaeogene and consist mainly of sedimentary rocks like sandstone, marl, and chalk. The major land application purposes on the watershed are: agriculture (40%), urban lands (50%), and water reservoirs (10%). The Lopan River receives mixed municipal and industrial wastewaters (about 600,000 m^3 per day) from Kharkiv city and its suburbs. The wastewater discharge contributes up to 5–6 $m^3\ s^{-1}$ to the natural flow downstream of the Kharkiv city (Vystavna et al. 2011). Wastewaters are discharged into the same river basins, which are used for water supply (NRDW 2006).

Sampling sites were chosen and named according to the results of the previous monitoring campaigns (Vystavna et al. 2009, 2010, 2011). The POCISs have been installed using a cotton net for membranes protection at three sites on the Jalle River (Fig. 1): J01 is located close to the source of the river in Saint Jean d'Illac; J02 is located on an area of agricultural activity of Eysines community, famous for the bio-agriculture, and approximately 0.4 km downstream of the "Cantinolle" WWTP (WWTP 1); and J03 is located inside the natural reservation area of Bruges, approximately 0.5 km downstream of the "L'Ile" WWTP (WWTP 2). Three sampling sites have been chosen in the Lopan River (Fig. 1): L03 is located upstream of the Kharkiv city and downstream (approximately 1 km) of the Veterinary Academy discharges; L08 is located in the Kharkiv city, upstream of the wastewater discharges; L09 is located approximately 0.7 km downstream of the wastewater discharge from the "Dykanivka" WWTP .

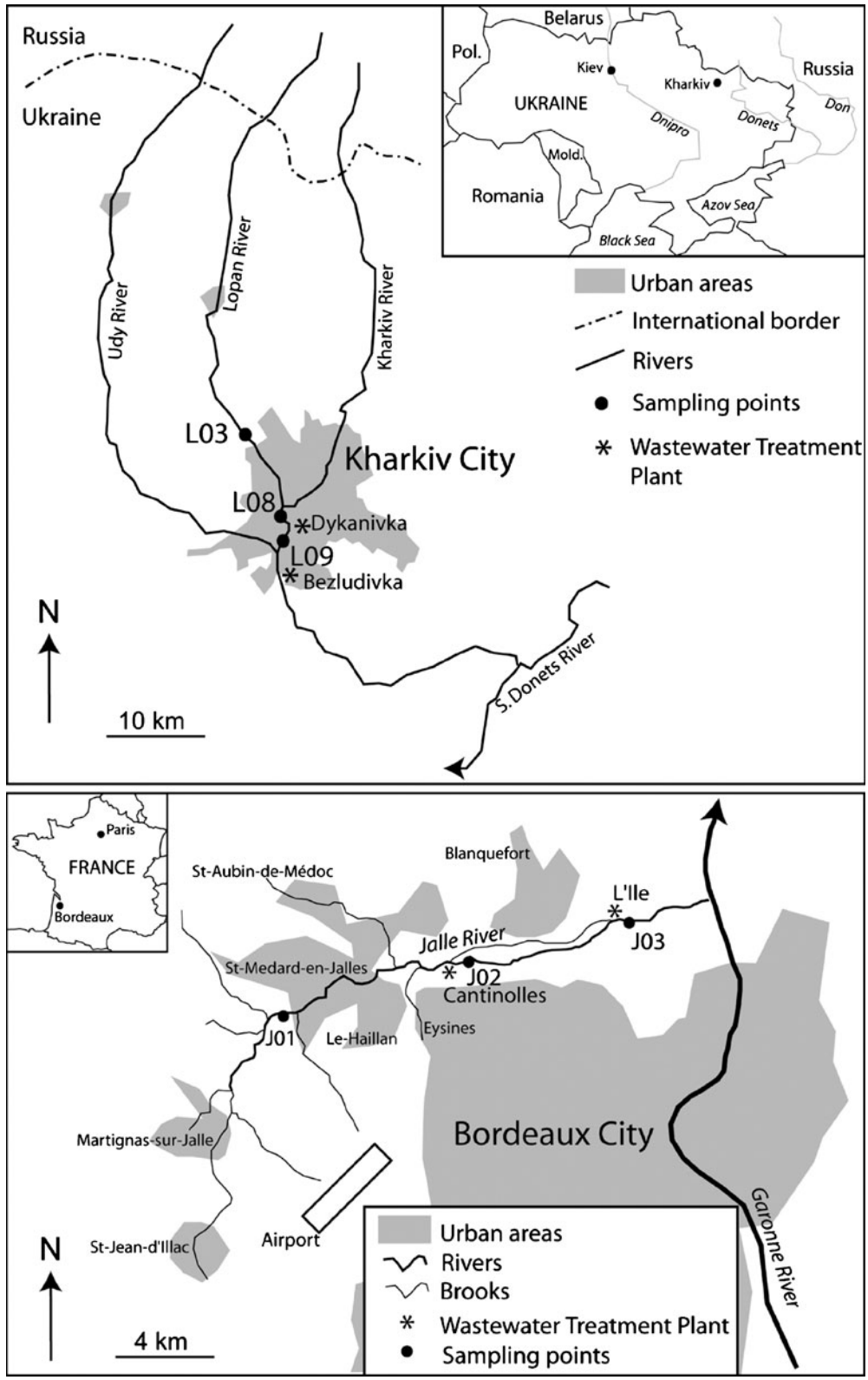

Fig. 1 The sampling sites location on the Jalle and the Lopan Rivers

All the sites both on the Jalle River and the Lopan River have been sampled in May and December 2009. Additional sampling has been provided in dry season (August 2009) on the Lopan River in the sites L03 and L09 in order to exclude the inputs of emerging pollutants due to precipitation and run-off. During the spring sampling campaign, the passive samplers at site L08 have been lost, possibly caused by pillage or active fishing of local population.

3 Materials and Method

3.1 Chemicals and Reagents

POCIS pharmaceuticals with the Oasis HLB sorbent were purchased from Expometer (Tavelsjö, Sweden). Acetone, dichloromethane, acetonitrile, and methanol (high-performance liquid chromatography reagent grade, Scharlau) were purchased from ICS (Belin-Beliet, France). Glass solid-phase extraction (SPE) cartridges of 6 mL with Teflon frits (20 μm porosity) filled with Oasis HLB bulk sorbent (60 μm) were purchased from Supelco (Saint Quentin-Fallavier, France) and Waters (Guyancourt, France), respectively. Ultrapure deionized water was obtained with a Milli-Q system (Millipore, Molsheim, France). All standards were purchased from Sigma Aldrich (St. Quentin Fallavier, France; Tapie et al. 2011).

