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Water treatment plants and pharmaceutical residues in Catalonia and Italy

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Summary. This study analyses the occurrence of commonly administered pharmaceuticals in urban and treated wastewater and surface waters in Catalonia and Italy, reviewing recently published investigations. The reported removal efficiencies in common municipal wastewater treatment plants are also discussed and pharmaceutical load discharged after these treatments are analysed. Finally, environmental risk posed by the presence of some of these compounds in surface water is discussed, and a case study highlighting the issue of pharmaceutical residues in the environment is presented. [**Contrib Sci** 10:135-150 (2014)]

Introduction

Over the last 15 years, as the annual consumption of pharmaceutical compounds (PhCs) has increased worldwide, increasing attention has been focused on their presence in different aquatic environments in many countries. Antibiotics, analgesics and anti-inflammatories, beta-blockers, lipid regulators, beta-agonists, hormones, antineoplastics, and iodinated contrast media (ICM) are some of the most commonly administered therapeutic and diagnosis classes of drugs. Consequently, they are the ones most often studied by researchers.

After administration, the active substances of medications are metabolized by the body, but only to a certain extent. The unmetabolized portion is excreted, largely in the urine and to a lesser extent in the faeces, unchanged, as a mixture of metabolites; alternatively, they may be conjugated by the attachment of an inactivating compound. This makes sewage and treated wastewater by far the greatest source of human PhCs that reach the surface water, whether

Keywords: pharmaceutical residues · environmental risk · surface water · wastewater · water treatment plants

after excretion or through inappropriate disposal. Additional sources of residues of active compounds in the environment are effluents from livestock farms (e.g., PhCs such as tylosin, oleandomycin and spiramycin are used as animal growth promoters) and wastewater from the pharmaceutical industry.

The pharmaceuticals detected with high frequencies in surface water are generally those administered in greater quantities, but many exceptions occur. In fact, some compounds (e.g., the antibiotic amoxicillin) are consumed in large amounts but are not detected in the environment because of their rapid degradation. Conversely, drugs used in smaller quantities (e.g., the psychiatric drug and anti-epileptic carbamazepine and the lipid regulator clofibric acid) are found in relatively high concentrations in receiving water bodies. The concentrations of PhCs in wastewater and treated effluent, i.e., the effluent from wastewater treatment plants (WWTPs), generally range from several ng/l to hundreds of µg/l, with few exceptions. This has led to these contaminants being described as “micro-pollutants.”

The difficulties in the detection and monitoring of micro-pollutants are mainly due to the sophisticated analytical techniques and instrumentation required, the time-consuming methodologies and the high costs involved. One of the first PhC monitoring campaigns in Italy was carried out by researchers from the Milan Istituto Mario Negri, in 2000 [34]. In that work, “major environmental contaminants” were identified for the first time, based on their consumption and theoretical loads, ubiquity in surface water, persistence and toxicity, after which methods to measure these compounds in the environment were devised. The selected PhCs were detected in many of the samples obtained from surface water (Po, Lambro and Adda rivers), river sediments, and waterworks in Milan, Varese and Lodi. In the years that followed, other Italian research groups carried out investigations on different aquatic environments: rivers and lakes, WWTP influents and effluents, hospital effluents, groundwater and tap water. The aims of those studies were: to (i) evaluate the occurrence of common PhCs; (ii) analyze the removal efficiencies of common WWTPs; (iii) suggest the best treatment sequence and operational conditions for optimal removal, and (iv) assess the environmental risk posed by the presence of PhC residues.

Within this framework, in this article we describe the occurrence of common PhCs in different water environments in both Italy and Catalonia and report the removal efficiencies achieved for most compounds in municipal WWTPs recently investigated in these areas. We also discuss the potential environmental risks posed by the presence of these compounds in surface water. Finally, we present a case study that highlights the findings to date. Note that current legislation in neither Italy nor Catalonia includes WWTP effluent limits for PhC concentrations (µg/l) or loads (g/year), although the health authorities in both countries are carrying out investigations aimed at identifying the most critical (target) compounds.

Investigation areas: Catalonia and Italy

Catalonia. The results reported here are taken from several previously published studies on the occurrence and distribution of PhCs in several Catalonian WWTPs, mainly in the Llobregat River basin (Fig. 1) and in the Barcelona metropolitan areas treating urban wastewaters from the city of Barcelona. The other investigated Catalonian WWTPs are situated in Girona and in the Ebro River basin and treat urban wastewater from Lleida and Tortosa. We have also included the results of several studies reporting PhC levels in other Catalonian WWTPs, but due to confidentiality agreements they must remain anonymous.

Italy. The main Italian investigations described herein were carried out in: surface waters, including (i) the Po, Adda, Lambro, Olona and Arno Rivers; (ii) Lake Maggiore and some of its tributaries, Lakes Vico and Bracciano; (iii) canals in the Po Valley surface water network, which are generally used for irrigation needs from May to October; (iv) the raw influent and treated effluents from 10 municipal WWTPs, mostly in northern Italy; (v) rivers and their sediments, and (vi) effluents from hospital of different sizes (number of beds).

The map in Fig. 2 shows most of the sampling sites. In some investigations, the confidential nature of the information provided prevented us from identifying the precise sites of the experimental campaigns.

