Source, Occurrence, and Fate of Pharmaceuticals in Natural Waters

Atlasi Daneshvar
Faculty of Natural Resources and Agricultural Sciences
Department of Aquatic Sciences and Assessment
Uppsala

Doctoral Thesis
Swedish University of Agricultural Sciences
Uppsala 2012

Acta Universitatis Agriculturae Sueciae
2012:67

Cover: River Fyris and Lake Mälaren in Central Sweden
(photo: Max Marcus, www.flygfoto.com)

ISSN 1652-6880
ISBN 978-91-576-7714-3

Print: SLU Service/Repro, Uppsala 2012

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Abstract

The consumption of pharmaceuticals has increased in the last few decades. After usage, pharmaceuticals are excreted via urine and feces and transported to wastewater treatment plants (WWTPs) where they are subjected to treatment processes, and finally discharged into rivers. In order to assess aquatic risk associated with short- and long-term exposure to pharmaceuticals, temporal-spatial variability in the concentrations should be monitored in different water compartments. In this thesis, occurrence and fate of pharmaceuticals and other organic pollutants were studied in Swedish and Canadian rivers and WWTPs, and the major sources of contaminations were identified.

The ranges of mean concentrations of the pharmaceuticals and personal care products (PPCPs), hormones, and pesticides were 2.4-13755 ng L^{-1} and 0.5-112 ng L^{-1} in treated wastewaters and rivers, respectively. WWTPs and combined sewer overflows (CSOs) were identified as major sources of PPCPs in rivers. However, a large gathering of people at a river shore could temporarily contribute to a high input of pharmaceuticals. A temporal study of mass flows and corresponding removal efficiencies (REs) of WWTP-derived pharmaceuticals showed winter accumulations for most of the compounds. This might reflect high water flow rates and negligible rates of bio- and phototransformation in this season. REs of beta-blockers were season-dependent, with the highest removal in the summer and fall. This was due to biotransformation, indicated by high water temperature and chlorophyll *a* mass flows during those seasons. Yearly median REs of nutrients were low compared to pharmaceuticals. Yet, REs of atenolol and nitrate-nitrogen (NO_3-N) were related and had similar seasonal trends. Carbamazepine REs were the lowest among the pharmaceuticals. The latter combined with the persistence of carbamazepine in WWTPs and a lake showed its potential as an indicator of cumulative contamination. A correlation between caffeine concentrations and fecal coliforms in rivers confirmed caffeine as an indicator of recent urban fecal contamination. A high caffeine/carbamazepine ratio might be indicative of raw sewage discharge in a river, justified by higher concentrations of caffeine than carbamazepine in raw sewage and negligible removal of carbamazepine in WWTPs. The outcomes of the thesis show that source characteristics, water flow rates, and environmental conditions are essential factors that control detection frequency, concentrations and associated mass flows, and the fate of pharmaceuticals in aquatic environments. Also, pharmaceuticals can be used as indicators of recent and cumulative fecal contamination in drinking water sources.

Keywords: pharmaceutical, source water, treated wastewater, occurrence, fate, indicator

Author's address: Atlasi Daneshvar, SLU, Department of Aquatic Sciences and Assessment, P.O. Box 7050, 750 07 Uppsala, Sweden
E-mail: Atlasi.Daneshvar@slu.se

Dedication

To my parents

One never notices what has been done; one can only see what remains to be done.

- Marie Curie

Contents

List of Publications

This thesis is based on the work contained in the following papers, referred to by Roman numerals in the text:

I Daneshvar, A., Svanfelt, J., Kronberg, L., Weyhenmeyer, G. A. (2010). Winter accumulation of acidic pharmaceuticals in a Swedish river. *Environmental Science and Pollution Research* 17(4), 908-916.

II Daneshvar, A., Svanfelt, J., Kronberg, L., Prévost, M., Weyhenmeyer, G. A. (2010). Seasonal variations in the occurrence and fate of basic and neutral pharmaceuticals in a Swedish river-lake system. *Chemosphere* 80(3), 301-309.

III Daneshvar, A., Svanfelt, J., Kronberg, L., Weyhenmeyer, G. A. (2012). Neglected sources of pharmaceuticals in river water-footprints of a Reggae festival. *Journal of Environmental Monitoring* 14(2), 596-603.

IV Daneshvar, A., Aboulfadl, K., Viglino, L., Broséus, R., Sauvé, S., Madoux-Humery, A. S., Weyhenmeyer, G. A., Prévost, M. (2012). Evaluating pharmaceuticals and caffeine as indicators of fecal contamination in drinking water sources of the Greater Montreal region. *Chemosphere* 88(1), 131-139.

V Daneshvar, A., Prévost, M., Fick, J., Kronberg, L., Weyhenmeyer, G. A. Natural waters remove pharmaceuticals faster than nutrients. (Manuscript).

The contribution of Atlasi Daneshvar to the papers included in this thesis was as follows:

I The respondent was involved in the planning of the sampling programme, in collecting the water samples, and in performing pharmaceutical analyses. In addition, she was the main responsible person for data interpretation and writing the paper.

II The respondent was involved in the planning of the sampling programme, in collecting the water samples, and in performing pharmaceutical analyses. In addition, she was the main responsible person for data interpretation and writing the paper.

III The respondent was mainly responsible for collecting the water samples and performing pharmaceutical analyses. She was the main responsible person for interpretation of the pharmaceutical data and the main responsible person for writing the paper.

IV The respondent participated in the pharmaceutical analyses. In addition, she was mainly responsible for interpreting the data as well as writing the paper.

V The respondent was mainly responsible for producing the pharmaceutical data. She was partly responsible for interpretation of the pharmaceutical data and partly responsible for writing the paper.

Abbreviations

AA	Acetic acid
ACE	Acebutolol
ACN	Acetonitrile
APPI	Atmospheric pressure photoionization
AS	L'Assomption
ATE	Atenolol
ATR	Atrazine
BEZ	Bezafibrate
CA	Canada
CAF	Caffeine
CBZ	Carbamazepine
Cl	Chloride
CSO	Combined sewer overflow
CYA	Cyanazine
DEA	Deethylatrazine
DIA	Deisopropylatrazine
DIC	Diclofenac
DP	Des Prairies
DWTP	Drinking water treatment plant
ESD	Estradiol
ESI	Electrospray ionization
ESI-	Negative ESI
ESI+	Positive ESI
ESN	Estrone
FA	Formic acid
GEM	Gemfibrozil
IBU	Ibuprofen
K	Potassium
K_d	Sorption distribution coefficient

KET	Ketoprofen
K_{ow}	Octanol-water partitioning coefficient
LC	Liquid chromatography
LOD	Limit of detection
MeOH	Methanol
MET	Metoprolol
Mg	Magnesium
MI	Mille-Iles
MS	Mass spectrometry
MW	Molecular weight
Na	Sodium
NAP	Naproxen
NH_4-N	Ammonium-nitrogen
NH_4OH	Ammonium hydroxide
NO_3-N	Nitrate-nitrogen
Pk_a	Acid dissociation constant
PPCP	Pharmaceuticals and personal care product
PRO	Progesterone
SE	Sweden
SIM	Simazine
SL	St. Lawrence
SOT	Sotalol
SPE	Solid phase extraction
TN	Total nitrogen
TOC	Total organic carbon
TP	Total Phosphorus
tQ	Triple quadrupole
TRI	Trimethoprim
WFD	Water framework directive
WWTP	Wastewater treatment plant

1 Introduction

Pharmaceuticals and personal care products (PPCPs), and hormones refer to a large class of chemical contaminants that are produced and consumed in large quantities worldwide. They are introduced directly into wastewater treatment plants (WWTPs) through different pathways including household and consumer products, excretion in forms of parent compounds and/or metabolites with feces and urine, disposal of unused or expired medicine in toilets, and hospital waste (Heberer, 2002; Daughton & Ternes, 1999; Halling-Sørensen *et al.*, 1998). Various works have reported that PPCPs and hormones are not totally eliminated in WWTPs by the available treatment techniques, therefore, complex mixtures of partially eliminated contaminants as well as their metabolites are continuously released into surface waters (Yoon *et al.*, 2010; Vieno *et al.*, 2006).

The first reports on steroid hormones occurring in municipal wastewater were published in the United States in the mid-1960s and early 1970s (Tabak & Bunch, 1970; Stumm-Zollinger & Gordon, 1965). A couple of years later, studies in the United States reported the occurrence of clofibric acid and salicylic acid in wastewater effluents (Garrison, 1977; Hignite & Azarnoff, 1977). However, the first European report highlighting the presence of synthetic steroids in treated wastewaters and rivers was published one decade later in the UK (Aherne & Briggs, 1989). The presence of PPCPs in aquatic environments received great attention in the late 1990s, shortly after demonstrating that endocrine disruption in fish is related to natural and synthetic estrogens (Desbrow *et al.*, 1998; Routledge *et al.*, 1998). Since then, a growing body of work has been published on this topic worldwide (Kim *et al.*, 2007; Castiglioni *et al.*, 2005; Zuccato *et al.*, 2005; Heberer, 2002; Kolpin *et al.*, 2002; Daughton & Ternes, 1999; Buser *et al.*, 1998; Halling-Sørensen *et al.*, 1998; Ternes, 1998).

In the 1970s, a preliminary list of priority pollutants was established in the United States, mainly based on the availability of analytical techniques

allowing for detection at low concentrations in aqueous matrices (Daughton, 2003). Three decades later, in 2000, a first list of 33 priority substances had been established within the context of the EU Water Framework Directive (WFD) (2000/60/EC) with updates every four years since then (Ellis, 2006). The priority substances were chosen according to their toxicity, persistency, and liability to bioaccumulation or similar qualities which give rise to an equivalent level of concern (Ellis, 2006). In the latest revision of the WFD in 2012, two hormones, i.e. 17 alpha-ethinylestradiol and 17 beta-estradiol, and one pharmaceutical, i.e. diclofenac were among 15 additional substances proposed for incorporation into the priority list (European Commission 2011).

During the last couple of years, sources and occurrence of PPCPs and hormones in different environmental compartments, especially water, have been studied in detail. Yet, there is little data available from specific geographical regions, and a significant knowledge gap exists in terms of their fate in natural waters. Consumption of PPCPs and hormones is increasing (3-4% by weight annually) (Ellis, 2006) and new compounds are continually being manufactured (Yu *et al.*, 2006). In addition, the available treatment processes remove them only partially (Gabet-Giraud *et al.*, 2010; Vieno *et al.*, 2006; Bendz *et al.*, 2005; Carballa *et al.*, 2004), therefore, they continuously enter surface waters. Those that are resistant to natural attenuation processes might be accumulated over time and consequently pose a threat to aquatic life through chronic exposure. Hence, in this thesis the main focus was to contribute to the available knowledge on the source, occurrence, and natural attenuation of PPCPs, hormones, and some other environmentally relevant contaminants in natural waters.

2 Background

2.1 Sources of Pharmaceuticals and Other Organic Pollutants in Rivers

PPCPs, hormones, and pesticides are introduced to aquatic environments continuously or occasionally via a number of point and non-point routes. Discharges of treated wastewaters have been identified to be major point sources of PPCPs and hormones in the environment (Gabet-Giraud *et al.*, 2010; Vieno *et al.*, 2007a). Production facilities can also be important local point sources of PPCPs and hormones in adjacent surface waters (Zuccato *et al.*, 2000), especially in middle-income countries such as China and India where strict regulations on discharge of drugs into the environment are not in place (Larsson *et al.*, 2007). Furthermore, urban and agricultural runoff, leakage from septic tanks, recreational activities, and combined sewer overflows (CSOs) during storm events or system failure tanks can occasionally become potential sources of PPCPs and hormones in natural waters (Benotti *et al.*, 2009; Godfrey *et al.*, 2007; Metcalfe *et al.*, 2003a).

Concentrations of pesticides in raw sewage mostly reflect the concentrations in drinking water and urban surface runoff in CSOs (Nitschke & Schüssler, 1998). However, concentrations of pesticides in surface waters reflect recent and cumulative concentrations from agricultural runoff as well as in-stream elimination processes (Hua *et al.*, 2006b; Albanis *et al.*, 1998; Nitschke & Schüssler, 1998)

2.2 Occurrence of Pharmaceuticals and Other Organic Pollutants in Treated Wastewaters and Rivers

In the last fifteen years several studies have demonstrated the presence of PPCPs, hormones, and pesticides in different water compartments. Presently,

data in about 150 peer-reviewed papers, covering different geographical regions with focus on industrialized countries from the northern hemisphere, are summarized in Table 1.

2.2.1 Treated Wastewater

Most of the presented data in Table 1 are based on studies conducted in Europe (61% for PPCPs, 58% for hormones, and 90% for pesticides), followed by North America (27% for PPCPs, 29% for hormones, and 10% for pesticides), and Asia (12% for PPCPs, 13% for hormones, while no data was found for pesticides). Among the thirteen PPCPs, highest concentrations in Europe were reported for ibuprofen (48240 ng L^{-1}) and caffeine (44000 ng L^{-1}) in Spain. The highest values for North America and Asia were reported for naproxen in Canada (34000 ng L^{-1}) and caffeine in Japan (3500 ng L^{-1}), respectively. Concentrations of estradiol, estrone, and progesterone were lower than PPCPs and in all the three regions. Estrone was found at the highest concentration of these three compounds, i.e. 82 ng L^{-1} in Italy, 96 ng L^{-1} in Canada, and 110 ng L^{-1} in Japan. Of the five pesticides the highest concentration was observed for simazine in Switzerland (200 ng L^{-1}).

Differences in concentrations of treated wastewaters between different compounds and countries generally reflect different usage patterns, per-capita water consumption, and treatment processes.

