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Existence of Pharmaceutical Compounds in Tertiary Treated Urban Wastewater that is Utilized for Reuse Applications

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Abstract Research on the effects of chemical pollution in the environment that is related to urban wastewaters' discharge and reuse until recently was focused almost exclusively on conventional pollutants. During the last several years though there has been a growing level of concern related to the hypothesis that various chemicals may exhibit endocrine disrupting effects. In addition, thousands of tons of pharmacologically active substances are used annually ending up in the wastewaters. In many countries facing prolonged droughts and implementing wastewater reuse schemes for irrigation and groundwater discharge, the existence of xenobiotic compounds in the tertiary treated wastewaters constitutes a new concern. This study describes the application of a recently developed multi-residue method for the determination of 29 multi-class pharmaceuticals using off line solid phase extraction followed by liquid chromatography–triple quadrupole mass spectrometry (LC–MS–MS). The method was applied for the analysis of pharmaceutical residues at three sewage treatment plants in Cyprus serving major coastal Mediterranean cities. The presence of 19 pharmaceuticals was confirmed. For some of the compounds high concentrations were obtained for the final effluents (e.g. ofloxacin: 4.82 μg/L, diclofenac: 5.51 μg/L, carbamazepine: 27.27 μg/L, metoprolol: 9.59 μg/L). Concerning the elimination potential, what was derived from the study is that the biological treatment step

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contributes the most to the removal of the compounds while sand filtration and chlorination steps reduce slightly the residual concentrations.

Keywords Cyprus · Multi-residue method · Pharmaceuticals · Reuse · Wastewater · Xenobiotics

1 Introduction

The utilization of treated urban wastewater either for irrigation purposes or groundwater replenishment due to prolonged drought periods constitutes a very important activity on a national level in Cyprus. Currently, there is an increasingly growing momentum towards the reuse of wastewater while at the same time the concern with respect to the existence of xenobiotic compounds including pharmaceutical residues in the treated wastewater effluents follows also an increasing trend. After application, some pharmaceuticals are largely metabolized before they are excreted, while others are only moderated or poorly metabolized. Others, like for example x-ray contrast media are excreted completely intact. After excretion, the pharmaceutical compounds either in the parent or metabolized form enter the municipal sewage treatment plants. If the compounds are not eliminated in the treatment plants, they may enter the aquatic environment reaching drinking water resources or accumulate on soil during irrigation. In reality their behavior, fate and sinks constitute nowadays a quite intense research field since the analytical methods that are needed for their quantification are far from been standardized and, the potential effects that may have on the environment are not determined. It is generally agreed that acute effects of pharmaceuticals to aquatic organisms are unlikely (Vieno et al. 2007). But at the same time, there are no sufficient data on the potential subtle and chronic changes that may be exhibited in the environment due to the continuous discharge of mixtures of pharmaceutical residues on a variety of organisms or crops that are irrigated with treated wastewater.

Most of the existing conventional treatment processes applied, are not designed to completely remove various classes of organic xenobiotic compounds including pharmaceutical active ingredients. In reality, pharmaceuticals' removal depends on their ability to biodegrade and adsorb on suspended matter. Many of these compounds are hydrophilic and their sorption to sludge is limited (Joss et al. 2006). Other, like fluoroquinolones, although being very hydrophilic, are mainly eliminated from the aqueous phase through sorption to sludge. This can be possibly attributed to the electrostatic interactions with the cell membranes of the microorganisms (Golet et al. 2003; Lindberg et al. 2006). There are many factors that can affect the removal, besides the compound itself, during the treatment. These factors include the hydraulic retention time (Tauxe-Würsch et al. 2005), the solids retention time (Kreuzinger et al. 2004; Clara et al. 2005) the dilution of raw sewage with rain water (Joss et al. 2006), the temperature (Castiglioni et al. 2006) and of course the type of treatment (Chelliapan et al. 2006; Gros et al. 2006; Al-Rifai et al. 2007; Gómez et al. 2007; Radjenovic et al. 2007; Vieno et al. 2007; Reif et al. 2008).