3.2 POCIS Extraction

The extraction procedures for POCIS were adapted from previously developed methods (Togola and Budzinski 2007a; Tapie et al. 2011). After 3 weeks of exposure, each individual POCIS device was retrieved from the water, briefly rinsed with ultrapure water in order to remove any materials adhering to the surface of the surface membrane (biofilm, particles, etc.).

The POCIS preparation and analysis have been performed in the ISM CNRS UMR Laboratory of University of Bordeaux 1, France. The surface membrane was detached from the stainless steel rings and rinsed with ultrapure water. The phase from the two membranes of each POCIS has been carefully transferred into an empty SPE tube by rinsing it with 5 mL of ultrapure water per each membrane in cartridges filled with cleaned by methanol Teflon frits and dried under vacuum for 1 h. The sorbent was eluted in each sample using 10 mL of each solution of: methanol, methanol/dichloromethane mixture (50:50), and dichloromethane and being spiked with internal standards (Budzinski et al. 2009).

The extracts obtained from the sorbent were finally evaporated to dryness using a nitrogen flux and transferred into injection vials 50 μL of acetonitrile. The mass of sorbent has been measured by gravimetry for each dried POCIS. Blanks were performed in the laboratory concurrently with water samples in order to monitor possible contamination. Recovery rates of the POCIS samples were determined by spike samples and vary from 79% to 97% of spiked amount (Table 1) for all chemicals, except aspirin, fluoxetine, and terbutaline with recoveries ranges from 51% to 62%. The lowest recovery rate (51%) has been observed for the aspirin. The residual standard deviation of the spikes values was in the range from 0% to 30% (theophylline and fluoxetine, respectively; n=3, Table 1). The aspirin (4 ng g^{-1}) and caffeine (5 ng g^{-1}) (Alvarez et al. 2005) have been detected in laboratory procedural blanks and corrections have been made for the data.

The target pharmaceuticals were selected based on resources of the chemical protocol and the list of leading medicaments, which are most frequently consumed in France (Ministère de la Santé et des Sports en France: http://www.sante-sports.gouv.fr) and Ukraine (Ministry of Health Protection in Ukraine: http://www.moz.gov.ua). Accordingly, the 21 pharmaceuticals from different therapeutic groups (psychiatric drugs: alprazolam (ALPZ), amitriptyline (AMI), diazepam (DZP), doxepin (DOX), fluoxetine (FLUOX), imipramine (IMI); nordiazepam (NDZP), carbamazepine (CBZ), bromazepam (BRMZ); analgesics: aspirin (ASP), paracetamol (PARA); broncholidator: clenbuterol (CLENB), salbutamol (SALB), terbutaline (TERB); non-steroidal anti-inflammatory drug: diclofenac (DICLO), ibuprofen (IBU), ketoprofen (KETO), naproxen (NAP); lipid regulator: gemfibrozil (GEMF); stimulants: caffeine (CAF), theophylline (THEO)) have been analyzed in samples using liquid chromatography/tandem mass spectrometry (LC/MS/MS) with an electrospray (ESI±) ionization source. The limit of the detection was around 1 ng g^{-1} of sorbent for all compounds (Table 1), which makes approximately a detection limit from 0.05 to 0.1 ng L^{-1} depending on the exposure time when considering sampling rates (R_s). Limits of detection are varied depending on the origin and kind

Table 1 The targeted pharmaceuticals (PP) detected by POCIS and analytical method performance

PP	CAS no.	Therapeutic class	LOD, ng g^{-1}	Recovery (n=3), %	
				Mean	RSD
Alprazolam	28981-97-7	Antidepressant	1	97	8.3
Amitriptyline	50-48-6	Antidepressant	1	79	19
Aspirin	50-78-2	Analgesic	1	51	13
Bromazepam	1812-30-2	Psychiatric drugs	1	93	11
Caffeine	58-08-2	Stimulant	1	88	4.1
Carbamazepine	298-46-4	Sedative	1	86	21
Clenbuterol	37148-27-9	Bronchodilator	1	92	6.9
Diazepam	439-14-15	Antidepressant	1	86	4.9
Diclofenac	15307-86-5	Non-steroidal anti-inflammatory drug	1	81	9.6
Doxepine	1668-19-5	Antidepressant	1	86	2.3
Fluoxetine	54910-89-3	Antidepressant	1	60	30
Gemfibrozil	25812-30-0	Lipid regulator	1	84	6.8
Ibuprofen	15687-27-1	Non-steroidal anti-inflammatory drug	1	90	5.5
Imipramine	50-49-7	Antidepressant	1	89	24
Ketoprofen	22071-15-4	Non-steroidal anti-inflammatory drug	1	89	3.9
Naproxen	22204-53-1	Non-steroidal anti-inflammatory drug	1	91	2.1
Nordiazepam	1088-11-5	Benzodiazepines active metabolite	1	82	8.5
Paracetamol	103-90-2	Analgesic	1	87	3.3
Salbutamol	18559-94-9	Bronchodilator	1	85	5.7
Terbutaline	23031-25-6	Bronchodilator	1	62	18
Theophylline	58-55-9	Stimulant	1	90	0.0

LOD limit of detection, *RSD* residual standard deviation

of water, as water presents different organic matter contents and matrix complexity. They can range between 0.1–1.5 and 0.1–2.5 ng L^{-1} for surface water (Togola and Budzinski 2008). These low detection levels allow quantifying pharmaceuticals in the studied environment. In our research only one matrix, i.e. surface water was considered. Thereby, the quantification was performed using the stable isotope-labeled compounds (internal standards) that were spiked into the POCIS sorbent prior to analysis in order to compensate for the mass loss during the sample preparation and the matrix effects during the LC/MS/MS process. The detection limits for targeted compounds were determined by measuring the coincident instrumental response of standard solutions and spiked blank POCIS extracts, respectively, using a signal to noise ratio of 3 and 10, correspondingly (Togola 2006).