2.2.2 River

Most of the collected information in Table 1 corresponds to the available data from Europe (68% of PPCPs, 59% of hormones, and 65% of pesticides) followed by North America (13% of PPCPs, 12% of hormones, and 25% of pesticides), and Asia (19% of PPCPs, 29% of hormones, and 10% of pesticides). In Europe, the highest concentrations of PPCPs, hormones, and pesticides were 43500 ng L^{-1} for caffeine, 81 ng L^{-1} for estrone, and 2218 ng L^{-1} for simazine, respectively. In North America, the highest values for PPCPs, hormones, and pesticides were 6000 ng L^{-1} for caffeine, 200 ng L^{-1} for estradiol, and 9840 ng L^{-1} for atrazine, respectively. In Asia, the highest values for PPCPs, hormones, and pesticides were 6000 ng L^{-1} for caffeine, 65 ng L^{-1} for estrone, and 780 ng L^{-1} for atrazine, respectively.

More than 96% of the presented data from treated waste- and surface waters belong to high-income countries where industrial discharges are supposed to be controlled, e.g. Good Manufacturing Practices and emission regulations in the United States (Velagaleti *et al.*, 2002). In contrast, only a few data are available from low- to middle-income countries where several manufacturing facilities are located and less strict regulations are applied, e.g. China and India. The

latter combined with a large variation in the concentrations of the studied compounds within and between countries indicate that the results from one region are not necessarily applicable to other regions.

Table 1. *Occurrence of the studied compounds (ng L^{-1}) in treated wastewaters and rivers in different countries around the world.*

	Sampling location	Treated wastewaters	Rivers	Reference
IBU	Austria	20-2400		(Clara *et al.*, 2005)
	Canada	140-6300		(Comeau *et al.*, 2008)
	Canada		143_{Mean}	(Yu *et al.*, 2007)
	Canada	381-1191		(Gagné *et al.*, 2006)
	Canada	773_{Max}		(Lishman *et al.*, 2006)
	Canada	2235-6718		(Verenitch *et al.*, 2006)
	Canada	110-2170		(Lee *et al.*, 2005)
	Canada	25000_{Max}		(Metcalfe *et al.*, 2003a)
	Canada	1885_{Mean}	790_{Max}	(Metcalfe *et al.*, 2003b)
	China		1417_{Max}	(Peng *et al.*, 2008)
	Croatia	40-800		(Gros *et al.*, 2006)
	Europe[I]	20-7110		(Andreozzi *et al.*, 2003)
	Europe[II]	18-1860	60-152	(Hernando *et al.*, 2006)
	Europe [III]		31323_{Max}	(Loos *et al.*, 2009)
	Finland		12-69	(Vieno *et al.*, 2007b)
	Finland		2-64	(Lindqvist *et al.*, 2005)
	France	18-219		(Rabiet *et al.*, 2006)
	Germany		<2-70	(Wiegel *et al.*, 2004)
	Germany	130_{Mean}		(Ternes *et al.*, 2003)
	Germany	3400_{Max}	530_{Max}	(Ternes, 1998)
	Italy		1.3-73	(Loos *et al.*, 2007)
	Italy	121_{Median}	20_{Median}	(Zuccato *et al.*, 2005)
	Italy		4.5-78.5	(Calamari *et al.*, 2003)
	Japan	40_{Mean}		(Kimura *et al.*, 2007)
	Japan	1.4-67		(Nakada *et al.*, 2006)
	Romania		61-115	(Moldovan, 2006)
	South Korea		1-51	(Yoon *et al.*, 2010)
	South Korea		ND-414	(Kim *et al.*, 2009)
	South Korea	10-137	11-38	(Kim *et al.*, 2007)
	Spain		6-2784	(Fernández *et al.*, 2010)
	Spain	240-28000		(Gomez *et al.*, 2007)
	Spain	20-690	14-44	(Pedrouzo *et al.*, 2007)
	Spain	780-48240		(Santos *et al.*, 2007)

	Sampling location	Treated wastewaters	Rivers	Reference
	Spain	42-10639		(Martinez Bueno *et al.*, 2007)
	Spain		150_{Max}	(Gros *et al.*, 2006)
	Spain/Croatia	<150-1050		(Petrovic *et al.*, 2006)
	Spain	10100_{Max}		(Santos *et al.*, 2005)
	Spain	910-2100		(Carballa *et al.*, 2004)
	Sweden	150_{Mean}	10-220	(Bendz *et al.*, 2005)
	Switzerland	5-1500	80_{Max}	(Ollers *et al.*, 2001)
	Switzerland	2-81		(Buser *et al.*, 1999)
	Taiwan	<12-34	<12-30	(Chen *et al.*, 2008)
	Taiwan	30_{Mean}		(Lin *et al.*, 2005)
	UK	65-491	<0.3-74	(Kasprzyk-Hordern *et al.*, 2009b)
	UK		0.6-37	(Kasprzyk-Hordern *et al.*, 2008)
	UK	27256_{Max}	5044_{Max}	(Ashton *et al.*, 2004)
	USA	250_{Mean}		(Yu *et al.*, 2006)
	USA		1000_{Max}	(Kolpin *et al.*, 2002)
NAP	Canada	210-6900		(Comeau *et al.*, 2008)
	Canada		83_{Mean}	(Yu *et al.*, 2007)
	Canada	217-325		(Gagné *et al.*, 2006)
	Canada	1189_{Max}		(Lishman *et al.*, 2006)
	Canada	633-7962		(Verenitch *et al.*, 2006)
	Canada	360-2540		(Lee *et al.*, 2005)
	Canada	34000_{Max}		(Metcalfe *et al.*, 2003a)
	Canada	524_{Mean}	551_{Max}	(Metcalfe *et al.*, 2003b)
	China		328_{Max}	(Peng *et al.*, 2008)
	Croatia	160_{Max}		(Gros *et al.*, 2006)
	Europe[I]	290-5220		(Andreozzi *et al.*, 2003)
	Europe[II]	625_{Max}	70_{Max}	(Hernando *et al.*, 2006)
	Europe [III]		2027_{Max}	(Loos *et al.*, 2009)
	Finland		13-32	(Vieno *et al.*, 2007b)
	France	42-289		(Rabiet *et al.*, 2006)
	Germany	261_{Mean}		(Quintana & Reemtsma, 2004)
	Germany	100_{Mean}		(Ternes *et al.*, 2003)
	Germany	80_{Mean}		(Heberer, 2002)
	Germany	520_{Max}	390_{Max}	(Ternes, 1998)
	Japan	99_{Mean}		(Kimura *et al.*, 2007)
	Japan	12-139		(Nakada *et al.*, 2006)
	Slovenia		17-313	(Kosjek *et al.*, 2005)

	Sampling location	Treated wastewaters	Rivers	Reference
	South Korea		5-100	(Yoon *et al.*, 2010)
	South Korea	20-483	1.8-18	(Kim *et al.*, 2007)
	Spain		2-640	(Fernández *et al.*, 2010)
	Spain	359-4200		(Martinez Bueno *et al.*, 2007)
	Spain	20-450		(Pedrouzo *et al.*, 2007)
	Spain	220-4280		(Santos *et al.*, 2007)
	Spain		50_{Max}	(Gros *et al.*, 2006)
	Spain	3120_{Max}		(Santos *et al.*, 2005)
	Spain	800-2600		(Carballa *et al.*, 2004)
	Sweden	250_{Mean}	90-250	(Bendz *et al.*, 2005)
	Switzerland	100-3500	10-400	(Ollers *et al.*, 2001)
	Taiwan	170_{Mean}	30_{Mean}	(Lin *et al.*, 2005)
	UK	<2-703	<0.3-146	(Kasprzyk-Hordern *et al.*, 2009b)
	UK		3-34	(Kasprzyk-Hordern *et al.*, 2008)
	USA	$<1_{Mean}$		(Vanderford & Snyder, 2006)
	USA	380_{Mean}		(Yu *et al.*, 2006)
	USA	81-106		(Boyd *et al.*, 2003)
KET	Canada	18-120		(Comeau *et al.*, 2008)
	Canada	210_{Max}		(Lishman *et al.*, 2006)
	Canada	8-351		(Verenitch *et al.*, 2006)
	Canada	40-90		(Lee *et al.*, 2005)
	Croatia	130-620		(Gros *et al.*, 2006)
	Europe[I]	1620_{Max}		(Andreozzi *et al.*, 2003)
	Europe [III]		239_{Max}	(Loos *et al.*, 2009)
	Finland		8-28	(Vieno *et al.*, 2007b)
	Finland		6.5-39	(Lindqvist *et al.*, 2005)
	France	22-1081		(Rabiet *et al.*, 2006)
	Germany	146_{Mean}		(Quintana & Reemtsma, 2004)
	Germany	380_{Max}	120_{Max}	(Ternes, 1998)
	Japan	445_{Mean}		(Kimura *et al.*, 2007)
	Japan	820_{Max}	24_{Max}	(Nakada *et al.*, 2007)
	Japan	68-204		(Nakada *et al.*, 2006)
	Spain		0.3-991	(Fernández *et al.*, 2010)
	Spain	225-954		(Martinez Bueno *et al.*, 2007)
	Spain	550-1500		(Santos *et al.*, 2007)
	Spain/Croatia	200-750		(Petrovic *et al.*, 2006)
	Spain	1760_{Max}		(Santos *et al.*, 2005)

	Sampling location	Treated wastewaters	Rivers	Reference
	Sweden	330_{Mean}	10-70	(Bendz *et al.*, 2005)
	Switzerland	200_{Max}	5_{Max}	(Ollers *et al.*, 2001)
	Taiwan	330-700	110-620	(Chen *et al.*, 2008)
	UK	<3-37	<0.5-12	(Kasprzyk-Hordern *et al.*, 2009b)
	UK		6_{Max}	(Kasprzyk-Hordern *et al.*, 2008)
	USA	280_{Mean}		(Yu *et al.*, 2006)
DIC	Austria	780-3464		(Clara *et al.*, 2005)
	Austria		16-36	(Ahrer *et al.*, 2001)
	Canada	25-190		(Comeau *et al.*, 2008)
	Canada		13_{Mean}	(Yu *et al.*, 2007)
	Canada	748_{Max}		(Lishman *et al.*, 2006)
	Canada	32-457		(Verenitch *et al.*, 2006)
	Canada	359_{Mean}	50_{Mean}	(Metcalfe *et al.*, 2003b)
	Croatia	390_{Max}		(Gros *et al.*, 2006)
	Europe[II]	32-1420	26-72	(Hernando *et al.*, 2006)
	Europe [III]		247_{Max}	(Loos *et al.*, 2009)
	Europe[IV]	250-5450		(Ferrari *et al.*, 2003)
	Finland		10-55	(Vieno *et al.*, 2007b)
	Finland		2-40	(Lindqvist *et al.*, 2005)
	France	211-486	1.4-1.7	(Rabiet *et al.*, 2006)
	Germany	3900_{Max}		(Stülten *et al.*, 2008)
	Germany	1561_{Mean}		(Quintana & Reemtsma, 2004)
	Germany		<1-40	(Wiegel *et al.*, 2004)
	Germany	1300_{Mean}		(Ternes *et al.*, 2003)
	Germany	2510_{Mean}		(Heberer, 2002)
	Germany	2100_{Max}	1200_{Max}	(Ternes, 1998)
	Greece	30-120		(Botitsi *et al.*, 2007)
	Ireland	<740-<2500		(Lacey *et al.*, 2008)
	Italy		1.7-158	(Loos *et al.*, 2007)
	Japan	145_{Mean}		(Kimura *et al.*, 2007)
	Japan	220_{Max}	3.3_{Max}	(Nakada *et al.*, 2007)
	Slovenia		9-282	(Kosjek *et al.*, 2005)
	South Korea		1-30	(Yoon *et al.*, 2010)
	South Korea	8.8-127	1.1-6.8	(Kim *et al.*, 2007)
	Spain		0.7-156	(Fernández *et al.*, 2010)
	Spain	140-2200		(Gomez *et al.*, 2007)
	Spain	10-460	25-41	(Pedrouzo *et al.*, 2007)

	Sampling location	Treated wastewaters	Rivers	Reference
	Spain	6-5922		(Martinez Bueno *et al.*, 2007)
	Spain		60_{Max}	(Gros *et al.*, 2006)
	Spain/Croatia	<50-500		(Petrovic *et al.*, 2006)
	Sweden	120_{Mean}	10-120	(Bendz *et al.*, 2005)
	Switzerland	100-700	20-150	(Ollers *et al.*, 2001)
	Switzerland	310-930	11-310	(Buser *et al.*, 1998)
	Taiwan	<2-30	24-62	(Chen *et al.*, 2008)
	UK	6-496	<0.5-261	(Kasprzyk-Hordern *et al.*, 2009b)
	UK	37-176		(Zhou *et al.*, 2009)
	UK		12_{Max}	(Kasprzyk-Hordern *et al.*, 2008)
	UK	68_{Mean}	3-15	(Zhang & Zhou, 2007)
	UK	2349_{Max}	568_{Max}	(Ashton *et al.*, 2004)
	USA	8-177	32_{Max}	(Spongberg & Witter, 2008)
	USA	$<0.5_{Mean}$		(Vanderford & Snyder, 2006)
	USA	90_{Mean}		(Yu *et al.*, 2006)
BEZ	Austria	73-4800		(Clara *et al.*, 2005)
	Austria		2-13	(Ahrer *et al.*, 2001)
	Canada	29-260		(Comeau *et al.*, 2008)
	Canada	68-72		(Gagné *et al.*, 2006)
	Canada	600_{Max}		(Metcalfe *et al.*, 2003a)
	Canada	259_{Mean}	200_{Max}	(Metcalfe *et al.*, 2003b)
	Croatia	10_{Max}		(Gros *et al.*, 2006)
	Europe [III]		1235_{Max}	(Loos *et al.*, 2009)
	Finland		3-20	(Vieno *et al.*, 2007b)
	Finland		3-24	(Lindqvist *et al.*, 2005)
	Germany	565_{Mean}		(Quintana & Reemtsma, 2004)
	Germany		<50-70	(Wiegel *et al.*, 2004)
	Germany	4600_{Max}	3100_{Max}	(Ternes, 1998)
	Italy		0.3-38	(Loos *et al.*, 2007)
	Italy	0.3-117		(Castiglioni *et al.*, 2005)
	Italy	55_{Median}	57_{Median}	(Zuccato *et al.*, 2005)
	Italy		0.8-57	(Calamari *et al.*, 2003)
	Japan	1500_{Max}	77_{Max}	(Nakada *et al.*, 2007)
	Spain		0.3-46	(Fernández *et al.*, 2010)
	Spain	70-340	16-363	(Pedrouzo *et al.*, 2007)
	Spain	61-484		(Martinez Bueno *et al.*, 2007)
	Spain		10_{Max}	(Gros *et al.*, 2006)