The main objective of this study was to investigate the occurrence and removal efficiency of 29 pharmaceutical compounds at the three largest urban wastewater treatment plants in Cyprus, which apply activated sludge treatment. The pharmaceuticals investigated are: analgesics and anti-inflammatories (ketoprofen, naproxen, ibuprofen, indomethacine, diclofenac, mefenamic acid, acetaminophen, propyphenazone), lipid regulators and cholesterol lowering statin drugs (clofibric acid, gemfibrozil, bezafibrate, pravastatin, mevastatin), psychiatric drugs (carbamazepine, fluoxetine, paroxetine), antiulcer agent (lansoprazole), histamine H_1 and H_2 receptor antagonists (loratadine, famotidine, ranitidine), antibiotics (erythromycin, azythromycin, sulfamethoxazole, trimethoprim, ofloxacin) and ß-blockers (atenolol, sotalol, metoprolol, propranolol). For the study of the compounds a simultaneous determination of the 29 multi-class pharmaceuticals using off line solid phase extraction (SPE) followed by liquid chromatography–triple quadrupole mass spectrometry (LC–MS–MS) was applied.

2 Materials and Methods

2.1 Description of Sampling Sites (UWTP)

Wastewater samples used in this study were collected from three different Urban Wastewater Treatment Plants (UWTP I, II and III) located in the south of Cyprus. All effluents are reused either for irrigation or groundwater replenishment. Only the UWTP II receives industrial inflows while plants I and II receive purely domestic sewage. During the sampling program UWTPs I-III were operating with an average daily flow of 6,000, 15,000 and 6,000 m^3/day correspondingly while the average influent BOD_5 was about 88, 121 and 300 mg O_2/L. Table 1 shows the qualitative parameters of the effluents of the three plants.

At UWTP I that serves a population of 27,500 (PE), primary treatment consists of a screen, bar racks, an aerated grit-removal chamber and a primary clarifier. The primary effluent is directed to the stage of the secondary treatment (biological), consisting of oxidation ditches, secondary settlement tanks and an effluent storage reservoir. The last stage of the process consists of a sand filtration and a chlorination unit. At UWTP II, that serves a population of about 70,000 (PE), the treatment plant facilities include screening, grid chamber, skimmer tanks and large solids removal 4in its primary processes. A primary sedimentation tank follows and then conventional secondary activated sludge treatment is applied. The secondary treatment process, consists of an aeration tank and the secondary settlement tanks. A mixture of primary and secondary (activated) sludge is processed (thickening, dewatering) and anaerobically digested. Finally the biologically treated wastewater undergoes sand filtration and chlorination. At UWTP III, that serves a population of 43,000 (PE), primary treatment consists of bar racks and grid chamber, following by two primary sedimentation tanks. At the secondary treatment stage, phosphorus biological removal, nitrification and denitrification take place in four tanks. The biological treatment unit consists of two denitrifying tanks, two nitrifying tanks and secondary

Table 1 Characteristics of wastewater from inlet (A), after secondary treatment (B) and outlet (C) for the period June 2007–January 2008

UWTP	I			II			III		
Parameter	A	B	C	A	B	C	A	B	C
pH	6.9–8.2	7.3–7.5	7.4–8.4	6.7–8.4	7.4–8.1	7.8–8.7	7.2–8.5	7.5–8.1	7.1–8.4
Temperature, (°C)	12.7–20.4	12.8–18.9	12–19–8	11.1–15.4	11–13.6	10.8–19.3	10.3–13	11.9–12.6	12.4–21.5
Conductivity, (mS/cm)	1.6–3.4	1.5–3.2	1.6–2.9	1.6–2.0	1.6–1.7	1.2–1.8	1.1–1.8	1.2–1.3	1.0–1.4
COD, (mg/L)	863–1,203	131–226	19–33	689–913	82–117	15–22	887–1,236	109–234	21–40
TSS, (mg/L)	386–534	3.1–5.6	1–1.5	379–568	4.6–9.7	0.9–1.2	357–675	3–5.2	0.8–1.2
Ammonia, (mg/L)	32–99	3.7–28	1.6–5.2	14–46.2	1.5–7.3	0.8–3.3	46–85	3.9–11.7	1–1.6

clarifiers with the sludge recycle going to the inlet of the first denitrification tank. Finally, sand filtration and chlorination follow.

2.2 Sampling

Samples were collected from the inlet, after the secondary treatment step and finally from the outlet. 24-h composite samples were collected in January 2008 using a time-proportional automatic sampler (ISCO 6712). The time between sampling and analysis was less than 7 days. Each sample was divided in two sub-samples and both of them are solid phase extracted. Each extracted sub-sample was divided again in two and in the end four samples were analyzed via chromatography. Tables 2 and 3 show the average value of the four measurements for each sample.