The behaviour of PhCs in different aquatic environments

PhCs comprise a wide spectrum of highly active substances designed to interact with biological receptors in humans and animals. They are generally grouped into therapeutic classes according to their physiological activity. However, these compounds, even if they belong to the same therapeutic class, may have very different chemical structures and physico-chemical properties, resulting in very different behaviors dur-

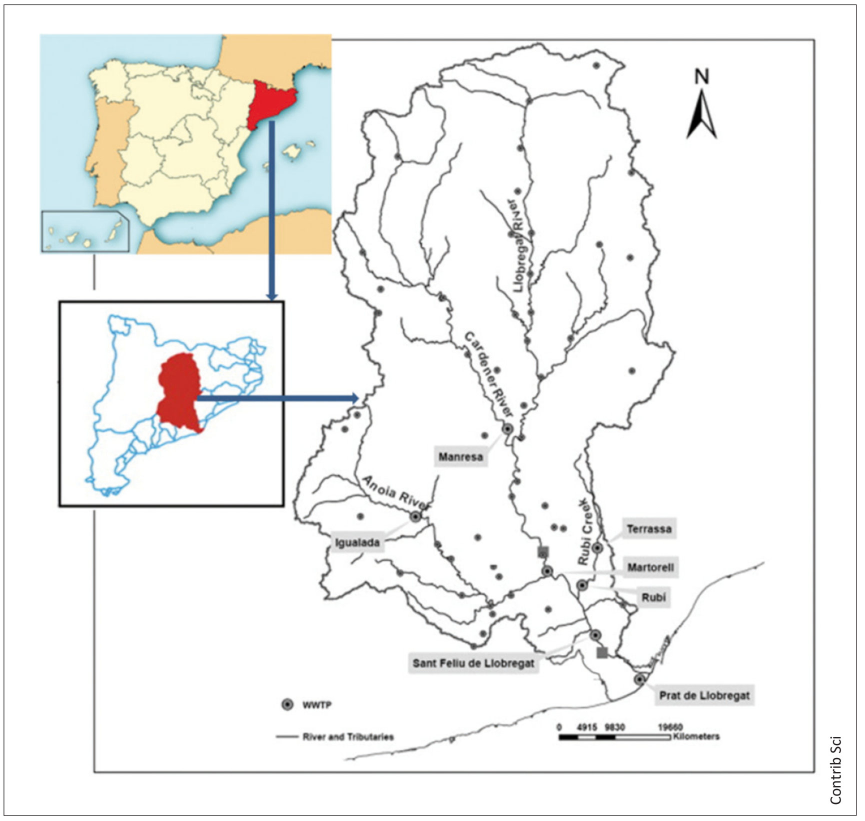

Fig. 1. Map showing the location of the Llobregat River basin in Catalonia, and several of the WWTPs investigated.

ing wastewater treatment. Moreover, many PhCs, including erythromycin, cyclophosphamide, naproxen and sulfamethoxazole, can persist in the environment for a year or more. Clofibric acid, for example, a metabolite of clofibrate, has an estimated environmental persistence of 21 years and is still detectable in lakes and rivers although the parent compound was withdrawn from the market long ago.

The complex behaviour of pharmaceuticals in the sewage network and during subsequent wastewater treatment correlates with the nature of their molecular structure, which may contain concomitant acidic and basic functional groups, as in the case of ciprofloxacin. These molecules may therefore be considered as neutral, cationic, anionic or zwitterionic, according to the particular environmental conditions, which will consequently affect their behaviour. Hence, a working knowledge of the physicochemical properties of PhCs allows a (rough) prediction of the processes occurring during their passage through WWTPs. These processes may involve sorption onto solids, biodegradation or chemical transformation. After their discharge into a surface water body, residual PhCs may be subjected to photolysis and photodegradation, which may reduce their environmental impact [18].

The PhCs monitored in the experimental campaigns described in this article were generally selected according to the following criteria: high consumption in the study area, widespread occurrence in raw urban wastewater and treated effluent throughout the world, and the availability of analytical methods. They mainly comprised members of the following therapeutic classes: analgesics and anti-inflammatories, antibiotics, antidiabetics, anti-hypertensives, beta-blockers, diuretics, lipid regulators, psychiatric drugs, receptor antagonists, hormones, beta-agonists, antineoplastics, topical products, antiseptics, and contrast agents. However, it is very difficult to obtain data pertaining to national or regional consumption of these compounds, as figures generally refer only to the sales of each active compound or therapeutic class.