	Sampling location	Treated wastewaters	Rivers	Reference
	UK	<85-667	<10-90	(Kasprzyk-Hordern *et al.*, 2009b)
GEM	Canada	6-710		(Comeau *et al.*, 2008)
	Canada	59-84		(Gagné *et al.*, 2006)
	Canada	436_{Max}		(Lishman *et al.*, 2006)
	Canada	80-478		(Verenitch *et al.*, 2006)
	Canada	80-2090		(Lee *et al.*, 2005)
	Canada	1300_{Max}		(Metcalfe *et al.*, 2003a)
	Canada	1493_{Mean}	112_{Max}	(Metcalfe *et al.*, 2003b)
	Croatia	320_{Max}		(Gros *et al.*, 2006)
	Europe[I]	60-4760		(Andreozzi *et al.*, 2003)
	Europe [III]		970_{Max}	(Loos *et al.*, 2009)
	France	13-17		(Rabiet *et al.*, 2006)
	Germany		<2-8	(Wiegel *et al.*, 2004)
	Germany	70_{Mean}		(Heberer, 2002)
	Germany	1500_{Max}	510_{Max}	(Ternes, 1998)
	Ireland	<32-330		(Lacey *et al.*, 2008)
	Italy		0.4-44	(Loos *et al.*, 2007)
	South Korea		0.25-13	(Yoon *et al.*, 2010)
	South Korea	3.9-17	1.8-9.1	(Kim *et al.*, 2007)
	Spain	2-28571		(Martinez Bueno *et al.*, 2007)
	Spain		60_{Max}	(Gros *et al.*, 2006)
	Sweden	180_{Mean}	170_{Max}	(Bendz *et al.*, 2005)
	USA	42-84	6_{Max}	(Spongberg & Witter, 2008)
	USA	9_{Mean}		(Vanderford & Snyder, 2006)
	USA	130_{Mean}		(Yu *et al.*, 2006)
	USA		790_{Max}	(Kolpin *et al.*, 2002)
ATE	Canada	642-1680		(Lee *et al.*, 2007)
	Croatia	1150_{Max}		(Gros *et al.*, 2006)
	Finalnd		17-55	(Vieno *et al.*, 2007b)
	Finland	40-1180		(Vieno *et al.*, 2007a)
	Finland	40-440	<12-25	(Vieno *et al.*, 2006)
	France	36-2257		(Gabet-Giraud *et al.*, 2010)
	Germany	360_{Mean}		(Ternes *et al.*, 2003)
	Italy	27-1168		(Castiglioni *et al.*, 2005)
	Italy	466_{Median}	241_{Median}	(Zuccato *et al.*, 2005)
	Italy		3.4-241	(Calamari *et al.*, 2003)
	Japan	930_{Max}	46_{Max}	(Nakada *et al.*, 2007)
	South Korea		2-150	(Yoon *et al.*, 2010)

	Sampling location	Treated wastewaters	Rivers	Reference
	South Korea		ND-690	(Kim *et al.*, 2009)
	Spain		2-334	(Fernández *et al.*, 2010)
	Spain	66-9929		(Huerta-Fontela *et al.*, 2010)
	Spain	618-1370		(Gros *et al.*, 2008)
	Spain	275-4850		(Martinez Bueno *et al.*, 2007)
	Spain/Croatia	<50-1200		(Petrovic *et al.*, 2006)
	Sweden	160_{Mean}	10-60	(Bendz *et al.*, 2005)
	Switzerland	404-678		(Maurer *et al.*, 2007)
	UK	1260-7606	<1-560	(Kasprzyk-Hordern *et al.*, 2009b)
	UK		3-60	(Kasprzyk-Hordern *et al.*, 2007)
	USA	879_{Mean}		(Vanderford & Snyder, 2006)
MET	Canada	177-402		(Lee *et al.*, 2007)
	Europe[1]	10-390		(Andreozzi *et al.*, 2003)
	Finland		39-107	(Vieno *et al.*, 2007b)
	Finland	280-1600		(Vieno *et al.*, 2007a)
	Finland	910-1070	<4-116	(Vieno *et al.*, 2006)
	France	16-435		(Gabet-Giraud *et al.*, 2010)
	Germany	1700_{Mean}		(Ternes *et al.*, 2003)
	Germany	2200_{Max}	2200_{Max}	(Ternes, 1998)
	Japan	23_{Max}		(Nakada *et al.*, 2007)
	Poland		51-155	(Kasprzyk-Hordern *et al.*, 2007)
	Spain		2-26	(Fernández *et al.*, 2010)
	Spain	113-407		(Huerta-Fontela *et al.*, 2010)
	Spain	79-547		(Gros *et al.*, 2008)
	Spain	18-154		(Martinez Bueno *et al.*, 2007)
	Spain	20-140		(Pedrouzo *et al.*, 2007)
	Sweden	190_{Mean}	70_{Max}	(Bendz *et al.*, 2005)
	Switzerland	103-161		(Maurer *et al.*, 2007)
	UK	34-130	<0.5-12	(Kasprzyk-Hordern *et al.*, 2009b)
	UK		8_{Max}	(Kasprzyk-Hordern *et al.*, 2007)
	USA	1200_{Max}		(Huggett *et al.*, 2003)
SOT	Canada	162-429		(Lee *et al.*, 2007)
	Croatia	210_{Max}		(Gros *et al.*, 2006)
	Finland		30-86	(Vieno *et al.*, 2007b)
	Finland	130-1120		(Vieno *et al.*, 2007a)

	Sampling location	Treated wastewaters	Rivers	Reference
	Finland	160-300	<4-52	(Vieno *et al.*, 2006)
	France	128-3334		(Gabet-Giraud *et al.*, 2010)
	Germany	1320_{Mean}		(Ternes *et al.*, 2003)
	Spain	11-168		(Huerta-Fontela *et al.*, 2010)
	Spain	230-308		(Gros *et al.*, 2008)
	Spain	12-155		(Martinez Bueno *et al.*, 2007)
	Switzerland	251_{Max}		(Maurer *et al.*, 2007)
ACE	Canada	184-662		(Lee *et al.*, 2007)
	Europe[I]	<10-130		(Andreozzi *et al.*, 2003)
	Finland		3-14	(Vieno *et al.*, 2007b)
	Finland	35-255		(Vieno *et al.*, 2007a)
	Finland	80-230	<1-8	(Vieno *et al.*, 2006)
	France	32-3648		(Gabet-Giraud *et al.*, 2010)
	Spain	4-50		(Huerta-Fontela *et al.*, 2010)
	Taiwan		10-17	(Lin *et al.*, 2010)
CBZ	Austria	465-1619		(Clara *et al.*, 2005)
	Austria		23-133	(Ahrer *et al.*, 2001)
	Canada		99_{Mean}	(Yu *et al.*, 2007)
	Canada	33-137		(Gagné *et al.*, 2006)
	Canada	251_{Mean}		(Miao *et al.*, 2005)
	Canada	2300_{Max}		(Metcalfe *et al.*, 2003a)
	Canada	126_{Mean}	650_{Max}	(Metcalfe *et al.*, 2003b)
	Canada	426_{Mean}	0.7_{Mean}	(Miao & Metcalfe, 2003)
	Europe[I]	300-1200		(Andreozzi *et al.*, 2003)
	Europe [III]		11561_{Max}	(Loos *et al.*, 2009)
	Europe[IV]	300-1200		(Ferrari *et al.*, 2003)
	Finland		21-80	(Vieno *et al.*, 2007b)
	Finland	290-2440		(Vieno *et al.*, 2007a)
	Finland	380-470	<1.5-66	(Vieno *et al.*, 2006)
	France	157-293		(Rabiet *et al.*, 2006)
	Germany	1900_{Max}	81_{Max}	(Hummel *et al.*, 2006)
	Germany		<30-70	(Wiegel *et al.*, 2004)
	Germany	2100_{Mean}		(Ternes *et al.*, 2003)
	Germany	1630_{Mean}		(Heberer, 2002)
	Germany	6300_{Max}	1100_{Max}	(Ternes, 1998)
	Ireland	160-880		(Lacey *et al.*, 2008)
	Italy		7-345	(Loos *et al.*, 2007)
	Italy	33-1318		(Castiglioni *et al.*, 2005)
	Italy	291_{Median}	175_{Median}	(Zuccato *et al.*, 2005)

	Sampling location	Treated wastewaters	Rivers	Reference
	Japan	86_{Max}	12_{Max}	(Nakada *et al.*, 2007)
	Japan	11-149		(Nakada *et al.*, 2006)
	Korea	<5-195	<5-36	(Choi *et al.*, 2008)
	Poland		311-794	(Kasprzyk-Hordern *et al.*, 2007)
	Romania		65-75	(Moldovan, 2006)
	South Korea		8-68	(Yoon *et al.*, 2010)
	South Korea		ND-595	(Kim *et al.*, 2009)
	South Korea	73-729	4.5-61	(Kim *et al.*, 2007)
	Spain		0.3-104	(Fernández *et al.*, 2010)
	Spain	5-175		(Huerta-Fontela *et al.*, 2010)
	Spain	110-230		(Gomez *et al.*, 2007)
	Spain	69-273		(Martinez Bueno *et al.*, 2007)
	Spain	80-290	9-37	(Pedrouzo *et al.*, 2007)
	Spain	120-1290		(Santos *et al.*, 2007)
	Spain/Croatia	<100-600		(Petrovic *et al.*, 2006)
	Spain	750_{Max}		(Santos *et al.*, 2005)
	Sweden	1180_{Mean}	500_{Max}	(Bendz *et al.*, 2005)
	Switzerland	100-800	30-250	(Ollers *et al.*, 2001)
	Taiwan	290-960	<0.5-120	(Chen *et al.*, 2008)
	Taiwan	420_{Mean}		(Lin *et al.*, 2005)
	UK	152-4596	<0.5-647	(Kasprzyk-Hordern *et al.*, 2009b)
	UK	233-1061		(Zhou *et al.*, 2009)
	UK		9_{Max}	(Kasprzyk-Hordern *et al.*, 2007)
	UK	652_{Mean}	20-140	(Zhang & Zhou, 2007)
	USA	188-207		(Guo & Krasner, 2009)
	USA	34-111	14_{Max}	(Spongberg & Witter, 2008)
	USA		6_{Max}	(Conley *et al.*, 2008)
	USA	187_{Mean}		(Vanderford & Snyder, 2006)
	USA	270_{Max}	186_{Max}	(Glassmeyer *et al.*, 2005)
	USA		2-263	(Kolpin *et al.*, 2004)
CAF	Canada	320-2100		(Comeau *et al.*, 2008)
	Canada	315-22000		(Gagné *et al.*, 2006)
	Canada	1742-8132		(Verenitch *et al.*, 2006)
	Canada	677_{Mean}	46_{Mean}	(Metcalfe *et al.*, 2003b)
	Europe [III]		39813_{Max}	(Loos *et al.*, 2009)
	France	255-2213		(Rabiet *et al.*, 2006)

	Sampling location	Treated wastewaters	Rivers	Reference
	Germany	220_{Mean}		(Ternes *et al.*, 2003)
	Germany	180_{Mean}		(Heberer, 2002)
	Italy		0.6-1056	(Loos *et al.*, 2007)
	Japan	3500_{Max}	2100_{Max}	(Nakada *et al.*, 2007)
	Korea	19-873	<10-373	(Choi *et al.*, 2008)
	Romania		428-9700	(Moldovan, 2006)
	South Korea		38-250	(Yoon *et al.*, 2010)
	South Korea	23-776	2.9-194	(Kim *et al.*, 2007)
	Spain		12-416	(Fernández *et al.*, 2010)
	Spain	30-43500		(Huerta-Fontela *et al.*, 2008)
	Spain	1400-44000		(Gomez *et al.*, 2007)
	Spain	20-1010	106-305	(Pedrouzo *et al.*, 2007)
	Spain	150-3200		(Santos *et al.*, 2007)
	Spain	262-24658		(Martinez Bueno *et al.,* 2007)
	Spain	4520_{Max}		(Santos *et al.*, 2005)
	Sweden	220_{Mean}	110_{Max}	(Bendz *et al.*, 2005)
	Switzerland	30-9500	26-250	(Buerge *et al.*, 2003)
	Taiwan		3500-6000	(Lin *et al.*, 2010)
	USA	48-202		(Guo & Krasner, 2009)
	USA	4-23	27-320	(Spongberg & Witter, 2008)
	USA		23-39	(Conley *et al.*, 2008)
	USA	190-9900		(Batt *et al.*, 2006)
	USA	7990_{Max}	2600_{Max}	(Glassmeyer *et al.*, 2005)
	USA		36-1390	(Kolpin *et al.*, 2004)
	USA		6000_{Max}	(Kolpin *et al.*, 2002)
TRI	Canada	100_{Mean}		(Segura *et al.*, 2007)
	Canada	60-70		(Gagné *et al.*, 2006)
	Canada	194_{Mean}		(Metcalfe *et al.*, 2003b)
	Croatia	70-310		(Gros *et al.*, 2006)
	Europe[1]	20-130		(Andreozzi *et al.*, 2003)
	France		45_{Max}	(Tamtam *et al.*, 2008)
	Germany		<30-30	(Wiegel *et al.*, 2004)
	Germany	340_{Mean}		(Ternes *et al.*, 2003)
	Germany	660_{Max}	200_{Max}	(Hirsch *et al.*, 1999)
	Greece	12-300		(Botitsi *et al.*, 2007)
	Hong Kong		2-22	(Gulkowska *et al.*, 2007)
	Ireland	<70-360		(Lacey *et al.*, 2008)
	Japan	56_{Max}		(Nakada *et al.*, 2007)
	Korea	<10-174	<10-26	(Choi *et al.*, 2008)