3.3 Calculation of POCIS Uptake Rates and Data Interpretation

Uptake rates (MacLeod et al. 2007; Bartelt-Hunt et al. 2009) have been calculated for a limited number of pharmaceuticals (Togola and Budzinski 2007a). At the present time, the research on the estimation of sampling rates of pharmaceuticals is under development (Miege et al. 2011). In this study, we estimated concentrations for most frequently detected pharmaceuticals using Eq. 1:

$$C_w = C_s M_s / (R_s t) \quad (1)$$

where, C_w and C_s are concentrations of compounds in the water (ng L^{-1}) and in the POCIS (ng g^{-1}) respectively; M_s is the mass of the sorbent in the POCIS (g); R_s is the sampling rate (L d^{-1}; Table 2);

Table 2 The sampling rates (R_s) for POCIS (pharmaceutical configuration), L d^{-1}

PPs	R_s, L d^{-1}
Amitriptyline[a]	0.41
Caffeine[a]	0.13
Carbamazepine[b]	0.29
Diclofenac[b]	0.15
Diazepam[a]	0.40
Fluoxetine[a]	0.24
Gemfibrozil[c]	0.19
Ibuprofen[a]	0.30
Ketoprofen[b]	0.13
Naproxen[a]	0.14
Nordiazepam[a]	0.39
Paracetamol[a]	0.03

[a] Togola 2006
[b] Budzinski et al. 2009
[c] MacLeod et al. 2007

and t is the sampling period (days; Petty et al. 2004; Arditsoglou and Voutsa 2008).

The R_s is not dependent on the concentration of target components in the sampling water (Arditsoglou and Voutsa 2008); however, it depends on the water temperature variation, salinity, pH, and other parameters (Togola and Budzinski 2007a). In our study, water turbulence and flow have no significant variations in the sampled rivers as they are alluvial and velocity has small changes during the sampling period, so these parameters were neglected for the estimation of the R_s. The pH of the rivers was 6.9–8.6 and at this low variation level has no significant influence on the diffusion of the components in the POCIS's membrane (Zhang et al. 2008). The water temperature variation has not been taken into account because of the lack of the data on POCIS calibration (Togola and Budzinski 2007a).

4 Results

4.1 Presence of Pharmaceuticals in Rivers

Among 21 targeted PPs of different therapeutic classes, 18 of them (ALPZ, ASP, AMI, BRMZ, CAF, CBZ, CLENB, DZP, DICLO, FLUOX, GEMF, IBU, KETO, NAP, NDZP, PARA, SALB, and THEO) have been identified in the Jalle River, France and 15 of targeted compounds (ALPZ, ASP, AMI, CAF, CBZ, DZP, DICLO, FLUOX, IBU, KETO, NAP, NDZP, PARA, SALB, and THEO) have been found in the Lopan River, Ukraine (Fig. 2). The values of DOX, IMI, and TERB were lower than detection limits in all sampling sites of both rivers (Rabiet et al. 2006). In both rivers, the accumulation and diversity of pharmaceuticals vary along the sampling sites and sampling seasons.

Three general accumulation levels of pharmaceuticals were identified in set up POCIS: high accumulation level (more than 1,000 ng g^{-1}; amount of pharmaceuticals in the sorbent of the passive sampler); medium accumulation level (100–1,000 ng g^{-1}); and low accumulation level (less than 100 ng g^{-1}; Fig. 2).

In the Jalle River, high accumulation was found only for KETO. Medium accumulation was detected for DICLO, CAF, THEO, NAP, IBU, and PARA. The BRMZ, FLUOX, GEMF, AMI, NDZP, ASP, CLENB, DZP, ALPZ, and SALB were identified at low-accumulation level. In the Lopan River, the maximum accumulation was measured for CBZ, DICLO, and CAF. The KETO, THEO, AMI, and DZP were found in the medium accumulation level and FLUOX, ASP, NDZP, SALB, and ALPZ were at the low accumulation level (Fig. 2).

According to the maximum accumulation level, the river in Ukraine was more contaminated by CBZ, DICLO, DZP, AMI, and ASP than the studied river in France (Fig. 2). The PARA, THEO, SALB, ALPZ, and FLUOX show approximately the same level of accumulation in POCIS installed in both studied rivers (Fig. 2). Among the other target compounds, CAF, DICLO, and CBZ were measured at all sampling sites on the both rivers and during all sampling campaigns.

4.2 Concentration of Pharmaceuticals in Two Rivers

The exact concentrations of AMI, CAF, CBZ, DICLO, DZP, FLUOX, GEMF, IBU, KETO, NAP, NDZP, and PARA have been estimated (Fig. 3) using Eq. 1 and the previously published sampling rates (Table 2). In the Lopan River, the concentration and diversity of PPs changed from the upstream (L03) to downstream (L09) sites. In the upstream site (L03), the contamination of pharmaceuticals presented the following order: KETO>CAF>PARA>DICLO>CBZ. In the city center (L08), ketoprofen has not been measured, possibly due to the reduction of sources, degradation (Nakada et al. 2008) and dilution from the upstream site, where presence of KETO

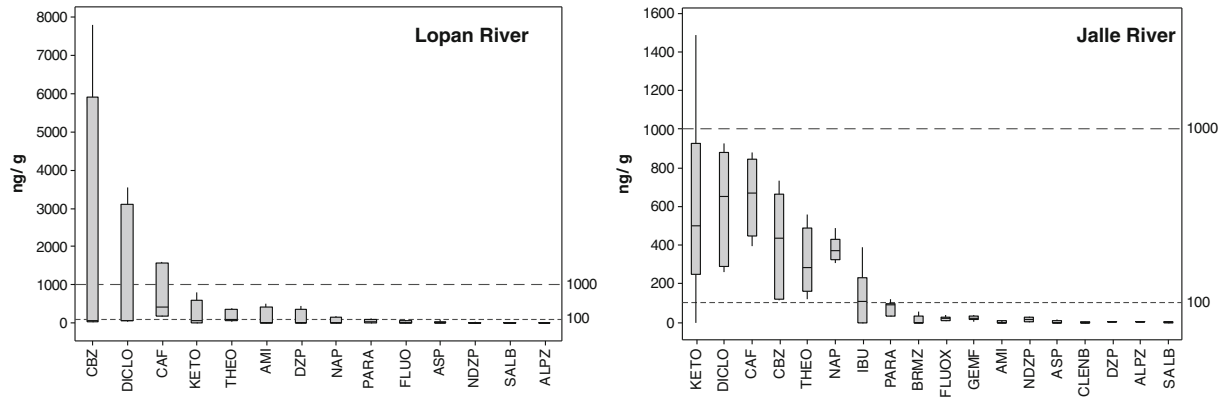

Fig. 2 *Box plots* of the accumulation of pharmaceuticals (ng g^{-1}) in POCIS installed in the Lopan and Jalle Rivers

relates to discharges from the Veterinary Academy located upstream L03 and/or with the run-off from farms (Lees et al. 2004; Curry et al. 2005). The concentration of other target compounds was in the following tendency: CAF>PARA≥DICLO>CBZ. Downstream of the WWTP (L09), the concentration and diversity of drugs were significantly different from upstream sites (L03 and L08). There are several additional target compounds of psychiatric (DZP, AMI, and FLUOX) and anti-inflammatory (NAP) drugs were measured together with KETO, CAF, CBZ, and DICLO. The range of the concentration in L09 represents the following order: CBZ>DICLO>CAF> KETO>NAP≥AMI≥DZP>PARA>FLUOX (Fig. 3).