Common municipal wastewater treatment plants

Domestic (also known as urban) wastewaters are generally subjected to a treatment sequence consisting of preliminary treatments (screening, grit removal, oil and grease removal),

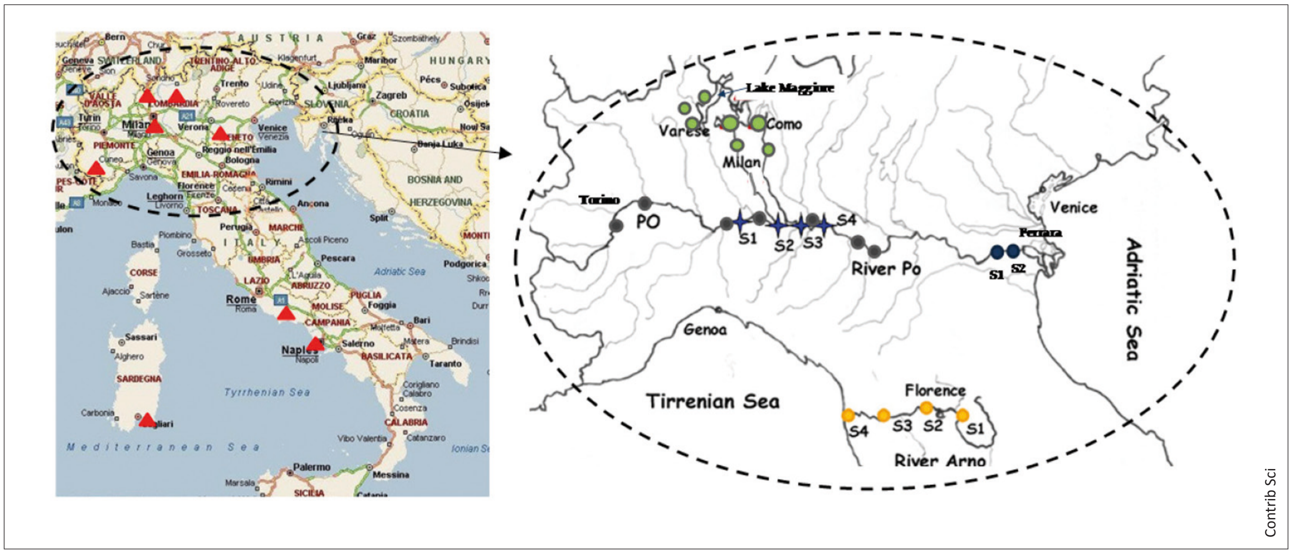

Fig. 2. Map of Italy showing the locations of most of the investigated WWTPs (left), and a map of the most-investigated area, including the surface water sampling points (right).

a primary gravity settling step (this step is sometimes omitted), secondary biological treatment (usually activated sludge systems) and tertiary treatments, sometimes including advanced methods (chemical coagulation, flocculation, sedimentation, activated carbon filtration, disinfection and/or chemical oxidation). The scheme in Fig. 3 shows the sequences generally adopted for raw wastewater and the resulting sludge, as well as the main routes by which pharmaceuticals originally intended for human use are released into the environment.

Activated sludge treatment is the most extensively employed secondary step in the processing of both urban wastewaters from small and large communities and industrial effluents. It consists mainly of flocculating microorganisms held in suspension and contact with wastewater in a mixed aerated tank. The so-called conventional activated sludge system consists of a biological reactor (where the activated sludge may develop and grow) followed by a secondary clarifier.

The biological reactor may consist of one or more com-

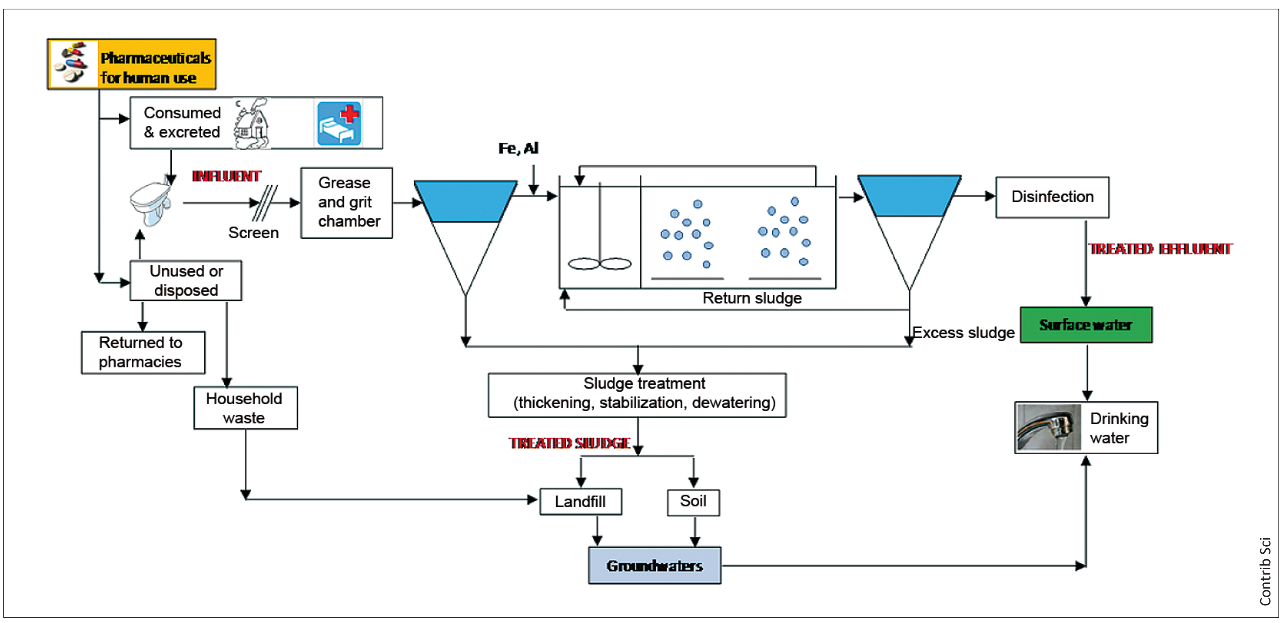

Fig. 3. Main PhC contamination routes in the water cycle and the sequence usually adopted for the treatment of domestic wastewaters.