	Sampling location	Treated wastewaters	Rivers	Reference
	Poland		8-27	(Kasprzyk-Hordern *et al.*, 2007)
	South Korea		1-17	(Yoon *et al.*, 2010)
	South Korea	10-188	3.2-5.3	(Kim *et al.*, 2007)
	Spain		0.4-23	(Fernández *et al.*, 2010)
	Spain	99-1264		(Martinez Bueno *et al.*, 2007)
	Spain/Croatia	<5-230		(Petrovic *et al.*, 2006)
	Sweden	613-1880		(Lindberg *et al.*, 2006)
	Sweden	40_{Mean}	20_{Max}	(Bendz *et al.*, 2005)
	Sweden	66-1340		(Lindberg *et al.*, 2005)
	UK	385-3052	<0.5-183	(Kasprzyk-Hordern *et al.*, 2009b)
	UK	1288_{Max}	42_{Max}	(Ashton *et al.*, 2004)
	USA		7_{Max}	(Conley *et al.*, 2008)
	USA	90-530		(Batt *et al.*, 2006)
	USA	550_{Max}		(Karthikeyan & Meyer, 2006)
	USA	$<0.5_{Mean}$		(Vanderford & Snyder, 2006)
	USA	353_{Max}	414_{Max}	(Glassmeyer *et al.*, 2005)
	USA		80_{Max}	(Kolpin *et al.*, 2004)
	USA		710_{Max}	(Kolpin *et al.*, 2002)
	Vietnam		7-44	(Managaki *et al.*, 2007)
ATR	Belgium	78_{Mean}	65_{Mean}	(Benijts *et al.*, 2004)
	Canada		7-79	(Hua *et al.*, 2006a)
	Canada		46-52	(Sabik & Jeannot, 1998)
	China		57-780	(Ma *et al.*, 2003a)
	Europe [III]		46_{Max}	(Loos *et al.*, 2009)
	Greece		310_{Max}	(Albanis *et al.*, 1998)
	Hong Kong		10_{Mean}	(Ma *et al.*, 2003b)
	Italy		3.2_{Max}	(Loos *et al.*, 2007)
	Italy		3.5-7	(Di Corcia *et al.*, 1997)
	Netherlands		510_{Mean}	(Steen *et al.*, 1999)
	South Korea		<0.25-1	(Yoon *et al.*, 2010)
	Spain	9_{Mean}		(Martinez Bueno *et al.*, 2007)
	Spain		2-1793	(Planas *et al.*, 2006)
	Spain		5-463	(Rodriguez-Mozaz *et al.*, 2004)
	Spain		120-170	(Carabias-Martínez *et al.*, 2002)
	Switzerland	10-90	10-80	(Ollers *et al.*, 2001)
	Switzerland		75_{Mean}	(Berg *et al.*, 1995)

	Sampling location	Treated wastewaters	Rivers	Reference
	USA	0.8_{Mean}		(Vanderford & Snyder, 2006)
	USA		<50-9840	(Rebich *et al.*, 2004)
DEA	Belgium	16_{Mean}	34_{Mean}	(Benijts *et al.*, 2004)
	Canada		24-36	(Sabik & Jeannot, 1998)
	China		652_{Mean}	(Ma *et al.*, 2003a)
	Greece		526_{Max}	(Albanis *et al.*, 1998)
	Italy		4-6.5	(Di Corcia *et al.*, 1997)
	Netherlands		19_{Mean}	(Steen *et al.*, 1999)
	Spain		8-874	(Planas *et al.*, 2006)
	Spain		4_{Max}	(Rodriguez-Mozaz *et al.*, 2004)
	Spain		300_{Mean}	(Carabias-Martínez *et al.*, 2002)
	Switzerland		198_{Mean}	(Berg *et al.*, 1995)
	USA		<50-1070	(Rebich *et al.*, 2004)
DIA	Belgium	12_{Mean}		(Benijts *et al.*, 2004)
	Canada		3-11	(Sabik & Jeannot, 1998)
	Italy		2-5	(Di Corcia *et al.*, 1997)
	Netherlands		6_{Mean}	(Steen *et al.*, 1999)
	Spain		10-802	(Planas *et al.*, 2006)
	Switzerland		41_{Mean}	(Berg *et al.*, 1995)
	USA		<50-560	(Rebich *et al.*, 2004)
CYA	Belgium	76_{Mean}		(Benijts *et al.*, 2004)
	Canada		3-10	(Sabik & Jeannot, 1998)
	USA		<50-810	(Rebich *et al.*, 2004)
SIM	Belgium	35_{Mean}	57_{Mean}	(Benijts *et al.*, 2004)
	Canada		6-9	(Sabik & Jeannot, 1998)
	Europe [III]		169_{Max}	(Loos *et al.*, 2009)
	Greece		317_{Max}	(Albanis *et al.*, 1998)
	Italy		8.5_{Max}	(Loos *et al.*, 2007)
	Spain	9-28		(Martinez Bueno *et al.*, 2007)
	Spain		2-605	(Planas *et al.*, 2006)
	Spain		8-2218	(Rodriguez-Mozaz *et al.*, 2004)
	Switzerland	20-200	10-100	(Ollers *et al.*, 2001)
	Switzerland	93_{Mean}	36_{Mean}	(Berg *et al.*, 1995)
	USA		<50-610	(Rebich *et al.*, 2004)
PRO	USA		199_{Max}	(Kolpin *et al.*, 2002)
	South Korea		$<0.5_{Max}$	(Yoon *et al.*, 2010)
ESD	Austria	3-30		(Clara *et al.*, 2005)
	Canada	<1-2		(Lee *et al.*, 2005)

	Sampling location	Treated wastewaters	Rivers	Reference
	Canada	0.2-14.7		(Servos *et al.*, 2005)
	Canada	64_{Max}		(Ternes *et al.*, 1999)
	China		2_{Max}	(Peng *et al.*, 2008)
	France	1-11		(Gabet-Giraud *et al.*, 2010)
	Germany	0.15-5	0.15-4	(Kuch & Ballschmiter, 2001)
	Germany	3_{Max}		(Ternes *et al.*, 1999)
	Italy		0.9_{Max}	(Loos *et al.*, 2007)
	Italy	0.35-3.5		(Baronti *et al.*, 2000)
	Japan	0.5-17		(Nakada *et al.*, 2006)
	Netherlands	12_{Max}	5.5_{Max}	(Belfroid *et al.*, 1999)
	South Korea		<0.5	(Yoon *et al.*, 2010)
	South Korea	<1		(Kim *et al.*, 2007)
	UK	0.7_{Mean}		(Koh *et al.*, 2007)
	UK	3-48		(Desbrow *et al.*, 1998)
	USA		200_{Max}	(Kolpin *et al.*, 2002)
	USA	<0.5-4		(Snyder *et al.*, 1999)
ESN	Austria	2-72		(Clara *et al.*, 2005)
	Belgium		22	(Benijts *et al.*, 2004)
	Canada		88_{Mean}	(Yu *et al.*, 2007)
	Canada	38_{Max}		(Lishman *et al.*, 2006)
	Canada	<1-54		(Lee *et al.*, 2005)
	Canada	1-96		(Servos *et al.*, 2005)
	Canada	48_{Max}		(Ternes *et al.*, 1999)
	China		65_{Max}	(Peng *et al.*, 2008)
	Europe [III]		81_{Max}	(Loos *et al.*, 2009)
	France	0.2-65		(Gabet-Giraud *et al.*, 2010)
	Germany	15_{Mean}		(Ternes *et al.*, 2003)
	Germany	0.35-18	0.1-4	(Kuch & Ballschmiter, 2001)
	Germany	70_{Max}	1.6_{Max}	(Ternes *et al.*, 1999)
	Italy		2.0_{Max}	(Loos *et al.*, 2007)
	Italy	30-48		(Castiglioni *et al.*, 2005)
	Italy	2.5-82		(Baronti *et al.*, 2000)
	Japan	3-110		(Nakada *et al.*, 2006)
	Netherlands	47_{Max}	3.4_{Max}	(Belfroid *et al.*, 1999)
	South Korea		0.2-4	(Yoon *et al.*, 2010)
	South Korea	2.2-36	1.7-5	(Kim *et al.*, 2007)
	Spain		4-22	(Rodriguez-Mozaz *et al.*, 2004)
	UK	3_{Mean}		(Koh *et al.*, 2007)
	UK	1.4-76		(Desbrow *et al.*, 1998)

Sampling location	Treated wastewaters	Rivers	Reference
USA		112_{Max}	(Kolpin *et al.*, 2002)

1. I for France, Greece, Italy, Sweden.
2. II for Spain, Belgium, Germany, Slovenia.
3. III for EU Member States.
4. IV for France, Greece, Italy, Sweden.

2.3 Fate of Pharmaceuticals in Rivers

Upon discharge of treated wastewaters into surface waters, concentrations of pharmaceuticals decline, mainly due to dilution to a varying extent being dependent upon factors such as stream flow rate conditions and percentage of treated wastewaters in the receiving water bodies.

Depending on chemical structure, environmental condition (e.g. temperature, light intensity, sediment type, turbidity, humic substances, nitrate), biotic and abiotic processes such as biotransformation, phototransformation, and sorption might also decrease concentrations of pharmaceuticals in the aquatic environment. For example, biotransformation has been highlighted as a potential elimination pathway of ibuprofen and naproxen once they have been released into the water column (Fono *et al.*, 2006; Löffler *et al.*, 2005; Buser *et al.*, 1999). Phototransformation occurs either directly by absorption of solar photons or indirectly by energy transfer from excited photosensitizers, e.g. nitrate and humic substances. Some pharmaceuticals such as diclofenac, naproxen, and ketoprofen have been reported to be amenable to direct photolytic reaction, with half-lives of less than three hours (Eriksson *et al.*, 2010; Lin *et al.*, 2006; Lin & Reinhard, 2005; Poiger *et al.*, 2001; Buser *et al.*, 1998), while ibuprofen was expected to undergo indirect phototransformation (Lin & Reinhard, 2005). It has been shown that the presence of humic substances hindered phototransformation of diclofenac and carbamazepine while nitrate enhanced the phototransformation rate of these compounds (Andreozzi *et al.*, 2003). Despite a positive effect of phototransformation in reducing drug levels in the environment, phototransformation can lead to the formation of transformation products which are more stable and toxic than the parent compounds, e.g. the carcinogenic acridine is formed during phototransformation of carbamazepine (Chiron *et al.*, 2006). There is also a concern about the enhanced toxicity of phototransformation products of diclofenac, e.g. diphenylamines and carbazoles as compared to the parent compound (Svanfelt & Kronberg, 2011; Schmitt-Jansen *et al.*, 2007). Sorption is mainly dependent on soil and sediment characteristics such as particle size and type (Scheytt *et al.*, 2005). Octanol-water partitioning coefficient (K_{ow}) is often used to predict ability of a

compound to be sorbed to soil and sediment particles. However, since degree of ionization of a compound is pH dependent and only the unionized species are partitioned into lipid phase, this approach is appropriate for neutral compounds (Vieno, 2007).

Even though several fate studies have been published during recent years, most of the reported data were based on bench scale studies where dynamic changes in hydraulic and chemical conditions differ from field studies, resulting in inconclusive statements on the attenuation mechanism of individual compounds. Lin *et al.* (2006) reported much shorter half-life time for ibuprofen (5.4 h) and naproxen (1.7-3.0 h) in a Californian river compared to data by Fono *et al.* (2006) in a Texan river (Dissipation half-life for ibuprofen 4.6 d and for naproxen 4.2 d). Based on a microcosm experiment, biotransformation was insignificant for naproxen (Lin *et al.*, 2006); however, it has been marked as a relevant loss mechanism in a Swiss lake (Tixier *et al.*, 2003) and a Texan river (Fono *et al.*, 2006). For ibuprofen, sedimentation and phototransformation were shown to be negligible (Yamamoto *et al.*, 2009; Löffler *et al.*, 2005), though, Tixier *et al.* (2003) argued that sorption of this compound, which has a relatively high sorption coefficient (Table 2), could not be ruled out.

2.4 Pharmaceuticals and Personal Care Products as Indicators of Fecal Contamination

Microbial safety of drinking water intakes associated with fecal contamination has traditionally been assessed by measuring indicator bacteria of water quality, most commonly, thermotolerant coliforms and *Escherichia coli* (Domingo ed., 2005). Bacterial test, however, is a time-consuming procedure (Glassmeyer *et al.,* 2005). In addition, indicator bacteria have a short survival time and their source specificity, i.e. differentiating between human and non-human sources of fecal contamination, is limited (Hagedorn & Weisberg, 2009; Glassmeyer *et al.*, 2005; Buerge *et al.*, 2003). Hence, in recent years, human-origin chemical markers with the advantage of shorter analysis times and being more source-specific have received considerable attention as potential alternatives to identify sources of pollution assigned to human activity. Nevertheless, application of chemical indicators was recommended during initial screening or as cross-validation supplements rather than replacement of conventional microbial markers (Hagedorn & Weisberg, 2009).