Thus, non-conservative compounds (CAF and PARA) were dominated in upstream sites and conservative compound (CBZ; Clara et al. 2004; Fenz et al. 2005; Huerta-Fontela et al. 2008) was in the majority downstream of WWTP on the Lopan River. The prescribed psychiatric drugs (NDZP, AMI, FLUOX, and DZP) were found in the Ukrainian river only downstream of the WWTP. The consumption of these medicaments is strongly regulated by the government (Ministry of Health, Ukraine: www.moz.gov.ua). These pharmaceuticals generally can enter the watercourses through the WWTP with contaminated effluents from hospitals and medical institutions.

In the Jalle River, the concentration and diversity of PPs were less varied in comparison with the Lopan River. In the J01, the contamination of pharmaceuticals represented the following structure: KETO≥ CAF>NAP≥PARA>DICLO>IBU>CBZ>GEMF. Downstream of WWTP 1 (J02), the concentration of KETO, CAF, and PARA decreased possibly due to the combination of different factors (reduction of sources, degradation, and dilution), but the concentration of DICLO and CBZ increased. At the J03, the concentration of all substances, previously measured at J02, grew and represented the following order: DICLO>CAF>PARA≥NAP>CBZ>KETO>IBU> GEMF>FLUOX>NDZP>AMI, which showed the domination of non-conservative substances.

Comparison with the research of Togola (2006) on the Jalle River showed, that in our study the concentration of CBZ was lower, inversely DICLO presented higher concentration level. This discrepancy can relate to the difference in the location of the sampling sites and sampling technique, but also to changes in the wastewater treatment process and drug consumptions during the last 7 years (the sampling of the Jalle River reported in Togola (2006) has been done in 2003).

The analysis of the pharmaceutical concentrations and accumulation in both rivers showed that the same trend of the accumulation of KETO was observed in the Lopan River and in the Jalle, where both the highest contamination were detected in upstream sites. The diclofenac and carbamazepine showed the tendency to accumulate along both study waters, what characterize the relatively conservative behavior of these substances (Clara et al. 2004; Fenz et al. 2005; Huerta-Fontela et al. 2008). The concentration of other widely prescribed psychiatric drugs (i.e. AMI, ALPZ, FLUOX, and DZP) increased only in the sites downstream WWTPs, thus, wastewaters can be considered as the general source of these medicaments in the studied rivers. The stimulant, caffeine, was detected upstream and downstream of the

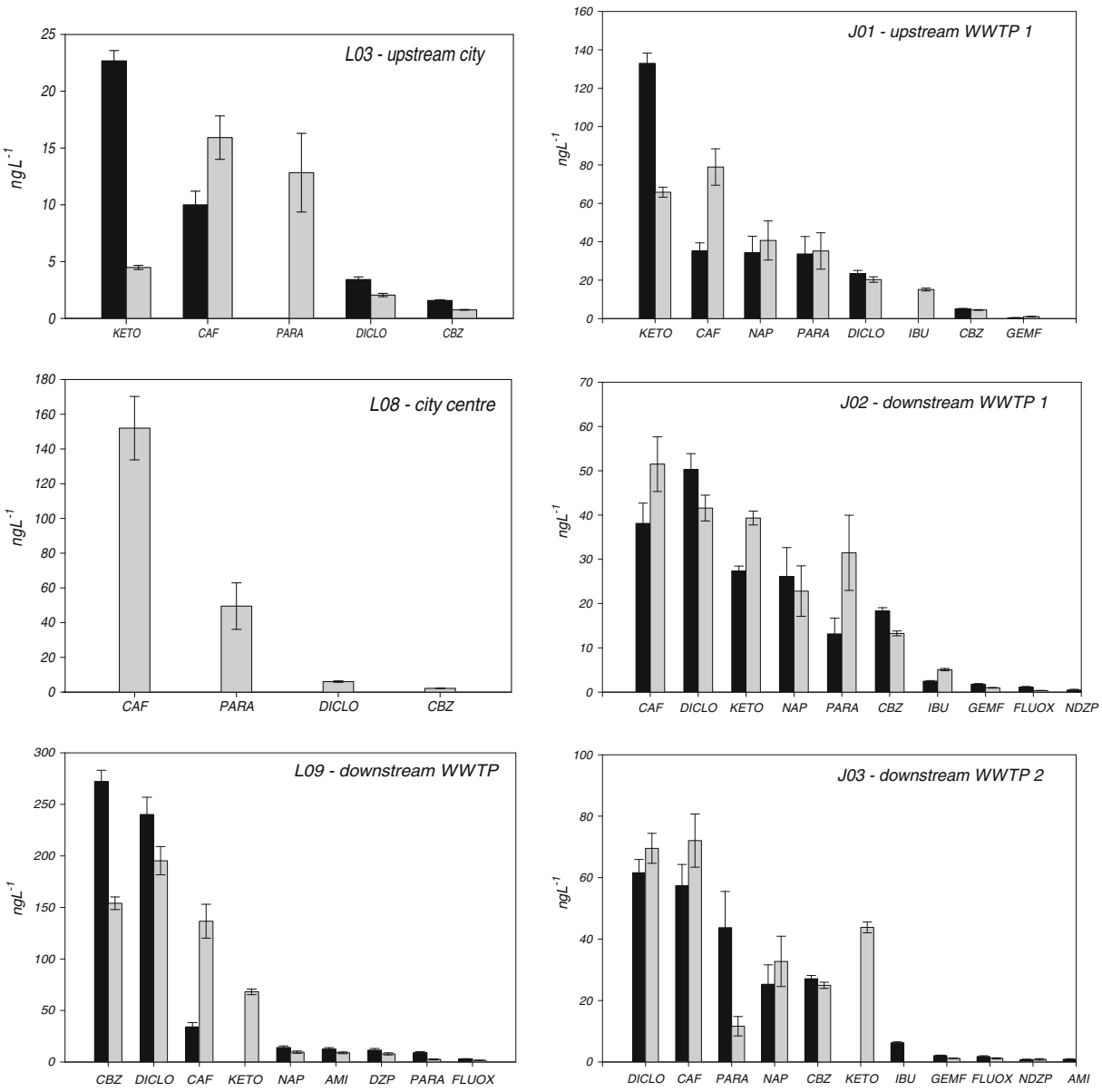

Fig. 3 The concentration of pharmaceuticals in the Lopan and Jalle Rivers: May 2009 (*black square*) and December 2009 (*gray square*)