partments (Fig. 3). Multiple compartments provide different operational conditions, namely aerobic and anaerobic, and thereby enable the removal of C, N and P. The main physical and biochemical processes occurring within the activated sludge process are adsorption, absorption, flocculation, oxidation, reduction and sedimentation. Degradation of the organic compounds in the influent wastewater by the biological reactor is mainly brought about by biochemical reactions (anabolic, catabolic and co-metabolic reactions), performed by the microorganisms suspended in the liquid, which flourish as these reactions take place. Organic compounds subject to biodegradation include not only lipids, proteins and carbohydrates, which are present in concentrations of the order of mg/l, but also micro-pollutants (i.e., pharmaceuticals and personal care products), which are generally detected at ng/l or µg/l concentrations.

After enough time for the appropriate biochemical reactions has elapsed, the mixed liquor is transferred to a settling tank (secondary clarifier) to allow gravity separation of the suspended solids (in the form of floc particles) from the treated effluent. Some of the settled solids are returned to the biological reactor (return activated sludge) in order to maintain its desired biomass concentration (about 3–4 g/l), and the remainder, considered as waste (so-called excess sludge), is subjected to thickening by the removal of a portion of the liquid fraction in order to increase the solid content. Through the processes of stabilization, dewatering, drying and combustion, both the water and organic fractions are considerably reduced, and the processed solids (treated or digested sludge) are then suitable for reuse or disposal.

Occurrence in different aquatic environments

The following figures report WWTP influent and effluent concentrations of common PhCs in the investigated full-scale plants in Catalonia and Italy. Compounds are reported in descending order of concentration detected in the water. Generally, the analysis refers to 24-hour composite water samples in order to provide a concentration representative of the sampling day.

WWTP influents in Italy and Catalonia

The concentration ranges of common PhCs reported in the raw influent to 10 Italian municipal WWTPs are shown in Fig. 4A, and the detected levels in influent waters to nine WWTPs in Catalonia are presented in Fig. 4B. In Italy, the compound with the highest maximum concentration was the anti-inflammatory ibuprofen (about 10 µg/l), followed by the analgesics/anti-inflammatories diclofenac, naproxen, acetaminophen and mefenamic acid, the antibiotics ciprofloxacin and ofloxacin, the beta-blocker atenolol, the anti-hypertensive hydrochlorothiazide, and the psychiatric drug carbamazepine. Ibuprofen, hydrochlorothiazide and atenolol were always detected at concentrations >1 µg/l.

This finding is consistent with the fact that most of these compounds are consumed for prolonged periods, and in some cases year round (in particular atenolol, hydrochlorothiazide and carbamazepine). The maximum concentrations of 25 of the other investigated compounds were between 100 and 950 ng/l, and those of the remaining 24 were between 1 and 99 ng/l. In another full-scale WWTP (data not shown), the raw influent concentrations of PhCs were significantly lower than those reported in Fig. 4A. In a study of 42 selected PhCs at this plant, all displayed influent concentrations <0.7 µg/l [15]. However, this was reportedly due to their dilution by infiltration of groundwater into the sewer system.

In Catalonia, non-steroidal anti-inflammatory drugs (NSAIDs) had the highest influent concentrations at the investigated WWTPs, as was expected due to their high level of consumption. Naproxen, ketoprofen and diclofenac were detected in all the samples at concentrations above the µg/l level.

Typically, this group of drugs accounted for roughly 65% of all the therapeutic agents analyzed in the influents. Lower, but still significant, concentrations of lipid-modifying agents (including fibrates and statins), antibiotics (ciprofloxacin, ofloxacin), diuretics (hydrochlorothiazide) and beta-blockers (atenolol) were also detected in the Catalonian WWTP influents. Other compounds typically present at high concentrations were carbamazepine, glibenclamide and sulfonamide antibiotics. A further 25 compounds were detected at levels reaching the range of 100–900 ng/l.

WWTP effluents in Italy and Catalonia

The concentration ranges of the investigated compounds in the secondary effluents of full-scale conventional municipal WWTPs in Italy are shown in Fig. 5A. The compounds are reported according to their descending order of concentration. The highest concentrations detected were 5.5 µg/l (diclofenac), 5.22 µg/l (naproxen) and 4.76 µg/l (gemfibrozil, a lipid regulator). For another six compounds, namely the diuretic