Nakada *et al.* (2008) reported crotamiton and carbamazepine as conservative indicators of sewage-derived contaminations in Japanese rivers. In another study, conducted in 40 sampling sites across the United States

evaluating the potential of 110 human-specific chemicals, caffeine, carbamazepine, and diphenhydramine were among the seven best promising indicators of human fecal material (Glassmeyer *et al.*, 2005). Caffeine was found to be ubiquitous in Swiss rivers and lakes in sufficiently high concentrations for reliable analytical quantification and has been proposed as an indicator of anthropogenic pollution (Buerge *et al.*, 2003). Recently, Sauvé *et al.* (2012) demonstrated relatively good correlations between fecal coliforms and caffeine concentrations in storm water collection systems, and suggested caffeine as an indicator of the source of sanitary contamination. It has also been suggested that the combination of conservative (e.g. carbamazepine) and labile (e.g. caffeine) markers might be beneficial in assessing percentage of raw and treated wastewater discharged to aquatic environments (Kasprzyk-Hordern *et al.*, 2009a; Nakada *et al.*, 2008).

Although a growing number of publications suggest the use of chemical markers for fecal tracking, geographical-temporal assessments appear desirable because of variations in usage pattern, consumer habits, water consumption, and removal by wastewater treatment (Hagedorn & Weisberg, 2009).

3 Objectives of the Thesis

The main objective of the thesis was to increase knowledge on temporal and spatial occurrence and removal of pharmaceuticals in natural surface waters that are exposed to continuous and intermittent anthropogenic sources. The specific objectives were:

1. To monitor the level of pharmaceuticals in WWTP effluents and river waters (papers I-V).

2. To identify continuous and intermittent sources of pharmaceuticals in river waters (papers I-V).

3. To identify suitable chemical indicators of fecal contaminations in river waters (paper IV).

4. To evaluate seasonal variations of pharmaceutical mass flows and their respective removal efficiencies in river waters (papers I, II).

5. To compare removal efficiencies of pharmaceuticals and nutrients in river waters (paper V).

4 Selected Compounds

The main focus of this work was on ten pharmaceuticals spanning a range of therapeutic classes, in particular four analgesics, four beta-blockers, one lipid regulator, and one antiepileptic, in Sweden. In addition we analyzed a diverse group of compounds, including PPCPs, hormones, and pesticides, in Canada. The compounds were selected on the basis of their high consumption in Sweden and Canada and availability of reliable analytical methods (Viglino *et al.*, 2008a; Viglino *et al.*, 2008b; Vieno *et al.*, 2006; Lindqvist *et al.*, 2005). Acebutolol, however, was an exception as it is not consumed in Sweden but detected in relatively high concentrations in WWTPs in Finland, a neighboring country (Vieno *et al.*, 2006). The target compounds represent different physico-chemical properties, e.g. molecular weight (MW) ranging from 173.6 to 361.8 g $mole^{-1}$, acid dissociation constant (Pk_a) ranging from 0.87 to 10.77, and log K_{ow} ranging from -0.07 to 4.77 (Table 2). About 80% of the compounds have medium to low affinity for sorption to hydrophobic surfaces, i.e. log $K_{ow} \leq 4.0$ (Rogers, 1996). However, in our river systems in which pH ranges from 7.6 to 8.2 (Papers I, II, IV), the majority of the compounds are ionizable; as a result, their K_{ow} might be subject to change. Hence, their degree of sorption to natural soil and sediments in aquatic environments should be instead evaluated based on sorption distribution coefficient (K_d) values (Table 2).

Table 2. *The target compounds and their physico-chemical properties.*

	Use	MW (g mol^{-1})	pKa	log K_{ow}	log $K_{d,\ sediment}$	Paper
IBU	Analgesic	206.3	4.91[1]	3.97[1]	-0.74-0.23[4]	I
NAP	Analgesic	230.3	4.15[1]	3.18[1]	0.46[6]	I, IV
KET	Analgesic	254.3	4.45[1]	3.12[1]	0.95[7]	I
DIC	Analgesic	296.2	4.15[1]	4.51[1]	-0.26-0.67[4]	I
BEZ	Lipid regulator	361.8	3.61[2]	4.25[1]	1.15_{soil}[7]	I
GEM	Lipid regulator	250.3	4.42[3]	4.77[3]	$-0.92\text{-}0.96_{soil}$[8]	IV
ATE	Beta blocker	266.3	9.60[1]	0.16[1]	0.11-0.91[9]	II
MET	Beta blocker	267.4	9.60[1]	1.88[1]	1.30[7]	II
SOT	Beta blocker	272.4	8.30-9.80[2]	0.24[1]	$2.56_{secondary\ sludge}$[10]	II
ACE	Beta blocker	336.4	9.33[1]	1.71[1]	3.28[11]	II
CBZ	Antiepileptic	236.3	14.00[4]	2.45[1]	-0.68-0.73[4]	II, IV
CAF	Stimulant	194.2	10.40[1]	-0.07[1]	1.40_{soil}-2.40[7,11]	IV
TRI	Anti-infective	290.3	7.12[1]	0.91[3]	1.4_{soil}[7]	IV
ATR	Herbicide	215.7	1.70[1]	2.61[1]	-0.85-0.15[12]	IV
DEA	ATR & SIM metabolite	187.6	1.40[5]	1.51[1]	$-1.70\text{-}(-0.20)_{soil}$[5]	IV
DIA	Herbicide	173.6	1.50[5]	1.15[1]	$-0.74\text{-}0.25_{soil}$[5]	IV
CYA	Herbicide	240.7	0.87[1]	2.22[1]	$0.22\text{-}0.6_{soil}$[13]	IV
SIM	Herbicide	201.7	1.62[1]	2.18[1]	-0.89-(-0.39)[14]	IV
PRO	Progestogen	314.5	Not Available	3.87[1]	$2.88\text{-}3.04_{sludge}$[10]	IV
ESD	Estrogen	288.4	10.71[3]	4.01[3]	-1.28[15]	IV
ESN	Estrogen	270.4	10.77[3]	3.13[3]	-1.39[15]	IV

1. Environment Science SRC PhysProp Database (2012).

2. Drug Information System (2012).

3. Li *et al.*, 2011.

4. Schyett *et al.*, 2005.

5. Vryzas *et al.*, 2007.

6. Vieno, 2007.

7. Barron *et al.*, 2011.

8. Fang *et al.*, 2012.

9. Yamamoto *et al.*, 2009.

10. Hörsing *et al.*, 2011.

11. Lin *et al.*, 2010.

12. Schwab *et al.*, 2006.

13. Schraer *et al.*, 2003.

14. Daniels *et al.*, 1998.

15. Cunha *et al.*, 2012.

5 Study Sites

In this thesis, most of the reported data are based on samples collected in River Fyris in Sweden and Mille-Iles (MI), Des Prairies (DP), L'Assomption (AS), and St. Lawrence (SL) rivers in Canada. Both water systems are described in detail below.

5.1 Uppsala, Sweden

Sample collections were mainly conducted in River Fyris (59°47'N, 17°39'E), a relatively small river which passes through the city of Uppsala in central Sweden and merges into Lake Mälaren (59°30'N, 17°12'E), Sweden's third largest lake. The river has a catchment area of 2,006 km^2 consisting of 65% forest and 25% agricultural land, with a mean water flow rate of 13 $m^3 s^{-1}$, and mean annual precipitation of 1.7 mm. A few water samples were also taken from Lake Mälaren. The reason for studying River Fyris was the fact that after receiving large amounts of treated wastewaters, it merges into Lake Mälaren, which is the source water for drinking water productions in the Stockholm area. Data presented for the river and lake are derived from water samples collected in the effluent of the WWTP, at six sites along River Fyris, and at different locations and depths in Lake Mälaren (Figure 1). Detailed information of sampling locations, times, and frequencies are presented in papers I, II, III, and V.

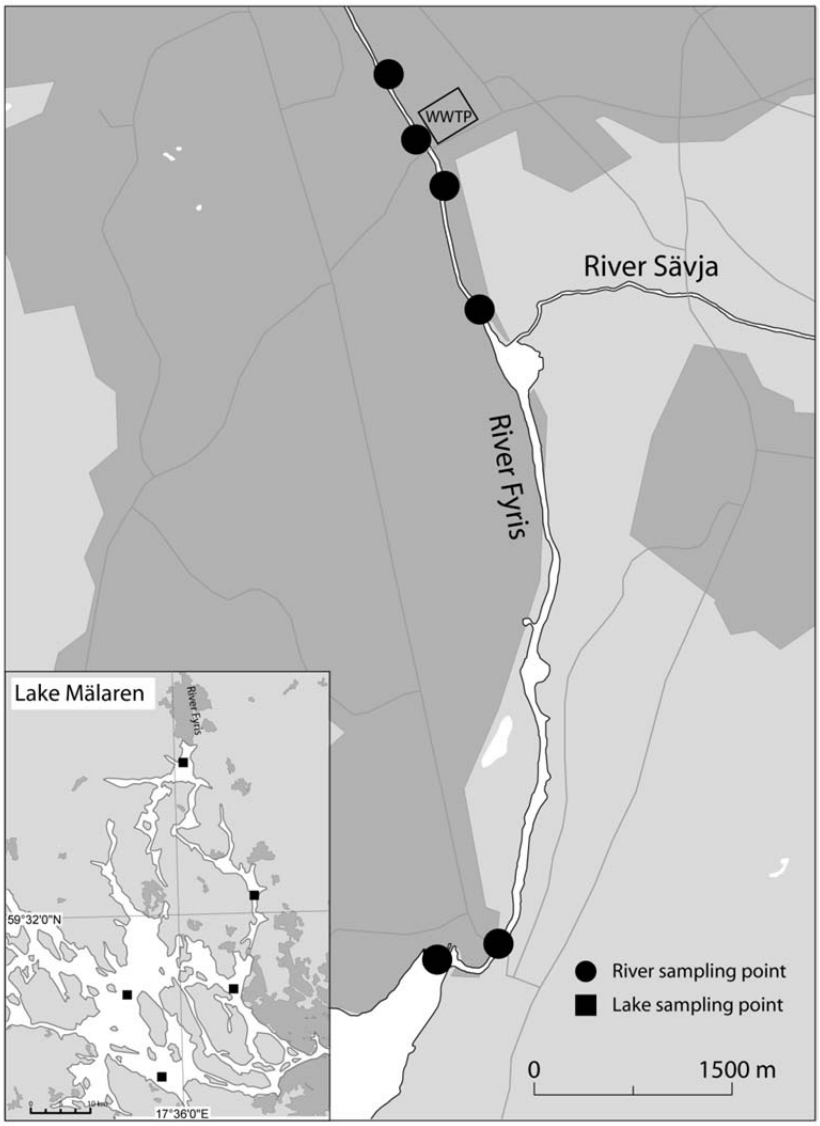

Figure 1. Sampling locations in River Fyris and Lake Mälaren.

5.2 Greater Montreal Region, Canada

Samples were collected in four rivers serving as the water sources for drinking water productions in the Greater Montreal region. Mille-Iles River receives effluents of several WWTPs, CSOs, and storm water discharges. Among the four rivers, Mille-Iles has the highest total organic carbon (TOC) (7.4 ± 0.5 mg L^{-1}), turbidity (14.9 ± 17.9 NTU), fecal contamination (494.5 ± 600.5 cfu 100 mL^{-1}), but the lowest average water flow rate (199 ± 157 $m^3 s^{-1}$) (supplementary material in paper IV). The Des Prairies River receives CSOs and storm water discharges and has comparable TOC (7.3 ± 0.4 mg L^{-1}), lower turbidity (8.4 ± 6.4 NTU), lower fecal contamination (20.8 ± 11.9 cfu 100 mL^{-1}), and higher average water flow rate (1104 ± 399 $m^3 s^{-1}$) compared to Mille-Iles River. The L'Assomption River receives the discharge of urban and agricultural wastes, and has lower TOC (6.0 ± 0.5 mg L^{-1}), lower turbidity (7.7 ± 2.3 NTU), and lower water flow rate (23.9 ± 20.4 $m^3 s^{-1}$) compared to the Mille-Iles and Des Prairies rivers. The St. Lawrence River receives water mainly from the Great Lakes and has the lowest TOC (3.0 ± 0.3 mg L^{-1}), turbidity (2.2 ± 2.4 NTU), fecal coliform (3.0 ± 4.1 cfu 100 mL^{-1}), but the highest average water flow rate (8185 ± 1130 $m^3 s^{-1}$) compared to the other three rivers. The differences between these rivers in terms of water flow rates, contamination sources, and TOC provide us with a unique opportunity to compare variability in the upstream-downstream concentrations of different classes of compounds and to assess the potential of chemical indicators as a complement to classic microbial indicators to track fecal contamination in drinking water sources. Data presented for these rivers represent water samples collected in the influent and effluent of two WWTPs in Mille-Iles River as well as seven sources of drinking water productions in the four rivers (Figure 2). Detailed information of sampling times and frequencies is discussed in paper IV.