WWTPs (Fig. 3). This compound has a non-conservative behavior (Buerge et al. 2003; Joss et al. 2006) and easily degrades during treatment processes (more than 90% of the removal efficiency on the conventional wastewater treatment plant; KNAPPE 2008) and under influence of biological factors. Consequently, the presence of stimulants along the river can be characterized by (1) the continuous discharge of not efficiently treated wastewaters, (2) other additional sources of pollution, e.g. run-off (Froehner et al. 2010) and/or (3) the regional "baseline" of the caffeine in water. According to the maximum concentration, the river in Ukraine was more contaminated by CBZ, DICLO, DZP, and AMI than the studied river in France (Fig. 3). The paracetamol, salbutamol, and alprazolam showed approximately the same level of contamination in studied rivers (Fig. 3).

Finally, found differences can be linked to various factors, e.g. (1) as a result of the disparity in the medicaments consumption and (2) efficiency of wastewater treatment facilities. In order to understand how the drug consumption rate per capita is related to the water quality, a mass balance approach has been applied.

4.3 Mass Balance Modeling of Drug Consumption Using Water Monitoring Data

Caffeine, carbamazepine, and diclofenac were found in all sampling sites of both rivers in the highest values compared to other compounds. In our study, the calculation of the theoretical consumption rate of these pharmaceuticals in regions of Ukraine and France has been done using the data of water monitoring and their comparison with reported national data on level of the drug use. A mass balanced model includes following (Eq. 2):

$$M_c = (Q_w C_w - Q_u C_u))/(K_1(1 - K_2)) \quad (2)$$

M_c drug consumption rate in a studied settlement, which is served by sewage system (g d^{-1})

K_1 drug excretion rate (a part of a pharmaceutical component which enters a sewage system as unchanged form by human excretion; g g^{-1}). Pharmacokinetics represents a very complex process and depends on the metabolism, age, activity, etc. We used previously reported data on the parent drugs excretion (Table 3).

K_2 the efficiency of wastewater treatment processes was estimated as a part of pharmaceuticals which are efficiently removed during the treatment (g g^{-1}). The efficiency has been used from previously published works for selected substances taking into account the treatment processes type. In the studied sites of France and Ukraine, WWTPs treatment processes have the conventional treatment scheme and consist of mechanical and biological operations.

C_w, C_u concentrations of pharmaceuticals in the river, downstream and upstream of WWTP (g m^{-3}), respectively.

Table 3 The excretion and treatment efficiency of caffeine, carbamazepine, and diclofenac (data for the mass balance modeling)

PPs	Drug excretion rate, g g^{-1}	The treatment efficiency, g g^{-1}	
		France	Ukraine
Caffeine	0.10[a]	0.80[c]	0.80[d]
Carbamazepine	0.31[b]	0.20[d]	0.04[d]
Diclofenac	0.02[b]	0.40[d]	0.12[d]

[a] Froehner et al. 2010

[b] Khan and Ongerth 2004

[c] Kosma et al. 2010

[d] KNAPPE 2008

Q_w, Q_u the water flow rate in the river, downstream and upstream of WWTP

The daily drug consumption rate per person (D) was estimated as:

$$D = M_c/P \quad (3)$$

where, P is the number of people using the sewage system (n=inhabitants).

In order to process the mass balance modeling, the following assumptions have been done for the estimation of the drug consumption rate:

1. Caffeine has been considered as the quickly biodegradable component, so the upstream influence has not been taken into account.
2. The served population was estimated: the Jalle River, WWTP 2—50,000 people; the Lopan River, WWTP—1,000,000 people.

We have not considered the veterinary consumption, environmental degradation, and sorption because of the absence of relevant data. The calculated data on carbamazepine and diclofenac consumption rates (Fig. 4) have been compared with reported data for France. For Ukraine, similar data were not available, as no any official statistics on the drug consumption exist and the insurance and social security system is under development (Ministry of Health Protection, Ukraine www.moz.gov.ua)

The calculated carbamazepine consumption rate (0.1 g per person per year) was of the same magnitude as the previously reported one (0.3 g per person per

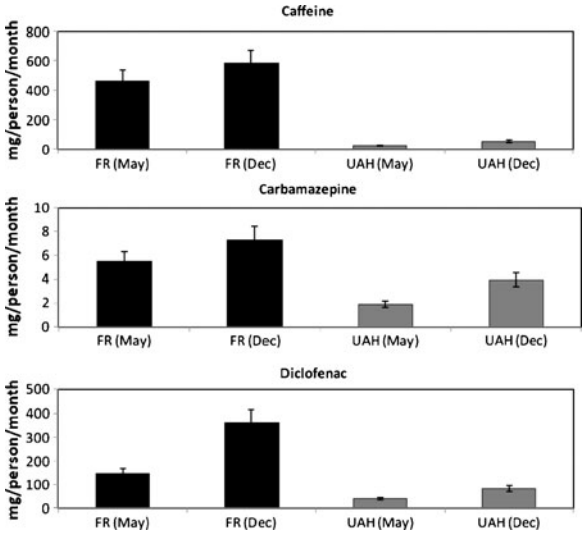

Fig. 4 The calculated drug consumption rate in the studied regions of France (FR) and Ukraine (UAH)

year; Coetsier et al. 2009). A good agreement between predicted environmental concentration and measured environmental concentration was found in previous research on carbamazepine in the South of France (Coetsier et al. 2009). For diclofenac, the discrepancy was much higher, as we estimated an annual consumption rate of 1.7 g per person (based on the May data) and 4.3 g per person (based on the December data). However, the reported data (Coetsier et al. 2009) were much lower, approximately 0.25 g per person per year. A high discrepancy between the calculated and measured concentrations of diclofenac has been presented in research in Sweden (Bendz et al. 2005) and France (Coetsier et al. 2009). As the reported data were based on the statistics of the social security reimbursement and present only a prescribed amount, we can assume that a significant amount of diclofenac is used without prescription. Also, the results of the mass balanced modeling showed that the consumption rate of carbamazepine was twofold higher in the studied regions of France than in the Ukrainian region, as well as threefold higher diclofenac and tenfold higher caffeine. In contrast, the river in Ukraine was higher contaminated by carbamazepine, diclofenac and caffeine than the studied river in France. This can be related to the lower dilution of wastewaters in the Lopan River (dilution rate can reach 21 (wastewater):1 (riverine water); Vasenko et al. 2006) compared to that for the Jalle River (dilution rate 1 (wastewater):3 (riverine water); Labadie 2004) and lower efficiency of the wastewater treatment. Also, the drug consumption was about 1.5- to 2-fold higher in December than in May in both countries. However, seasonal variation of these pharmaceuticals needs additional research taking into account the social and environmental data.