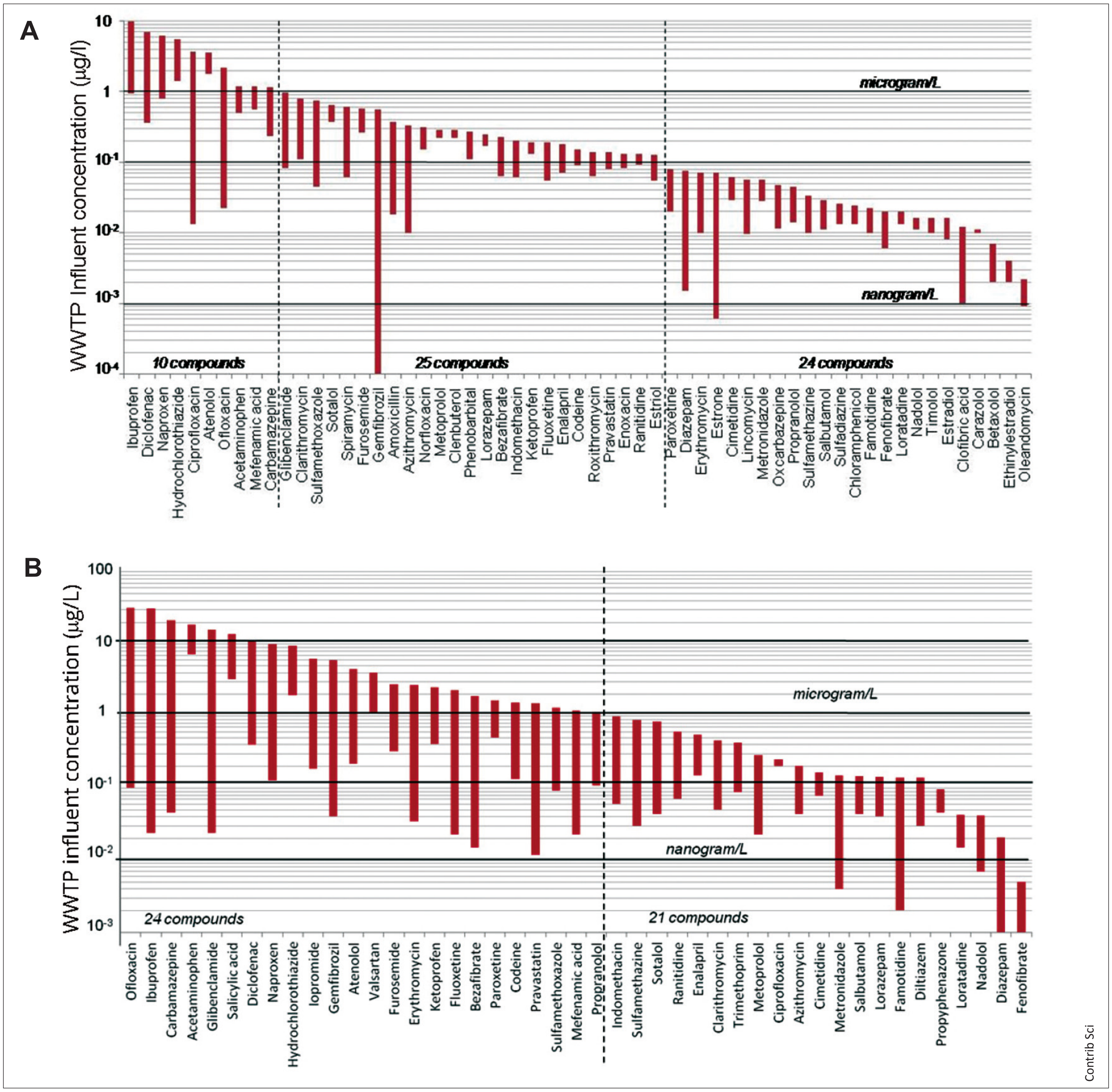

Fig. 4. (A) Concentration ranges of common PhCs in the raw influents of Italian municipal WWTPs. Data from [3,8,22,26,35,36]. **(B)** Concentration ranges of common PhCs in the raw influents of municipal WWTPs in Catalonia. Data from [11,15,16,23].

furosemide, the anti-hypertensive hydrochlorothiazide, the psychiatric drug carbamazepine, the beta-blocker atenolol, and the antibiotics ciprofloxacin and ofloxacin, the maximum values were >1 µg/l. The maximum concentrations of 28 other investigated compounds were between 100 and 950 ng/l, 17 were between 1 and 99 ng/l, and seven <1 ng/l. The analgesics ibuprofen (0.18 µg/l) and acetaminophen (0.058 µg/l), detected at the highest concentrations in the WWTP influent, thus belonged to the second and third groups, respectively, in the secondary effluent.

In the Catalonian WWTP effluents, the compounds found at the highest concentrations were iodinated X-ray contrast agent (iopromide), followed by the diuretics hydrochlorothiazide and furosemide, the NSAIDs ibuprofen and diclofenac,