2.3 Chemicals

All pharmaceutical standards used were of high purity grade (>90%). Ibuprofen, naproxen, ketoprofen, diclofenac and gemfibrozil were kindly supplied by Jescuder (Rubí, Spain). Indomethacine, acetaminophen, mefenamic acid, clofibric acid, bezafibrate, mevastatin, azythromycin dihydrate, erythromycin hydrate, carbamazepine, fluoxetine hydrochloride, lansoprazole, loratadine, famotidine, ranitidine hydrochloride, sulfamethoxazole, trimethoprim, ofloxacin, atenolol, metoprolol, propranolol hydrochloride and sotalol hydrochloride were purchased from Sigma-Aldrich (Steinheim, Germany). Propyphenazone, pravastatin and paroxetine hydrochloride were from LGC Promochem (London, UK). Isotopically labelled compounds, used as internal standards, were ^{13}C-phenacetin obtained from Sigma-Aldrich, mecoprop-d_3 from Dr. Ehrenstorfer (Augsburg, Germany), ibuprofen-d_3, atenolol-d_7 and carbamazepine-d_{10} from CDN Isotopes (Quebec, Canada).

Individual stock standard solutions were prepared on a weight basis in methanol and stored at −20°C. A mixture of all pharmaceutical standards was prepared by appropriate dilution of individual stock solutions. Further dilutions of this mixture were prepared in methanol–water (25:75, v/v) before each analytical run and were used as working standard solutions. Stock solutions of ofloxacin, pravastatin and sulfamethoxazole were renewed monthly before their use due to their limited stability. Stock solutions of internal standards were also prepared in methanol and were stored at −20°C. A mixture of these standards, used for internal standard calibration, was also prepared by diluting the individual stock solutions in methanol.

The cartridges used for solid phase extraction were Oasis HLB (60 mg, 3 mL and 200 mg, 6 mL) from Waters Corporation (Milford, MA, USA). 1 μm glass fiber and 0.45 μm nylon membrane filters were purchased from Whatman (UK).

HPLC-grade methanol, acetonitrile and water (LiChrosolv) were supplied by Merck (Darmstadt, Germany). Hydrochloric acid 37%, NH_4Ac and HAc were from Merck (Darmstadt, Germany). Nitrogen for drying 99.995% of purity was from Air Liquide (Spain).

2.4 Identification and Quantification of Compounds

The method of analysis is presented elsewhere in detail (Gros et al. 2006) and is shortly illustrated herein. Target pharmaceuticals were extracted by off line SPE using Oasis HLB cartridges (60 mg, 3 mL) at sample pH. Elution was performed with 2 × 4 mL of methanol. The extract was evaporated under a gentle nitrogen stream and reconstituted with 1 mL of methanol–water (25:75, v/v). Finally, 10 μL of a 10 ng/μL standard mixture of the internal standards mecoprop-d_3, ibuprofen-d_3, for the analysis in negative ion (NI) mode and ^{13}C-Phenacetin, atenolol-d_7 and carbamazepine-d_{10}, for the analysis in positive ion (PI) mode, were added in the extract for internal standard calibration and to compensate possible matrix effects. LC analysis was performed using a Waters 2690 HPLC system (Milford, MA, USA) coupled to a Micromass Quattro triple quadrupole mass spectrometer, equipped with a Z-spray ESI interface (Manchester, UK). Chromatographic separation was achieved with a Purospher Star RP-18 end capped column (125 × 2.0 mm, particle size 5 μm) and a C_{18} guard column, both supplied by Merck (Darmstadt, Germany). For the analysis in NI mode, eluent A was methanol and eluent B was water at a flow

Table 2 Recoveries (mean value of the four replicates ± RSD) of detected target analytes