The results of this basic mass balance approach show that water quality monitoring can be useful for the estimation of social indicators such as the medical drug consumption rate and the illicit drug consumption rate (Huerta-Fontela et al. 2008; Zuccato et al. 2008). For further development of the approach: temporal variations, environmental degradation and other uncertainty factors can be incorporated in the mass balance model.

4.4 Molecular Indicators of Wastewaters in the River

Caffeine, carbamazepine, and diclofenac show differences in behavior and diverse sources. These properties were considered for the further analysis of these pharmaceuticals as potential indicators of anthropogenic activities.

In our study, carbamazepine and caffeine showed a high abundance in natural water (with a range for carbamazepine of 17–27 ng L^{-1} in the Jalle River, France; 2–272 ng L^{-1} in the Lopan River, Ukraine, and for caffeine: 40–75 and 10–152 ng L^{-1}, respectively). By using a passive sampling technique, these compounds can be detected in such values. Carbamazepine exhibits the most persistent behavior during both May and December (SD ±10% (J03) and SD ±40% (L09)) and was resistant to degradation in the natural environment. However, carbamazepine can be useful for tracing pathways of sewage water, even the treated one. In contrast, caffeine is a labile compound and easily degraded during the water treatment processes and in natural waters: it can be used for the identification of effluents of untreated wastewaters. In our study caffeine, carbamazepine, and diclofenac were detected in the Lopan River during the dry weather in August 2009 on the upstream site (L03; Fig. 5) and their occurrence can characterize uncontrolled discharges of untreated wastewaters, since the volume of the run-off is extremely small during the dry period. Untreated wastewater can come from households, which are not connected to the sewage, but also from the Veterinary

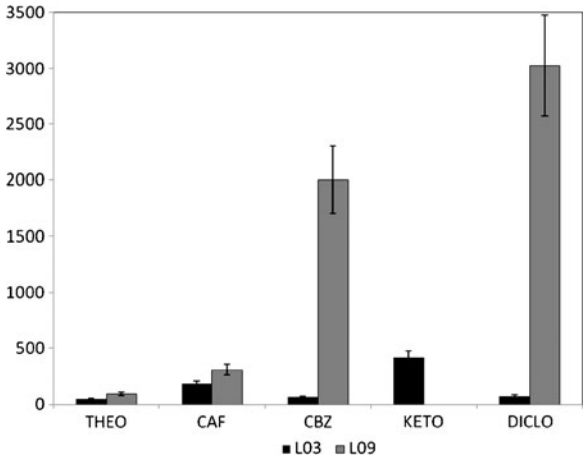

Fig. 5 The detection of the pharmaceuticals in the Lopan River during the dry period (August 2009), ng g^{-1}

Academy. Further monitoring is necessary to fully understand the occurrence of pharmaceuticals in the water as they can be used as a wastewater marker for surface and ground waters pollution by treated and untreated discharges.

4.5 The Application of the POCIS Method

Our practical experience of the passive sampling application shows that this technique is simple for the installation in contrasted climate conditions including the ice cover on the river. Also, the installation and retrieval was handy and does not need specific knowledge. Other positive aspect is that POCIS can be easier delivered to the laboratory for the analysis, even in the case of the sample manipulation in the different geographical regions. The passive technique has limitations on the exact assessment of PPs concentrations, however for pilot and research monitoring (Allan et al. 2006) focused on the identification of the presence of compounds, pollution sources, and their behavior the quantitative data analysis can be used in order to save the expenses on the laboratory analysis and experiments.

5 Conclusions

1. Eighteen pharmaceuticals and their potential sources in the natural water have been detected in the Jalle River (France) and 15 in the Lopan River (Ukraine) during the May 2009 and December 2009 using the POCIS passive sampling technique.
2. The accumulation of pharmaceuticals in the POCIS and the concentration of PPs in the rivers varied along the sampling sites and sampling seasons. Generally, the Lopan River was more contaminated by medicaments than the Jalle River in terms of the concentration of target compounds.
3. Caffeine, carbamazepine, and diclofenac were found in all samples with the high accumulation and concentration in urban area. The presence of ketoprofen was related mostly to upstream sites.
4. Mass balance modeling has been applied to estimate approximate consumption rates of carbamazepine, diclofenac, and caffeine in Bordeaux and Kharkiv regions. The results showed higher consumption rates of these pharmaceuticals in France than in Ukraine. In contrast, the levels of contamination of carbamazepine and diclofenac were higher in the Ukrainian river, this can be related to distinct efficiency in wastewater management and treatment.
5. Due to the abundance and stability in the water environment, some of measured pharmaceuticals (e.g. carbamazepine, caffeine, and diclofenac) have been proposed as potential wastewater's markers in the river for identification of different uncontrolled wastewaters discharges.

Finally, our study underlines the presence and behavior of pharmaceuticals in the Jalle River, Bordeaux (France) and the Lopan River, Kharkiv (Ukraine). It demonstrates the successful application: (1) of passive sensors to monitor water quality, (2) of mass balance modeling to estimate drug consumption rates and (3) of pharmaceuticals compounds as potential indicators of wastewater treatment efficiency.

Acknowledgements This research was conducted in the framework of Collaborative Program "Partenariat Hubert Curien DNIPRO" (Grant no 19744VJ 2009/2010) with the financial support from both the French Ministry of Foreign Affairs and the Ukrainian Ministry of Education and Science. Some authors have been granted through the ERASMUS MUNDUS External Cooperation Window Program (Lot 6/7—Belarus, Moldova and Ukraine), and by the Embassy of France to Ukraine (Bourse de Court Séjour de Recherche). The support of Ms. Maria Gonzalez Rey, Universidade do Algarve and Mr.