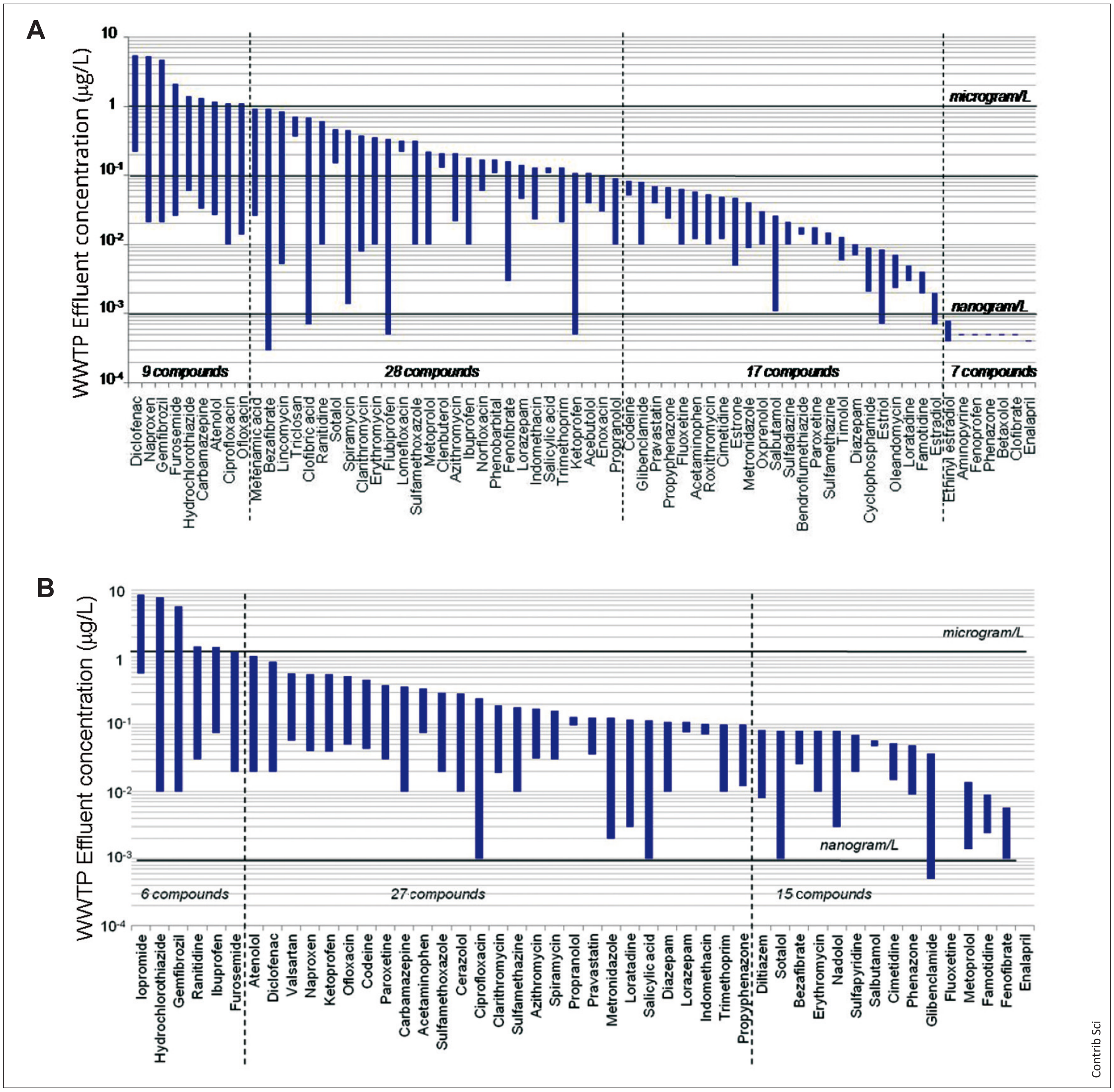

Fig. 5. (A) Concentration ranges of common PhCs in the effluents of Italian municipal WWTPs. Data from [1,2,3,6,22,26,35,36]. **(B)** Concentration ranges for common PhCs in the effluents of municipal WWTPs in Catalonia. Data from [11,15,16,23].

the lipid regulator gemfibrozil, and the histamine H2-receptor antagonist ranitidine (Fig. 5B). However, the concentrations detected varied substantially, depending on the removal efficiency of the WWTP and/or the physicochemical properties of the compounds in question. Overall, the compounds detected and their concentrations were very similar to those found in Italian WWTPs.

Observed removal efficiencies in conventional municipal WWTPs

The removal efficiencies from the liquid phase evaluated in five Italian WWTPs and six Catalonian WWTPs treating domestic wastewater are reported in Fig. 6A according to the schematic in Fig. 1. The removal efficiency for each PhC may