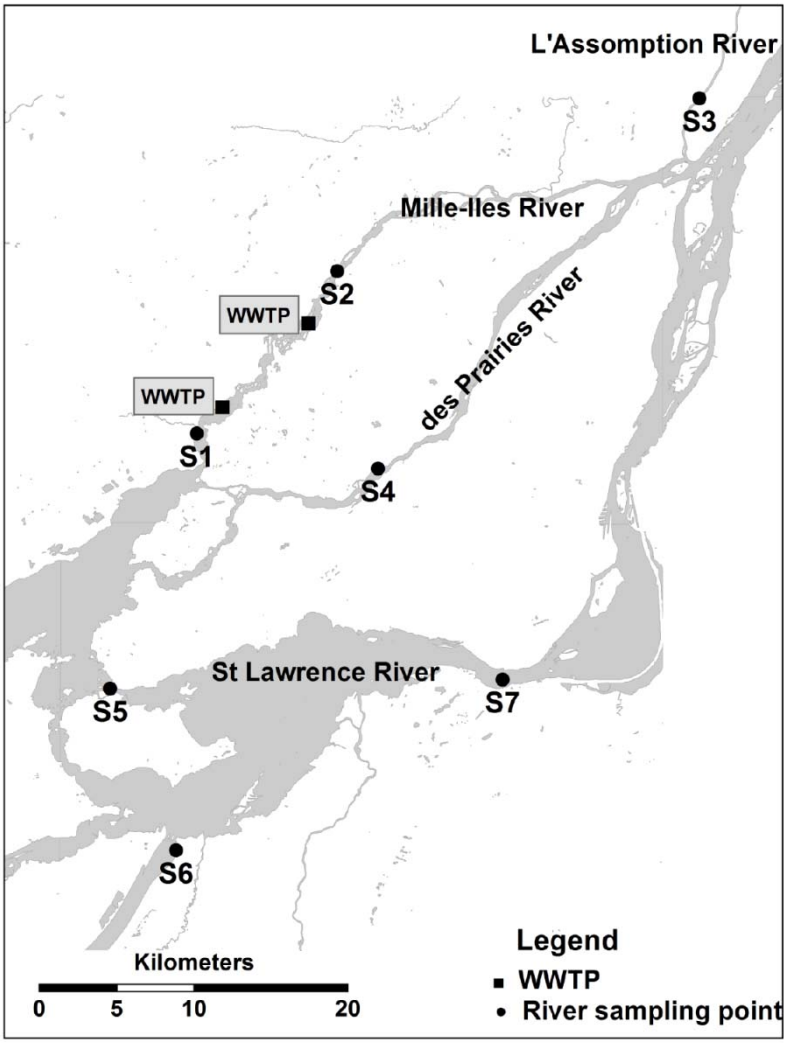

Figure 2. Sampling Locations in Mille-Iles, Des Prairies, L'Assomption, and St. Lawrence Rivers.

6 Analytical Methods

The pharmaceutical residues in the water were either extracted by an off-line or an on-line solid-phase extraction (SPE) technique. The detection and quantification were performed by a tandem mass spectrometry (MS) system coupled to a liquid chromatographic (LC) column. In this chapter, a short summary of the sample preparation and analytical methods is provided. The reader is, however, encouraged to read the specific paper in the appendix for full details.

6.1 Sample Preparation (Papers I-V)

In both off-line and on-line SPE/LC-MS-MS methods, sample preparations were quite similar. Colloidal and particulate matter in the water samples were filtered either through a 0.7-µm glass-fiber followed by 0.45-µm mixed cellulose membranes or 0.45-µm mixed cellulose membranes, depending on the amount of humic substances present. To prevent degradation of the studied compounds and improve their retention on SPE materials, the pH of the samples was adjusted to either ~2 or ~10 (Table 3). To minimize the uncertainty in quantification due to ion suppression or enhancement resulting from a high amount of matrix components, suitable internal standards were added to the samples.

6.2 Off-line SPE/LC-MS-MS (Papers I, II, III, V)

The off-line method was used in the analyses of pharmaceuticals in all the study sites in Sweden (Figure 1). Due to differences in physico-chemical properties of the pharmaceuticals, they were divided into two groups, i.e. acidic and basic/neutral, where SPE materials, elution solvents, material and mobile phase in LC separation columns, and detection method differed (Table 3).

During off-line SPE step, developed by Lindqvist *et al.* (2005) and Vieno *et al.* (2006), 500 mL of water sample was passed through the SPE material, dried with nitrogen gas, and eluted with appropriate organic solvent. The resulting extract was evaporated over a gentle nitrogen stream, and diluted with the aqueous LC eluent to a final volume 500 µL. 30 µL of each extract was injected to a LC-system where it passed through a guard column followed by the LC column. The target compounds were eluted from the LC column using a linear binary gradient elution method and were detected with a triple-quadrupole mass spectrometer. The guard column, the LC column, and the binary gradients were not exactly identical to those used in the previous studies and therefore the method was validated in terms of absolute and relative recoveries as well as intraday and interday repeatability.

6.3 On-line SPE/LC-MS-MS (Paper IV)

Previously developed on-line SPE/LC-MS-MS methods, validated for the same matrix constitutes (Viglino *et al.*, 2008a; Viglino *et al.*, 2008b), were used to quantify PPCPs, triazines and their metabolites, and hormones in water samples collected in the Greater Montreal region in Canada. In this method, only 1 mL of a water sample was preconcentrated while passing through an online SPE column and a pump, controlled automatically by an on-line setup. The rest of the procedures were almost similar to the off-line SPE/LC-MS-MS method (section 6.2), with slight differences in LC separation column and ionization sources (Table 3). Due to the elimination of several steps in on-line SPE, namely evaporation, reconstitution, and injection, the whole analysis time for each sample in the on-line method was a couple of hours shorter than for the off-line method.

6.4 Quantification (Papers I-V)

Independent of the analytical method chosen, the target compounds were quantified by the use of two internal standard-based calibration curves, one in surface water and one in wastewater, for each sampling occasion. The calibration curve samples were set up by spiking with the appropriate amount of each compound together with isotopically-labeled internal standards and were analyzed using the same procedure as for the water samples.

Table 3. *Analytical methods used in the environmental analyses of the target compounds.*

Analyzed compounds	SPE			LC		Detection method	Paper
	Mode	pH	Elution solvent	Separation column	Mobile phase		
IBU, NAP, KET, DIC, BEZ	Off-line	2.0	Acetone	C18	NH_4OH/ACN	ESI (-), tQ	I, III, V
ATE, MET, SOT, ACE, CBZ	Off-line	10.0	MeOH	C18	Aq. AA/ACN	ESI (+), tQ	II, III, V
CAF, TRI, CBZ, NAP, GEM, ATR, DEA, DIA, CYA, SIM	On-line	2.4	MeOH	C18	Aq. FA/MeOH	ESI (+), tQ	IV
PRO, ESD, ESN	On-line	2.4	MeOH	C18	Aq. FA/MeOH	APPI, tQ	IV

7 Results and Discussion

Three WWTPs, five rivers, and one lake were sampled in Sweden and Canada. A total of 14 raw sewage, 30 treated wastewater, 182 river water, and 13 lake samples were collected and analyzed in duplicate.

7.1 Occurrence of Pharmaceuticals and Other Organic Pollutants in Treated Wastewaters and Rivers (Papers I-V)

PPCPs, hormones, and pesticides were detected at least once in the analyzed samples from the rivers, whereas in the treated wastewaters some of the pesticides and hormones were not detected at all (Table 4 and 5). Mean concentrations of pharmaceuticals in the treated wastewater in Sweden ranged from 2.4 ng L^{-1} for acebutolol to 731 ng L^{-1} for diclofenac. In the two WWTPs in Canada, caffeine (13755 ng L^{-}), deethylatrazine (18 ng L^{-1}), and estrone (274 ng L^{-1}) had the highest mean concentrations among the PPCPs, pesticides, and hormones, respectively (Table 4). In the Swedish river, mean concentrations of pharmaceuticals varied from 0.5 ng L^{-1} for acebutolol to 110 ng L^{-1} for carbamazepine. In the four Canadian rivers, mean concentrations of PPCPs ranged between lower than the limit of detection (LOD) for gemfibrozil and trimethoprim and 112 ng L^{-1} for caffeine. Pesticides ranged between 5 ng L^{-1} for simazine and 53 ng L^{-1} for deisopropylatrazine, and hormones ranged between 4 ng L^{-1} for progesterone and 16 ng L^{-1} for estrone (Table 5).

Although concentrations in the treated wastewaters and surface waters fall within previously reported ranges (Table 1), large variations in the concentrations were observed between studies. In general, concentrations of individual PPCPs and hormones in raw sewage and treated wastewaters reflect consumption profile and removal efficiencies, respectively. On the other hand, concentrations in surface waters are controlled by the concentration levels of point and non-point sources, dilution factor, residence time, and degree of attenuation processes. For example, removal efficiencies of ibuprofen in the

Uppsala WWTP (Fick *et al.*, 2011) and the Finnish WWTPs (Lindqvist *et al.*, 2005) were quite similar whereas mean annual sales of ibuprofen were higher in Finland (Lindqvist *et al.*, 2005) compared to the Uppsala region in Sweden (Paper I). As a result, mean concentration of ibuprofen in the treated wastewaters in Finland (Lindqvist *et al.*, 2005) was higher than the corresponding value in the Uppsala WWTP in Sweden (Table 4).

Table 4. *Mean concentrations and standard deviations (SDs) of the target compounds in the treated wastewaters in Sweden and Canada.*

Compounds	Sampling location	Mean ± SD (ng L^{-1})	# Positive	paper
IBU	1 WWTP in River Fyris, SE	117 ± 61	8/15	I, III
NAP	1 WWTP in River Fyris, SE	232 ± 82	15/15	I, III
KET	1 WWTP in River Fyris, SE	281 ± 129	15/15	I, III
DIC	1 WWTP in River Fyris, SE	731 ± 405	15/15	I, III
BEZ	1 WWTP in River Fyris, SE	336 ± 237	15/15	I, III
ATE	1 WWTP in River Fyris, SE	309 ± 109	13/13	II, III
MET	1 WWTP in River Fyris, SE	288 ± 171	13/13	II, III
SOT	1 WWTP in River Fyris, SE	182 ± 48	13/13	II, III
ACE	1 WWTP in River Fyris, SE	2.4 ± 2.5	7/13	II, III
CBZ	1 WWTP in River Fyris, SE	516 ± 178	13/13	II, III
CAF	2 WWTPs in MI River, CA	13755 ± 12563	13/14	IV
TRI	2 WWTPs in MI River, CA	66 ± 34	14/14	IV
CBZ	2 WWTPs in MI River, CA	262 ± 159	14/14	IV
NAP	2 WWTPs in MI River, CA	1899 ± 1771	14/14	IV
GEM	2 WWTPs in MI River, CA	95 ± 76	9/14	IV
ATR	2 WWTPs in MI River, CA	14 ± 10	10/14	IV
DEA	2 WWTPs in MI River, CA	18 ± 34	7/12	IV
DIA	2 WWTPs in MI River, CA	Not detected	0/12	IV
CYA	2 WWTPs in MI River, CA	Not detected	0/12	IV
SIM	2 WWTPs in MI River, CA	Not detected	0/12	IV
PRO	2 WWTPs in MI River, CA	<LOD[1]	1/6	IV
ESD	2 WWTPs in MI River, CA	Not detected	0/6	IV
ESN	2 WWTPs in MI River, CA	274 ± 81	3/6	IV

1. LOD for PRO is 3 ng L^{-1}.

Mean concentration of carbamazepine in the treated wastewater in Sweden (516 ng L^{-1}) was almost two times higher than the mean value in the two WWTPs in Canada (262 ng L^{-1}) (Table 4). In River Fyris in Sweden, however, mean concentration of carbamazepine was about 15 times higher than the

corresponding value in Mille-Iles River in Canada (Table 5 and supplementary material in Paper IV). Considering the level of resistance that carbamazepine has to natural attenuation processes (Matamoros *et al.*, 2009; Löffler *et al.*, 2005), the large variability is most likely a consequence of the 15-times higher average water flow rate in River Mille-Iles (199 m^3 s^{-1}) compared to River Fyris (13 m^3 s^{-1}).

Table 5. *Mean concentrations and SDs of the target compounds in the rivers in Sweden and Canada.*

Compounds	Sampling location	Mean ± SD (ng L^{-1})	# Positive	paper
IBU	River Fyris, SE	31 ± 18	13/36	I
NAP	River Fyris, SE	33 ± 25	36/36	I
KET	River Fyris, SE	40 ± 40	21/36	I
DIC	River Fyris, SE	72 ± 36	31/36	I
BEZ	River Fyris, SE	38 ± 45	36/36	I
ATE	River Fyris, SE	38 ± 38	30/30	II
MET	River Fyris, SE	47 ± 61	29/30	II
SOT	River Fyris, SE	27 ± 27	30/30	II
ACE	River Fyris, SE	0.5 ± 0.4	12/30	II
CBZ	River Fyris, SE	110 ± 74	30/30	II
CAF	MI, DP, AS, SL Rivers, CA	112 ± 134	76/81	IV
TRI	MI, DP, AS, SL Rivers, CA	<LOD[2]	15/81	IV
CBZ	MI, DP, AS, SL Rivers, CA	5 ± 2	88/89	IV
NAP	MI, DP, AS, SL Rivers, CA	20 ± 15	41/89	IV
GEM	MI, DP, AS, SL Rivers, CA	<LOD[3]	1/89	IV
ATR	MI, DP, AS, SL Rivers, CA	24 ± 17	77/89	IV
DEA	MI, DP, AS, SL Rivers, CA	18 ± 19	38/54	IV
DIA	MI, DP, AS, SL Rivers, CA	53 ± 27	10/54	IV
CYA	MI, DP, AS, SL Rivers, CA	9 ± 9	19/54	IV
SIM	MI, DP, AS, SL Rivers, CA	5 ± 3	27/54	IV
PRO	MI, DP, AS, SL Rivers, CA	4 ± 2	14/51	IV
ESD	MI, DP, AS, SL Rivers, CA	6 ± 2	6/51	IV
ESN	MI, DP, AS, SL Rivers, CA	16	1/51	IV

1. The mean concentrations in River Fyris represent the average of data collected at 300, 1320, and 6490 m downstream the Uppsala WWTP.
2. LOD for TRI is 9 ng L^{-1}.
3. LOD for GEM is 24 ng L^{-1}.