Michael van der Valk, the Netherlands National Committee IHP-HWRP, with editing this paper are greatly acknowledged.

References

Allan, I. J., Mills, G. A., Vrana, B., Knutsson, J., Holmberg, A., Guigeus, N., et al. (2006). Strategic monitoring for the European Water Framework Directive. *Trends in Analytical Chemistry, 25*, 704–714.

Alvarez, D. A., Stackelberg, P. E., Petty, J. D., Huckins, J. N., Furlong, E. T., Zaugg, S. D., et al. (2005). Comparison of a novel passive sampler to standard water—column sampling for organic contaminants associated with wastewater effluents entering a New Jersey stream. *Chemosphere, 61*, 610–622.

Arditsoglou, A., & Voutsa, D. (2008). Passive sampling of selected endocrine disrupting compounds using polar organic chemical integrative samplers. *Environmental Pollution, 156*, 316–324.

Barnes, K., Kolpin, D., Furlong, E., Zaugg, S., Meyer, M., & Barber, L. (2008). A national reconaissance of pharmaceuticals and other organic wastewater contaminants in the United States—I) groundwater. *Science of the Total Environment, 402*, 192–200.

Bartelt-Hunt, S. L., Snow, D. D., Damon, T., Shockley, J., & Hoagland, K. (2009). The occurrence of illicit and therapeutic pharmaceuticals in wastewater effluent and surface waters in Nebraska. *Environmental Pollution, 157*, 786–791.

Bendz, D., Paxeus, N., Ginn, T., & Loge, F. (2005). Occurrence and fate of pharmaceutically active compounds in the environment, a case study: Hoje River in Sweden. *Journal of Hazardous Materials, 122*, 195–204.

Benotti, M. J., & Brownawell, B. J. (2007). Distributions of pharmaceuticals in an urban estuary during both dry- and wet-weather conditions. *Environmental Science and Technology, 41*, 5795–5802.

Budzinski, H., Soulier, C., Lardy, S., Capdeville, M.J., Tapie, N., Vrana, B., Miege, C., & Ait Aissa, S. 2009. Passive sampler for chemical substance monitoring and associated toxicity assessment in water. Abstract presented at the International Conference on Xenobiotics in the Urban Water Cycle, 11–13 March 2009, Cyprus.

Buerge, I. J., Poiger, T., Muller, M. D., & Buser, H. R. (2003). Caffeine, an anthropogenic marker for wastewater contamination of surface waters. *Environmental Science and Technology, 37*, 691–700.

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

Cleuvers, M. (2003). Ecotoxicity of pharmaceuticals including the assessment of combination effects. *Toxicology Letters, 142*, 185–194.

Coetsier, C. M., Spinelli, S., Lin, L., Roig, B., & Touraud, E. (2009). Discharge of pharmaceutical products (PPs) through a conventional biological sewage treatment plant: MECs vs PECs. *Environment International, 35*, 787–792.

Comeau, F., Surette, C., Brun, G. L., & Losier, R. (2008). The occurrence of acidic drugs and caffeine in sewage effluents and receiving waters from three coastal watersheds in Atlantic Canada. *Science of the Total Environment, 396*, 132–146.

Curry, S. L., Cogar, S. M., & Cook, J. L. (2005). Nonsteroidal anti-inflammatory drugs: a review. *Journal of the American Animal Hospital Association, 41*, 298–309.

Fenz, R., Blaschke, A. P., Clara, M., Kroiss, H., Mascher, D., & Zessner, M. (2005). Quantification of sewer exfiltration using antiepileptic drug carbamazepine as marker species for wastewater. *Water Science and Technology, 52*, 209–217.

Froehner, S., Scuza, D. B., Machado, K. S., & da Rosa, E. C. (2010). Tracking anthropogenic inputs in Barigui River, Brazil using biomarkers. *Water Air and Soil Pollution, 210*, 33–41.

Glassmeyer, S. T., Furlong, E. T., Kolpin, D. W., Cahill, J. D., Zaugg, S. D., Werner, S. L., et al. (2005). Transport of chemical and microbial compounds from known wastewater discharges: potential for use as indicators of human fecal contamination. *Environmental Science and Technology, 39*, 5157–5169.

Grabic, R., Jurcikova, J., Tomsejova, S., Ocelka, T., Halirova, J., Hypr, D., et al. (2010). Passive sampling methods for monitoring endocrine disruptors in the Svratka and Svitava rivers in the Czech Republic. *Environmental Toxicology and Chemistry, 29*, 550–555.

Heberer, T. (2002). Tracking persistent pharmaceutical residues from municipal sewage to drinking water. *Journal of Hydrology, 226*, 175–189.

Huerta-Fontela, M., Galceran, M. T., Martin-Alonso, J., & Ventura, F. (2008). Occurrence of psyhoactive stimulatory drugs in wastewaters in north-eastern Spain. *Science of the Total Environment, 396*, 31–40.

Jones-Lepp, T. L., Alvarez, D. A., Petty, J. D., & Huckins, J. N. (2004). Polar organic chemical integrative sampling and liquid chromatography–electrospray/ion-trap mass spectrometry for assessing selected prescription and illicit drugs in treated sewage effluents. *Archives of Environmental Contamination and Toxicology, 47*, 427–439.

Joss, A., Zabczynski, S., Gobel, A., Hoffmann, B., Loffler, D., McArdell, C., et al. (2006). Biological degradation of pharmaceuticals in municipal wastewater treatment: proposing a classification scheme. *Water Research, 40*, 1686–1696.

Kasprzyk-Hordern, B., Dinsdale, R. M., & Guwy, A. J. (2009). Illicit drugs and pharmaceuticals in the environment—forensic applications of environmental data, part 1: estimation of the usage of drugs in local communities. *Environmental Pollution, 157*, 1778–1786.

Khan, S. J., & Ongerth, J. E. (2004). Modelling of pharmaceutical residues in Australian sewage by quantity of use and fugacity calculations. *Chemosphere, 54*, 355–367.

KNAPPE (2008) D. 2.1.: Report on the limitations of conventional treatment processes of the most resistant PPs and new development. In: D. Buncher (ed). pp. 45–57.

Kosma, C. I., Lambropoulou, D. A., & Albanis, T. A. (2010). Occurrence and removal of PPCPs in municipal and hospital wastewaters in Greece. *Journal of Hazardous Materials, 179*, 804–817.