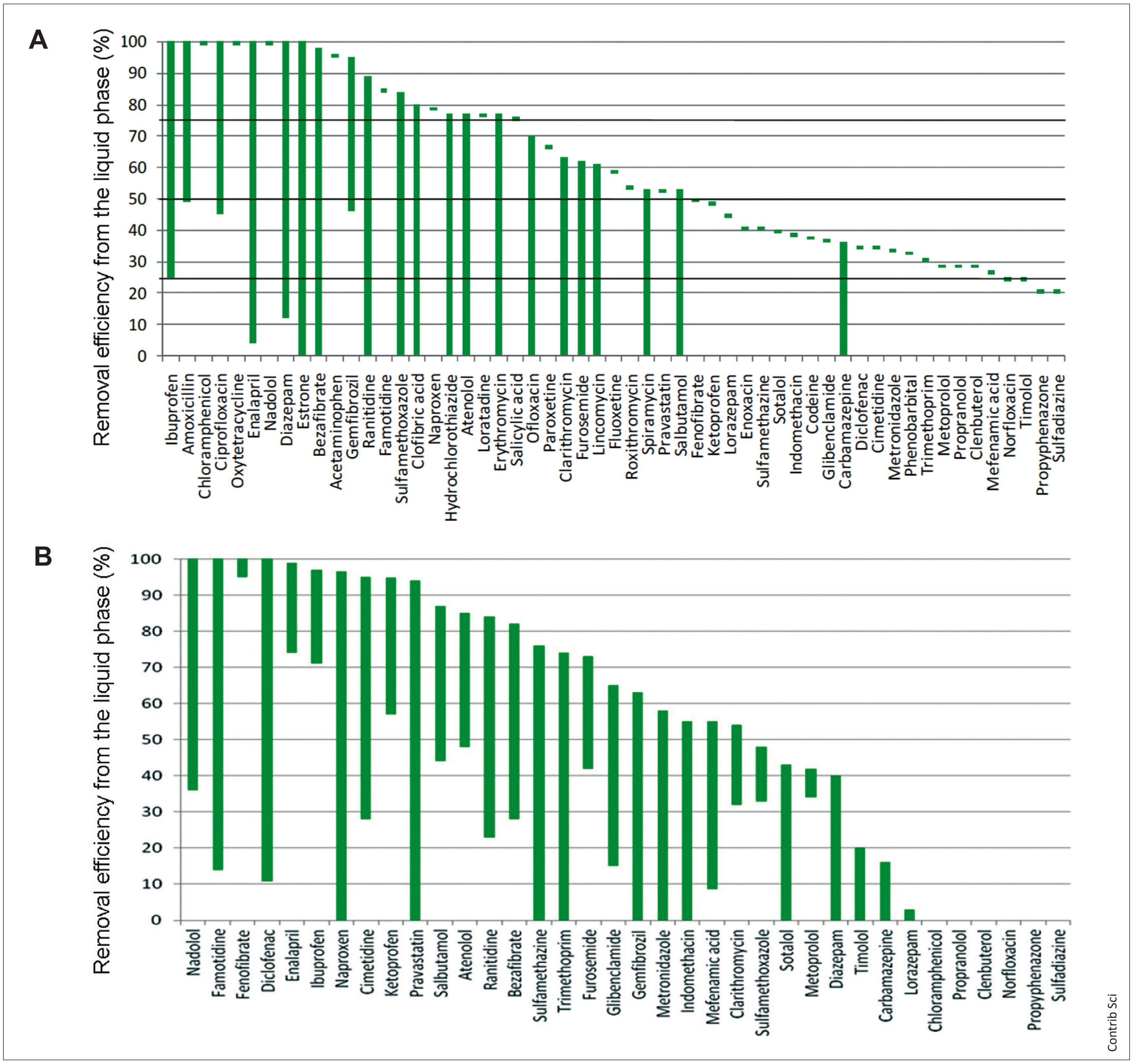

Fig. 6. **(A)** Variability of the removal efficiencies for common PhCs in full-scale Italian WWTPs. Data from [5,6,31,35,36]. **(B)** Variability of the removal efficiencies for common PhCs in full-scale Catalonian WWTPs. Data from [11,15,16,23].

vary over a wide range due to many factors affecting the different removal mechanisms that occur within the WWTP, namely biodegradation, adsorption onto sludge and chemical reactions, as discussed in [27].

The most important factors affecting removal efficiency are related to operational conditions (mainly hydraulic retention time, sludge retention time, pH, redox conditions, biomass concentration in the aeration tank), environmental conditions (mainly temperature) and biological reactor configurations (number and shape of the compartments and feeding mode). In addition, the removal efficiencies in summer and winter may differ.

According to Castiglioni et al. [7], PhCs can be grossly divided into three groups: those with higher removal efficiencies in summer than in winter, which include amoxicillin (median about 75% in winter and 10% in summer), atenolol (10% and 55%), bezafibrate (15% and 87%), enalapril (18% and 100%), furosemide (8% and 54 %), ibuprofen (38% and 93%), ranitidine (39% and 84%) and sulfamethoxazole (17% and 71%); those with fairly uniform removal over the course of the year, including ciprofloxacin (60%), hydrochlorothiazide (30%) and ofloxacin (50%); and a third group with negligible removal in both seasons (carbamazepine, clarithromycin, erythromycin, lincomycin, salbutamol, spiramycin and estrone). In general, the removal efficiencies for the different compounds are higher under aerobic than anaerobic conditions in the biological reactor.

The PhC removal achieved in conventional municipal WWTPs that feature activated sludge as secondary treatment is illustrated in Fig. 6. In many WWTPs a final disinfection step consists of the addition of sodium hypochlorite (NaClO), but its overall effect on PhC removal is quite modest. Zuccato et al. [36] found that the effect of NaClO addition varies depending on the compound, greatly improving the removal of ranitidine, diazepam and hydrochlorothiazide, but only modestly improving that of ciprofloxacin, vancomycin, ofloxacin, furosemide and lincomycin, and having little effect on the overall removal of salbutamol, atenolol, atorvastatin and bezafibrate.

Occasionally, negative removal efficiencies have been reported. While for some compounds this phenomenon is clearly ascribable either to the presence of deconjugates that interfere with biological transformation of the deconjugated compounds or to the release of PhC sorbed onto the particulate matter and dissolving after biological treatment, for others mechanism is unknown and requires investigation. However, note that at the low level of concentrations of some PhCs detected in the influent and secondary effluent, instrumentation errors may lead to their apparent release during their passage through the treatment plant.