Therapeutic group	Compound	Recoveries (RSD %)	
		Effluent	Influent
Analgesics and anti-inflammatories	Ketoprofen	53 (12)	52 (4)
	Naproxen	81 (9)	34 (5)
	Ibuprofen	87 (7)	111 (9)
	Indomethacine	50 (13)	51 (5)
	Diclofenac	60 (3)	89 (4)
	Mefenamic acid	65 (4)	nd
	Acetaminophen	50 (3)	47 (1)
	Propyphenazone	60 (15)	nd
Lipid regulators and cholesterol lowering statin drugs	Clofibric acid	30 (12)	56 (4)
	Gemfibrozil	71 (11)	80 (9)
	Bezafibrate	107 (3)	79 (5)
	Pravastatin	70 (5)	113 (8)
	Mevastatin	50 (11)	34 (2)
Psychiatric drugs	Carbamazepine	93 (12)	105 (10)
	Fluoxetine	74 (2)	67 (12)
	Paroxetine	76 (12)	84 (4)
Antiulcer agent	Lansoprazole	75 (4)	87 (5)
Histamine H1 and H2 receptor antagonists	Loratadine	93(12)	91 (3)
	Famotidine	104 (5)	50 (3)
	Ranitidine	86 (11)	38 (1)
Antibiotics	Erythromycin	50 (13)	98 (9)
	Azythromycin	30 (15)	63 (2)
	Sulfamethoxazole	50 (3)	101 (3)
	Trimethoprim	83 (15)	106 (2)
	Ofloxacin	75 (3)	106 (3)
ß-blockers	Atenolol	96 (5)	97 (2)
	Sotalol	71 (7)	56 (5)
	Metoprolol	114 (6)	86 (12)
	Propranolol	44 (4)	70 (6)

rate of 0.2 mL/min. The elution gradient started with 20% of eluent A, increasing to 80% in 20 min, raising to 90% in a 4 min gradient and then, back to initial conditions within 3 min. The analysis in PI mode was performed using as eluent A mixture of acetonitrile–methanol (2:1) and as eluent B a buffer consisting in NH_4Ac 5 mM / HAc at pH = 4.7, also at a flow rate of 0.2 mL/min. The elution gradient started with 15% of eluent A, keeping isocratic conditions for 3 min. Then, eluent A increased to 95% in 22 min and was held for 7 min. The sample injection volume was set at 20 μL.

Mass spectrometry was performed using a Waters Quattro Ultima triple quadrupole mass spectrometer, equipped with a Z-spray ESI interface (Micromass, Manchester, UK). The mass spectrometer was operated in the multiple-reaction-monitoring mode (MRM) selecting two transitions for each compound (for detailed explanation see Gros et al. 2006). The first one was for quantitation purposes whereas the second one was used for confirmation. The recoveries obtained were generally higher than 60% (Table 2). The overall variability of the method was below 15%, for all compounds with method detection limits (MDL) for wastewater matrix varying between 3 and 160 ng/L.

Table 3 Detected levels of the target analytes in wastewater samples (in μg/L)

UWTP	I			II			III		
Compounds	A	B	C	A	B	C	A	B	C
Ketoprofen	0.34	bld	bld	bld	bld	bld	1.75	0.27	bld
Naproxen	bld	bld	bld	bld	bld	bld	0.21	0.03	bld
Ibuprofen	1.43	0.52	bld	1.31	0.28	0.28	2.20	4.34	3.46
Indomethacine	bld	bld	bld	bld	bld	bld	bld	bld	bld
Diclofenac	0.61	2.11	0.68	2.43	15.41	5.51	0.73	2.99	0.12
Mefenamic acid	bld	bld	bld	bld	bld	bld	bld	bld	bld
Acetaminophen	309.29	0.11	0.07	77.56	0.11	0.07	405.37	0.05	0.10
Propyphenazone	bld	0.04	0.03	bld	bld	bld	bld	bld	bld
Clofibric acid	bld	bld	bld	0.00	0.00	0.00	bld	bld	bld
Gemfibrozil	bld	0.00	bld	0.00	0.00	0.00	bld	bld	bld
Bezafibrate	0.51	0.14	0.05	0.73	0.29	0.22	0.99	0.14	0.11
Pravastatin	bld	bld	bld	bld	bld	bld	bld	bld	bld
Mevastatin	bld	bld	bld	bld	bld	bld	bld	bld	bld
Carbamazepine	0.76	0.84	0.57	14.45	24.54	27.27	2.61	1.49	1.38
Fluoxetine	bld	bld	bld	bld	bld	bld	bld	bld	bld
Paroxetine	bld	bld	bld	bld	bld	bld	bld	bld	bld
Lansoprazole	bld	bld	bld	bld	bld	bld	bld	bld	bld
Loratadine	bld	bld	bld	bld	bld	bld	bld	bld	bld
Famotidine	1.00	0.59	bld	2.78	5.06	bld	1.30	0.38	bld
Ranitidine	0.07	0.08	bld	0.14	0.47	bld	0.43	0.31	bld
Erythromycin	0.38	0.20	0.03	0.28	0.25	0.40	0.70	0.42	bld
Azythromycin	1.15	1.60	0.18	0.66	0.30	0.20	1.68	0.53	0.03
Sulfamethoxazole	1.07	0.19	0.01	1.51	0.78	0.46	5.41	0.64	0.03
Trimethoprim	0.05	bld	bld	0.14	0.09	blq	0.35	0.06	bld
Ofloxacin	22.62	3.02	1.29	34.74	5.93	4.82	59.38	3.33	1.90
Atenolol	3.29	0.12	0.13	3.15	0.89	0.73	5.81	0.92	0.94
Sotalol	2.81	0.10	0.11	2.70	0.76	0.62	4.97	0.79	0.81
Metoprolol	1.30	0.98	0.57	2.09	1.23	9.59	1.49	1.31	0.69
Propranolol	0.27	0.49	blq	0.41	0.59	0.28	0.23	0.44	blq