In Lake Mälaren, where a much higher degree of dilution is expected compared to River Fyris, pharmaceuticals, except for carbamazepine, were

either not detected or detected at low concentrations. Carbamazepine was found in relatively comparable concentrations at all sampling sites (84-95 ng L^{-1}) and in the water column (84-100 ng L^{-1} in 0.5-40 m depth) of Lake Mälaren (Table III in paper II). Similarly, a low degree of fluctuation in the concentrations of this compound was previously reported in the water column of Lake Greifensee in Switzerland (30-58 ng L^{-1}) (Tixier *et al.*, 2003). Both observations point to the high persistency of carbamazepine in the aquatic environment.

7.2 Sources of Pharmaceuticals and Other Organic Pollutants in Rivers (Papers I-V)

In order to locate the contamination sources, concentrations of the most frequently detected compounds (Table 4 and 5) were compared between upstream and downstream of the rivers receiving discharges from WWTPs and CSOs. In River Fyris, this was achieved by calculating the ratio of concentrations at the effluent discharge point over upstream point. The calculated ratios for all the studied compounds were higher than one, i.e. ranging from 1.8 for ibuprofen to 62.0 for metoprolol (Figure 3). In addition, at all the sampling events, concentrations in the treated wastewaters were higher than the corresponding values in the WWTP upstream (supplementary materials in Papers I and II). Hence, the Uppsala WWTP has been indicated as a major source of pharmaceuticals in this river.

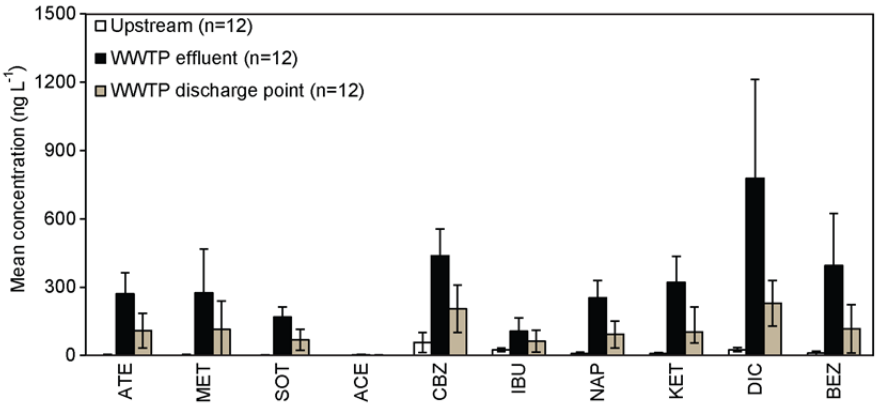

Figure 3. Annual mean concentrations and SDs (ng L^{-1}) of pharmaceuticals in upstream, wastewater effluent, and effluent discharge point in River Fyris.

However, considering the detection of trace levels of the compounds in the river upstream as well as the increase in concentrations of some compounds

after the merging of River Fyris to River Sävja (R6) (paper I and II) - a small river without any WWTP - inputs from city runoff, diffuse sources, and septic tanks cannot be completely ruled out. In addition, after a large gathering in the vicinity of River Fyris close to the upstream site which was accompanied with a heavy rainfall, concentrations of the pharmaceuticals increased from a factor 3.0 for acebutolol to 86 for atenolol (Figure 4). This pointed to the potential contribution of an intermittent source to the occurrence of pharmaceuticals in surface waters.

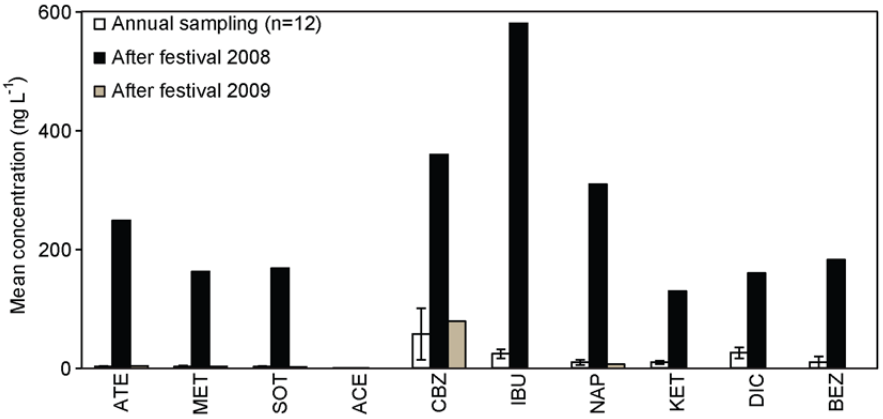

Figure 4. Comparison between annual mean concentrations of pharmaceuticals (ng L^{-1}) at upstream site of the Uppsala WWTP with the corresponding values 24 hours after the Uppsala Reggae festival in 2008 and 2009.

In the Canadian rivers, concentrations of caffeine, carbamazepine, naproxen, and atrazine increased in the downstream of Mille-Iles River after discharges of several WWTPs and CSOs (Figure 5a). This indicated that inputs from WWTPs and CSOs are the main sources of contaminations in this river. Nevertheless, higher average concentration of atrazine in the downstream of this river (26 ng L^{-1}) (Figure 5a) compared to the treated wastewaters (14 ng L^{-1}) (Table 4) pointed to the presence of other sources such as agricultural runoff. At a downstream site of Des Prairies River, receiving only CSOs discharges, mean concentration of carbamazepine remained relatively constant, mean concentrations of caffeine and naproxen increased, and mean concentration of atrazine decreased (Figure 5b). This showed that CSOs are potential intermittent sources of the PPCPs in this river. Moving toward a downstream of St. Lawrence River, receiving only cumulative contaminations from the Great Lakes, mean concentration of atrazine remained relatively constant while mean concentrations of caffeine and carbamazepine decreased (Figure 5c).

This highlighted the role of cumulative agricultural runoff as a potential source of atrazine.

The results from Sweden and Canada indicate that release of organic pollutants into aquatic environments mainly occurs via continuous/intermittent and urban/agricultural sources. Hence, to control and minimize discharges of these compounds into natural waters, all possible potential sources need to be carefully identified and controlled.

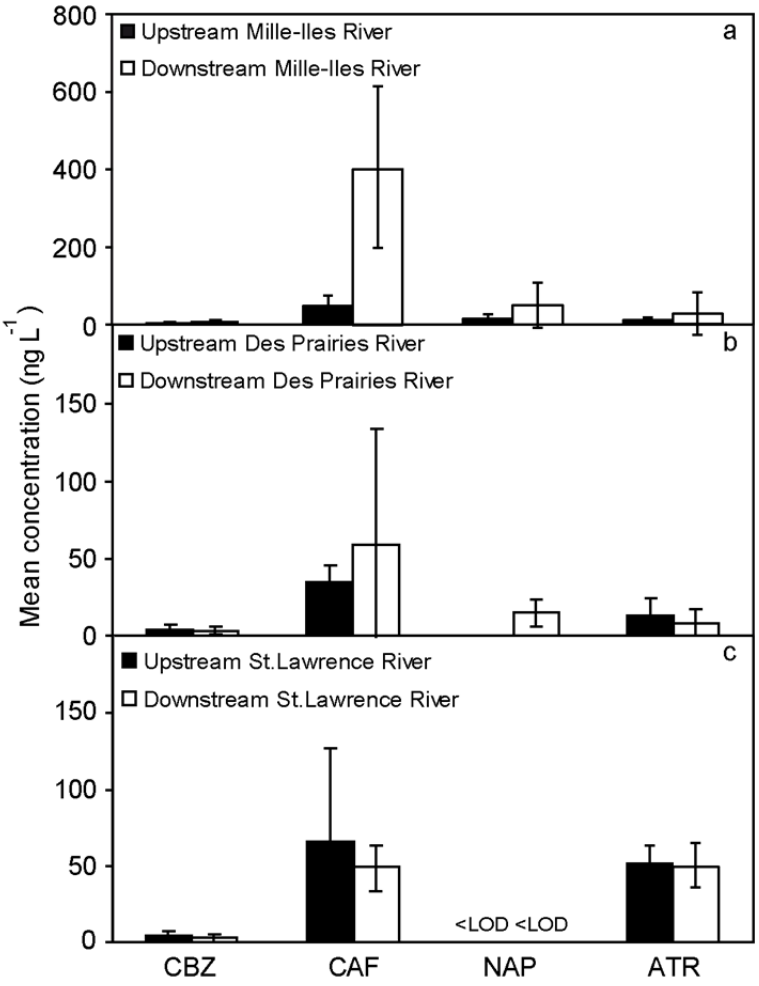

Figure 5. Mean concentrations and SDs of selected compounds, upstream and downstream of (a) Mille-Iles River (b) Des Prairies River, and (c) St. Lawrence River.

7.3 Seasonal Accumulations of Pharmaceuticals in Rivers (Papers I, II)

The effect of seasonal variations on the accumulation of pharmaceuticals was evaluated in River Fyris. This was achieved by comparing temporal-spatial mass flows of pharmaceuticals, calculated by multiplying concentration and water flow rate at different sampling locations and occasions. With the exception of bezafibrate, a clear winter accumulation was observed for all the compounds with mean mass flows ranging from 9 μg s^{-1} for acebutolol to 1809 μg s^{-1} for diclofenac (Table 6). The highest mean mass flow of bezafibrate was however measured during the spring season (1122 μg s^{-1}) (Table 6) when effluent mass flow of this compound was also the highest (Figure 2 in paper I). The high mass flows during the winter mainly reflect high water flow rates during this season (mean flow rate of 22.8 m^3 s^{-1}) compared to the other seasons (mean flow rates of 12.9 m^3 s^{-1} in spring, 3.3 m^3 s^{-1} in summer, and 2.9 m^3 s^{-1} in fall). In addition, negligible rates of biotransformation and phototransformation in winter may also govern higher accumulation of the pharmaceuticals during this season.

Table 6. *Mean mass flows and SDs (μg s^{-1}) of pharmaceuticals in River Fyris. The presented data are an average of mass flows at the effluent discharge point as well as 300, 1320, and 6490 m downstream the Uppsala WWTP.*

Compounds	Spring	Summer	Fall	Winter	Paper
IBU	Not detected	162 ± 46	Not detected	464 ± 209	I
NAP	515 ± 438	89 ± 54	150 ± 86	645 ± 481	I
KET	708 ± 293	177 ± 102	143 ± 130	505 ± 350	I
DIC	1355 ± 1130	168 ± 95	201 ± 126	1809 ± 1293	I
BEZ	1122 ± 888	134 ± 134	105 ± 91	465 ± 409	I
ATE	Not available	113 ± 59	196 ± 110	614 ± 547	II
MET	Not available	159 ± 78	307 ± 166	268 ± 399	II
SOT	Not available	94 ± 46	115 ± 62	355 ± 315	II
ACE	Not available	1 ± 0.5	1 ± 0.4	9 ± 12	II
CBZ	Not available	467 ± 134	387 ± 145	1503 ± 1229	II

7.4 Fate of Pharmaceuticals in Rivers (Papers I-V)

The potential of natural attenuation processes in removing certain pharmaceuticals from water column was assessed by quantifying pharmaceuticals in samples collected over a distance of 1320 m in a Swedish river. Furthermore, to obtain a clearer picture on the extent of pharmaceuticals' transformation/adsorption in natural waters; we compared removal efficiencies

of WWTP-derived pharmaceuticals with the corresponding values for nutrients. The results indicated higher yearly median removal efficiencies of acidic (42 %) and basic (28 %) pharmaceuticals compared to nutrients (10 %) (Figure 6), despite the potential of some nutrients to be additionally transformed into gaseous fractions.

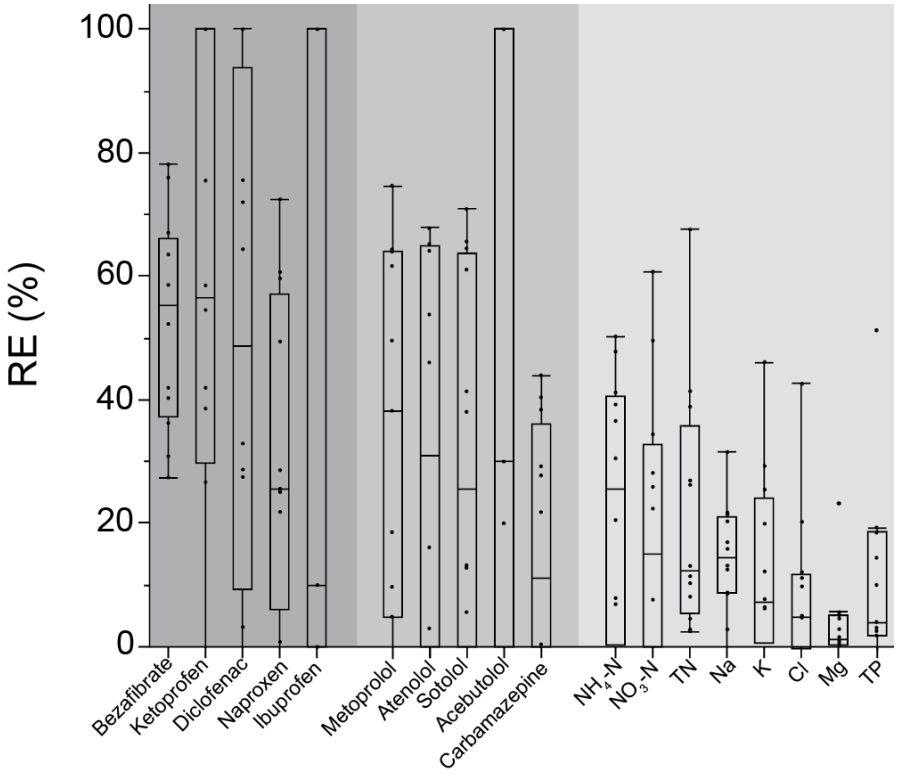

Figure 6. Box plot of removal efficiencies (RE%) of acidic pharmaceuticals, basic/neutral pharmaceuticals, and nutrients on a distance of 1320 m in River Fyris. If mass flows at the downstream site R4 exceed the sum of those at site R1 and R2, RE can become negative.