Kuster, M., Lopez de Alda, M. J., Hernando, M. D., Petrovic, M., Alonso, J. M., & Barcelo, D. (2006). Analysis and occurrence of pharmaceuticals, estrogens, progestogens and polar pesticides in sewage treatment plant effluent, river water and drinking water in the Llobregat river basin (Barcelona, Spain). *Journal of Hydrology, 358*, 112–123.

Labadie, P., 2004. Determination des steroids hormonaux dans l'environemment: developpements analytiques et application. Thèse de Doctorat en chimie analytiques et environnement, Université Bordeaux 1, 270 p.

Lees, P., Landoni, M. F., Ciraudel, J., & Toutain, P. L. (2004). Pharmacodynamics and pharmacokinetics of nonsteroidal antiinflammatory drugs in species of veterinary interest. *Journal of Veterinary Pharmacology and Therapeutics, 27*, 479–490.

Li, H., Helm, P. A., & Metcalfe, C. D. (2010). Sampling in the Great Lakes for pharmaceuticals, personal care products, and endocrine—disrupting substances using the passive polar organic chemical integrative sampler. *Environment and Chemistry, 29*, 1–12.

MacLeod, S. L., McClure, E. L., & Wong, C. S. (2007). Laboratory calibration and field deployment of the polar organic chemical integrative sampler for pharmaceuticals and personal care products in wastewater and surface water. *Environmental Toxicology and Chemistry, 26*, 2517–2529.

Miege, C., Budzinski, H., Jacquet, R., Soulier, C., Pelte, T., Coquery, M., et al. (2011). L'échantillonage integratif par POCIS—application pour la surveillance des micropolluants organiques dans les eaux résiduaries traitées et les eaux de surface. *Techniques Sciences et Methode, 1–2*, 80–94.

Nakada, N., Kiri, K., Shinohara, H., Harada, A., Kuroda, K., Takizawa, S., et al. (2008). Evaluation of pharmaceuticals and personal care products as water-soluble molecular markers of sewage. *Environmental Science and Technology, 42*, 6347–6353.

NRDW (2006) National Report on drinking water quality and supply in 2006 year. http://www.minjkg.gov.ua/editattach/bigdoc/nd_voda2006.doc (in Ukrainian). Accessed 1 March 2010

Othoniel, C. (2006) La croissance du biofilm photosynthétique : un indicateur du statut trophique des rivières? Thèse de Doctorat en Biogéochimie de l'Environnement, Université Bordeaux 1. p 277.

Petty, J. D., Huckins, J. N., Alvarez, D. A., Brumbaugh, W. G., Cranor, W. L., Gale, R. W., et al. (2004). A holistic passive integrative sampling approach for assessing the presence and potential impacts of waterborne environmental contaminants. *Chemosphere, 54*, 695–705.

Rabiet, M., Togola, A., Brissaud, F., Seidel, J.-L., Budzinski, H., & Elbaz-Poulichet, F. (2006). Consequences of treated water recycling as regards pharmaceuticals and drugs in surface and ground waters of a medium-sized Mediterranean catchment. *Environmental Science and Technology, 40*, 5282–5288.

Söderström, H., Lindberg, R. H., & Fick, J. (2009). Strategies for monitoring the emerging polar organic contaminants in water with emphasis on integrative passive sampling. *Journal of Chromatography. A, 1216*, 623–630.

Tapie, N., Devier, M. H., Soulier, C., Creusot, N., Le Menach, K., Aït-Aïssa, S., et al. (2011). Passive samplers for chemical substance monitoring and associated toxicity assessment in water. *Water Science and Technology, 63* (10), 2418–2426.

ter Laak, T. L., van der Aa, M., Houtman, C. J., Stoks, P. C., & van Wezel, A. P. (2010). Relating environmental concentrations of pharmaceuticals to consumption: a mass balance approach for the river Rhine. *Environment International, 36*, 403–409.

Togola, A., 2006. Presence and devenir des substances pharmaceutiques dans les ecosystems aquatiques. PhD thesis. Universite Bordeaux 1, France.

Togola, A., & Budzinski, H. (2007a). Development of polar organic integrative samplers for analysis of pharmaceuticals in aquatic systems. *Analytical Chemistry, 79*, 6734–6741.

Togola, A., & Budzinski, H. (2007b). Analytical development for analysis of pharmaceuticals in water samples by SPE and GC-MS. *Analytical and Bioanalytical Chemistry, 388*, 627–635.

Togola, A., & Budzinski, H. (2008). Multi-residue analysis of pharmaceutical compounds in aqueous samples. *Journal of Chromatography. A, 177*, 150–158.

Vasenko, O.G., Lungu, M.L., Iljevska, Y.A., Klymov, O.V. et al. (2006) Research report. The integrated field research of environmental conditions of water bodies of the Udy water basins (sub-basin of the Seversky Donets River)/"Rayder" Publ., Kharkiv, 156 p. (in Ukrainian).

Vrana, B., Mills, G. A., Allan, I. J., Dominiak, E., Svensson, K., Knutsson, J., et al. (2005). Passive sampling techniques for monitoring pollutants in water. *Trends in Analytical Chemistry, 24*, 845–868.

Vystavna, Y. Y, Le Coustumer, P., Huneau, F., & Vergeles, Y. (2009). Trace metals and pharmaceuticals in transboundary waters, their monitoring, toxicity and regulation. UNESCO: International workshop on Water and Health , Koblenz, 6–7 December 2009 (available: www.hydrology.nl/)

Vystavna Y., Le Coustumer, P., & Huneau, F. (2010). The distribution and accumulation of emerging pollutants in urban waters of Eastern Ukraine. Abstract volume. World Water Week in Stockholm, September 5–11, 2010 Published by Stockholm International Water Institute. Sweden, 420–421.

Vystavna, Y., Huneau, F., Motelica-Heino, M., Le Coustumer, P., Vergeles, Y., & Stolberg, F. (2011). Monitoring and flux determination of trace metals in rivers of the Seversky Donets basin (Ukraine) using DGT passive samplers. *Environmental Earth Sciences*. doi:10.1007/s12665-011-1151-4.

Zhang, Z., Hibberd, A., & Zhou, J. L. (2008). Analysis of emerging contaminants in sewage effluent and river water: comparison between spot and passive sampling. *Analytica Chemica Acta, 607*, 37–44.

Zuccato, E., Castiglioni, S., Bagnati, R., Chiabrando, C., Grassi, P., & Fanelli, R. (2008). Illicit drugs, a novel group of environmental contaminants. *Water Research, 42*, 961–968.