bld below limit of detection, *blq* below limit of quantitation, *A* inlet, *B* after secondary treatment, *C* outlet

3 Results and Discussion

3.1 Presence of Pharmaceutical Compounds in the Raw, Secondary and Tertiary Treated Effluent

The data obtained from all samples analyzed are presented in Table 3. From the 29 compounds studied 19 were actually determined and quantified. The concentrations of indomethacine, mefenamic acid, pravastatin, mevastatin, fluoxetine, paroxetine, lansoprazole and loratadine were always found to be below the detection limit of the method (MDL) in all samples. The concentrations of gemfibrozil and clofibric acid were below the method detection limit in all samples besides those of UWTP III where no concentrations were detected. Ketoprofen was detected only in the influent of UWTPs I (0.34 μg/L) and III (1.75 μg/L) and in the secondary treated effluent of UWTP III (0.27 μg/L). Santos et al. (2007) reported a concentration range for ketoprofen of 0.2 in the effluent to 2.5 in the influent μg/L. Gros et al. (2006) reported a concentration range for the same compound of 0.13 μg/L in the effluent to 0.97 μg/L in the effluent. Therefore, the concentrations determined in Cyprus fall within an expected range of concentration.

Naproxen was found only in the influent (0.21 μg/L) and the secondary treated effluent (0.03 μg/L) of UWTP III. Conversely, Santos et al. (2007) pointed out a concentration range for this compound of 1.1–27.4 μg/L in the influents and of 0.22 to 4.28 μg/L in the effluent samples. Gros et al. (2006) reported a concentration range of bld–0.16 μg/L in the effluents and of blq–0.19 μg/L in the influents. Hence, the concentration of this compound was found in low levels in Cyprus in comparison to the other studies. Propyphenazone was found only in the secondary and finally treated effluent at UWTP I (0.03–0.04 μg/L correspondingly). Gros et al. (2006) reported a concentration level that was below the detection limit while Koutsouba et al. (2003) report a concentration range of 0.01–0.02 μg/L. Clofibric acid and gemfibrozil were not found to exist in UWTP II while in all other samples were found to be below MDL. Famotidine, ranitidine and trimethoprim were found in the influents and in the samples taken after the secondary treatment in all treatment plants. Their concentrations though, were below the MDL in the final effluents at all treatment plants. In the study performed by Gros et al. (2006), the mean concentration of ranitidine in the influents was 0.188 μg/L and in the effluents 0.135 μg/L while famotidine was always found below the limit of detection of the method.

In all influent samples, all the β-blockers, all the antibiotics, famotidine, ranitidine, carbamazepine, bezafibrate, acetaminophen, diclofenac, and ibuprofen were detected above their LOQ. The highest concentrations recorded were for acetaminophen; 405.37 μg/L at UWTP III, 309.29 μg/L at UWTP I and 77.56 μg/L at UWTP II. Acetaminophen was found in the raw wastewater at significantly higher concentrations than any other target compound. Similar results were obtained by Gómez et al. (2007). In their study, acetaminophen was also found to be in much higher concentrations than any other compound but the concentration found (up to 246 μg/L) was lower than the one found in the present study in Cyprus. In both studies however, despite this very high input, the elimination efficiency reached during the treatment was almost 100%. This can be attributed to the fact that the compound probably undergoes a rapid biodegradation since the complete removal