Among the basic and neutral pharmaceuticals, the four beta-blockers showed substantial higher removal efficiencies compared to carbamazepine, in particular during summer/fall (Figure 7). This can be mainly attributed to biotransformation and adsorption (paper II). Despite higher median removal efficiencies of atenolol compared to nitrate-nitrogen, their removal efficiencies in River Fyris were significantly related ($R^2 = 0.72$), with the highest removal in the summer and fall (Figure 3 in paper V). Overall, this study showed that natural waters have a high potential for further removal of pharmaceuticals that have already passed WWTPs. Also, elimination of pharmaceuticals in WWTPs

could be substantially improved if pharmaceutical natural attenuation processes found in surface waters are included in wastewater treatment processes (paper V).

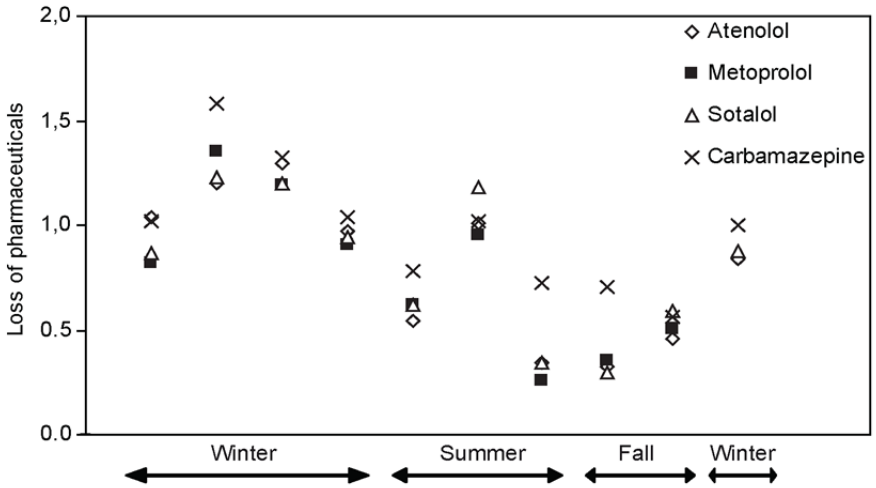

Figure 7. Seasonal variations in the loss of pharmaceuticals in River Fyris as a result of natural removal processes. Loss is calculated as the ratio of the sum of the mass flows at the upstream of the Uppsala WWTP and treated wastewater over the downstream.

7.5 Indicators of Fecal Contamination in Rivers (Paper IV)

Fecal coliforms are widely used to assess level of fecal pollution in drinking water intakes. However, analysis of fecal indicator bacteria is a time-consuming process which does not differentiate between human and animal fecal sources (Hagedorn & Weisberg, 2009; Glassmeyer *et al.*, 2005; Buerge *et al.*, 2003). Therefore, in this work we evaluated the potential of more persistent organic pollutants as indicators. This has been done by establishing a relationship between the fecal coliforms and the most abundant PPCPs in the Canadian rivers and treated wastewaters, i.e. caffeine and carbamazepine (Tables 4 and 5). These compounds have also been previously suggested as indicators of anthropogenic tracers (Buerge *et al.*, 2003; Metcalfe *et al.*, 2003b). Looking into downstream sites in the four Canadian rivers (S2, S3, S4, and S7 in Figure 2), a positive correlation between concentrations of caffeine and fecal coliforms (R^2 = 0.45) was found. The highest concentrations corresponded to Mille-Iles River, receiving discharges of several WWTPs and CSOs, and the lowest to St. Lawrence River, impacted by cumulative contamination load from the Great Lakes (Figure 8). Therefore, we proposed caffeine as a potential indicator of recent fecal contamination with a threshold

value of 100 ng L^{-1} to be indicative of a source water of <100 cfu 100 mL^{-1} (Figure 8). A linkage between caffeine concentrations and fecal coliforms has been recently reported in an urban watershed (Sauvé *et al.*, 2012).

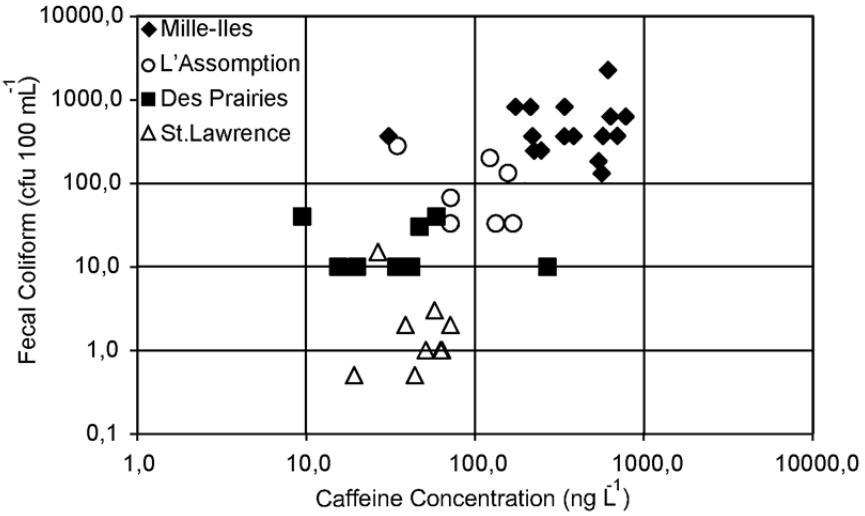

Figure 8. Logarithmic correlation between fecal coliform and caffeine concentrations. The black lines represent an arbitrary threshold limit for fecal coliform at 10, 100, and 1000 cfu 100 m L^{-1}.

In contrast to caffeine, no clear relationship was noted for carbamazepine concentrations and fecal coliforms in the Canadian rivers (Fig 5b in Paper IV). Nevertheless, carbamazepine was frequently detected in the Swedish and Canadian WWTPs and rivers (Table 4 and 5). In addition, relatively low removal of this compound was reported in the Canadian WWTPs (Table 1 in Paper IV) as well as the Swedish WWTP (Fick *et al.*, 2011), river (Figure 6 and 7), and lake (Table 3 in Paper II). As a result, carbamazepine can be a promising indicator of cumulative persistent compounds.

The mean concentration of caffeine in the raw sewage of the two Canadian WWTPs located in Mille-Iles River was about 135 times higher than carbamazepine (Table 1 in Paper IV) and removal efficiencies of carbamazepine in the WWTPs were up to a factor of 99 lower than caffeine. Therefore, a high ratio of caffeine/carbamazepine might be indicative of discharges of raw sewage into surface waters.

8 Summary of Results

The main results of this thesis can be summarized as:

- WWTPs and CSOs are the major sources of PPCPs and hormones while recent and cumulative agricultural runoff are major sources of pesticides (Papers I, II, IV)
- Caffeine is a promising indicator of recent urban fecal contamination while carbamazepine is a good indicator of cumulative persistent compounds (Paper IV)
- A high caffeine to carbamazepine ratio might be indicative of raw sewage discharge in rivers (Paper IV)
- A large outdoor gathering in the vicinity of surface waters can occasionally be a greater source of pharmaceuticals in surface waters than a WWTP (Paper III)
- River flow rates, nature of contamination sources, i.e. urban versus agricultural and continuous/intermittent versus cumulative, and natural attenuation processes are the major factors controlling the relative frequency of detection, concentrations, and mass flows of PPCPs, hormones, and pesticides in natural waters (Papers I-V)
- Natural waters have a high potential for further removal of WWTP-derived pharmaceuticals and removal efficiencies depend on the compound and/or seasonal variations, e.g. in River Fyris beta-blockers have the highest removal during summer/fall and the lowest during the winter (Papers I-V)
- Yearly median removal efficiencies of the pharmaceuticals were higher than the nutrients. However, median removal efficiencies of atenolol and NO_3-N were significantly related over the course of a year with the highest removal in summer and fall (Paper V)

9 Conclusions and Future Work

In this section I present the major conclusion of the thesis as well as questions and issues that have arisen during the course of this work which need to be further addressed.

Concentrations of pharmaceuticals and caffeine in the treated wastewaters of the Swedish and Canadian WWTPs as well as rivers fall partially within the reported data from other countries, except for acebutolol and sotalol. While concentrations of acebutolol in the Swedish WWTP were lower than the reported data, concentrations of sotalol in the Swedish river were higher.

In both Sweden and Canada, WWTPs were shown to be the main sources of contaminations in the studied rivers, similar to previous findings. Based on the amount of sales, excretion rates, and removal efficiencies of individual compounds in WWTPs, it might be possible to theoretically estimate effluent concentrations. However, due to an increasing trend toward buying over-the-counter drugs through online retailers rather than pharmacies, it might not be possible to trace the amount of drug sales. Consequently, this approach may give rise to a major underestimation of drug concentrations in treated wastewaters.

Although several publications are available that describe the occurrence of drugs in WWTPs and different aquatic compartments, sufficient data from middle-income countries are not available. In addition, most of the target compounds in the publications were selected based on sales data rather than their potential behavioral disturbances to aquatic organisms. For example, there are twice as much data available for the occurrence of over-the-counter pharmaceuticals in surface and treated wastewater, e.g. ibuprofen (more than 50 studies in 20 countries), compared to more persistent and toxicologically concerned compounds such as natural and synthetic hormones (about 25 studies in 10 countries).

Water flow rates can vary significantly both temporarily and spatially, hence interpretation of mass flow and corresponding removal efficiency of individual compounds in natural waters based on mean water flow rate for the whole river should be considered carefully.

Considering the low degree of natural attenuation processes in wintertime, in particular biotransformation and phototransformation, removal efficiencies of drugs in natural waters are expected to be lower during this season compared to the rest of the year. The current knowledge on the extent of different attenuation mechanisms of compounds in surface waters is very limited and the available data are mainly based on bench scale studies where it is difficult to reproduce similar conditions as natural systems. Hence, there is a need to perform further studies in different geographical regions, where differences in temperature, precipitation, and sunlight availability could result in unexpected temporal and spatial removal patterns. Furthermore, in order to gain a better understanding of the role of individual mechanisms, abiotic and biotic variables such as water residence time, suspended solids, lights intensity, temperature, and characteristic of microbial community should be carefully monitored at the time of sampling.

Given the high variability in drug consumption, efficiencies of treatment processes, and environmental factors, concentrations and fate of caffeine and fecal coliforms are subject to change. Therefore, prior to the consideration of caffeine as an indicator of recent fecal contaminations, correlation between caffeine and fecal coliforms needs to be confirmed in different geographical regions. Similar approaches should be applied when caffeine to carbamazepine ratio is used to evaluate discharge of raw sewage into surface waters.

To develop new policy and legislation for implementing appropriate tools to identify sanitary contaminations and for setting allowable levels for the discharge of compounds into natural waters, uncertainty in their spatiotemporal levels and role of different natural attenuation mechanisms should be tackled more closely and be coupled with knowledge of environmental risk associated with mixture effect.

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Acknowledgements

I would like to express my sincere gratitude to the following people in my academic and personal life who made this dissertation possible:

My main supervisor, Gesa Weyhenmeyer, for believing in me and for providing me with tremendous help and invaluable guidance. Her enthusiasm, optimism, and strong attitude have been the guiding forces behind my research and kept me motivated through the ups and downs.

My co-supervisor, Michèle Prévost, for introducing me to this interesting subject and for generously sharing her knowledge in this field. Her encouragement, unwavering support, trust, and patience have always been the source of inspiration both in my research and personal life.

My co-supervisor, Leif Kronberg, for providing me with the opportunity to conduct part of my experimental work in his lab and for fruitful collaboration and scientific support.

My co-supervisor, Jenny Krueger, for her positive attitude and endless help whenever I needed it.

My co-supervisor, Jerker Fick, for his contribution in the early planning of this project and scientific advice.

Jesper Svanfelt and Liza Viglino for giving me the thorough instruction on LC-MS/MS and sharing their theoretical and experimental skills in chemistry.

Technical staff from the geochemical laboratory at SLU and CREDEAU laboratory at École Polytechnique de Montréal for their assistance with water chemistry analyses.

Herman Paz for the computer support, and Annika Lundberg, Hans Eurell, and Maria Bywall for the administrative support.

The present and former roommates and colleagues in Sweden and Canada, especially Emma Göthe, Ina Bloch, Simon Hallstan, Maria Khalili, Salar Valinia, Jenny Rydh Stenström, Ana Villa, Karin Eklöf, Karin Johansson,

Marcus Wallin, Anna Lundqvist, Peter Carlson, Nilofar Åkerlund, Stina Drakare, Mikael Östlund, Lars Sonesten, Ulf Grandin, Gunborg Alex, Märit Peterson, Eva Lundgren, Åsa Ramberg, Christer Jansson, Shokoufeh Noor, Romain Broséus, Khadija Aboulfadl, Anne-Sophie Madoux-Humery, France Boisclair, Sébastien Sauvé for their support, generous help, friendship, and enjoyable discussions.

My family, relatives, and friends all over the world, especially my mom, Farideh, my dad, Mehran, my sister, Arghavan, and my brothers, Ardeshir and Ashkan, for dedication, patience, unconditional love, and encouragement through this journey.

My little princess, Clarice, for showing me the real sense of joy in life and Ardeshir, the true love of my life, for his generous support, incredible patience, and for standing beside me during the hardest moments of my life. I am very lucky to have them in my life!

Financial support of this project was mainly provided by the Swedish Research Council for Environment, Agricultural Sciences, and Spatial Planning (Formas) and partly by NSERC-Industrial Chair on Drinking Water at École Polytechnique de Montréal. The financial support is gratefully acknowledged.

Atlasi Daneshvar
Uppsala, September 2012