was achieved already during the secondary treatment (Table 2). The concentrations of ibuprofen fluctuated between 0.28 and 4.34 μg/L, which is in accordance with other concentrations reported by other studies for this compound (Tauxe-Würsch et al. 2005; Buser et al. 1999; Stumpf et al. 1999). However in the study of Santos et al. (2007) higher concentrations were observed i.e. 12.1–373.1 μg/L in the influent samples and 0.8–4.82 μg/L in the effluent samples. Moreover, in the study of Gómez et al. (2007) the concentrations of ibuprofen reached 168 μg/L. Ofloxacin showed the second highest concentration; 59.38 μg/L at UWTP III, 34.74 μg/L at UWTP II and 22.62 μg/L at UWTP I. Vieno et al. (2007) reported a mean concentration of 100 ng/L in the influent and 14 ng/L in the effluent while in the study undertaken by Gros et al. (2006) the concentrations of ofloxacin were bld in al samples examined. Conversely, Peng et al. (2006) reported a concentration of up to 5.7 μg/L while Radjenovic et al. (2009) up to 31 μg/L.

The pharmaceutical residues were not entirely eliminated by the applied treatment processes. The β-blockers, antibiotics (except trimethoprim), carbamazepine, diclofenac, bezafibrate and ibuprofen were found in all effluent samples. The highest concentration value in the effluents was found for carbamazepine (27.27 μg/L at UWTP II).

The concentrations of pharmaceuticals in the urban wastewaters depend on several parameters. For example, the consumption pattern of the drugs varies from country to country and also within country. This might explain the various differences observed in respect to the concentrations determined at the UWTPs in Cyprus in comparison to others elsewhere. Furthermore, the flow rate of the raw and treated sewage varies and so does the efficiency of the treatment process to eliminate pharmaceuticals. The concentrations can vary greatly among UWTPs and even within an UWTP at different time periods as can be seen in the study of Tixier et al. (2003). Variation in the effluent loads is expected since the load is affected by the efficiency of the treatment process to eliminate pharmaceuticals. The difference however that is observed for a number of compounds like for example sulfamethoxazole, carbamazepine, acetaminophen, diclofenac and ketoprofen in the influent of the three UWTPs is most probably attributed to variations in the consumption patterns among regions.

Although water recycling strategies including reuse for irrigation, are designed to address the problem of water scarcity, it is vital that, in attempting to solve this particular problem, we do not unintentionally introduce other problems (Tangsubkul et al. 2005), by introducing for example pharmaceuticals and other xenobiotic compounds in the environment Hence, a thorough qualitative analysis, in regards to such compounds must be integrated in the treatment–reuse program, in order to safe guard the environment. More advanced technologies may need to be applied to be able to remove these contaminants and hinder their release.

4 Conclusions

The analytical method described in the present work, based on SPE following by LC–ESI–tandem MS, proved to be a reliable and rapid evaluation tool for the pharmaceutical residues examined. While the data are still the results of one short-term study, the presence of many pharmaceutical compounds is confirmed. In

addition to this, in comparison with the results obtained by other studies in other countries some of the compounds quantified in this investigation, are present in high concentrations in the final effluents such as ofloxacin at all UWTPs, diclofenac at UWTP II, carbamazepine mainly at UWTP II and also at UWTP III, and metoprolol at UWTP II. Concerning the elimination potential, what was derived from the study is that the biological treatment step contributes the most to the removal of the compounds while sand filtration and chlorination decrease slightly the residual concentrations.

Since the treated effluents are used for irrigation purposes, negative environmental impacts may occur over prolonged periods of irrigation since persistence and bioconcentration can enhance the potential of the compounds to cause adverse effects to non-target organisms. A lot of work is still to be done in the direction of chronic toxicity, estrogenicity, genotoxicity and a number of other biological effects. Moreover, a lot of effort must be directed towards the evaluation of the effects of pharmaceutical degradation products and their potential concentrations in the treated effluents and also the existence of such compounds in crops irrigated by treated effluents. One has to bear in mind that since the toxicity of one pharmaceutical could be enhanced by the presence of other compounds with similar activity, the overall risk could be important. Therefore further work is required to develop tailored guidelines for different water reuse applications in respect to the presence of xenobiotic compounds including pharmaceutical active ingredients in urban wastewater.

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