Polishing treatments can further reduce the residual PhC content in final effluents. As suggested by Verlicchi et al. [31], in small communities in particular, a final treatment by means of constructed wetlands (horizontal subsurface flow beds) can be useful to this effect.

The data reported in Fig. 6A and 6B only pertain to the water phase, and thus PhC occurrence only in the influent and the effluent. However, as some compounds may be removed by sorption onto sludge, the calculation of the overall

Table 1. Fraction discharged with the effluent, sorbed onto sludge and removed during treatment. Modified from [15]

Compounds	Effluent (%)	Sorbed onto sludge (%)	Removed (%)
Ketoprofen	21		79
Naproxen	13		83
Diclofenac	64	1	35
Bezafibrate	27		73
Gemfibrozil	39		61
Atorvastatin	42	2	56
Lorazepam	48	3	49
Carbamazepine	73	2.5	24.5
Ranitidine	12		88
Trimethoprim	40		60
Metronidazole	20		80
Clarithromycin	48.5	3	48.5
Azithromycin	56		44
Atenolol	40		60
Sotalol	56		44
Salbutamol	31		69
Furosemide	24	2	66
Hydrochlorothiazide	55	1.5	43.5
Enalapril	6		94
Glibenclamide	24	4	72

removal efficiency of a WWTP has to take into account also the solid phase. Nonetheless, very few investigations have attempted to evaluate PhC occurrence in sludge. Indeed, in Italy, only Jelic et al. [15] analyzed sludge samples, evaluating the fraction (with respect to the influent load) discharged with the liquid effluent, sorbed onto sludge and removed during treatment. Their results (Table 1) clearly show that the quantity of the selected compounds removed by sorption is generally quite modest.

PhC loads

To evaluate the impact of a treated effluent in a surface water body, daily average loads are considered. In this study, these were generally lower in treated water than in untreated wastewater, with some exceptions. Indeed, in some cases, spiramycin and erythromycin were more abundant in effluents than in influents, as they can bind to particles and suspended solids from which they are later released.

Table 2 lists the minimum and maximum loads of commonly administered PhCs, expressed as mg/day/1000 inhabitants, reported for the investigated Italian WWTPs (of different nominal sizes) employing the treatment sequence shown in Fig. 1.

Castiglioni et al. [7] compared the winter and summer loads of the Varese Olona WWTP. They monitored eight common pharmaceuticals belonging to five therapeutic classes. The differences in the concentrations of these drugs were not statistically significant: in particular, loads of atenolol, furosemide, hydrochlorothiazide and ranitidine were comparable in the two seasons, while for ibuprofen, ciprofloxacin, ofloxacin and sulfamethoxazole the loads were higher in summer than in winter. This result is consistent with the consumption pattern, which remains constant throughout the year for beta-blockers (atenolol), diuretics (furosemide and hydrochlorothiazide) and antiulcer drugs (ranitidine), but features seasonal peaks in winter for antibiotics (ciprofloxacin, ofloxacin and sulfamethoxazole) and anti-inflammatories (ibuprofen).

Surface water

Researchers in Italy have investigated various aquatic environments: major rivers (the Po in north and the Arno in central Italy); tributaries (Adda, Lambro and Olona) [4,34–36]; surface water network canals [1,23]; mountain rivers; Lake Maggiore [19], and drinking (tap) water [9,19,34]. Rivers were investigated at different sampling points along their course, downstream of both the inlets of the main influents and of the major towns. Data are reported in Fig. 7A. The right-hand panel of Fig. 2 shows the main sites investigated by the different experimental campaigns; the different symbols indicate the different investigations.

Po River. The Po is the longest river in Italy (652 km), running from the western Alps to the Adriatic Sea. It collects wastewater from a catchment area of about 71,000 km^2 in the most densely populated and industrialized region of Italy (about 18 million inhabitants) and sewage from about half of all the livestock farms in Italy. The average and maximum flow rates at Pontelagoscuro (Ferrara, 50 km from the Adriatic Sea) are, respectively, 1500 and 10,300 m^3/s. All the major towns and livestock farms along the Po are equipped with secondary WWTPs.

Arno River. The Arno is the fifth largest river in Italy. It flows through Tuscany (central Italy) and out into the Tyrrhenian Sea. It is 241 km long and its catchment area is 8247 km^2. The Arno River is fast-flowing due to the nature of the land along which its waters flow (marlstone and impervious clay, with the exception of a short stretch of its tributary, the Elsa), and the average amount of water that flows through its outlet to the sea varies greatly (between 6 and >2200 m^3/s).

Despite their very different characteristics, PhC concentrations generally increased from source to mouth in both rivers, exhibiting peaks corresponding to input from the main cities along their length (Turin, Piacenza, Cremona, Parma). This is particularly evident in the case of antibiotics [4,35], due to the high load of these pollutants entering the surface water along with the treated effluent from municipal WWTPs. The most abundant compounds in the Po River were ciprofloxacin, lincomycin and vancomycin, whose average concentrations ranged from 5 to 10 ng/l. In the Arno River, the highest average concentrations were those of ciprofloxacin and clarithromycin, at about 20 ng/l.

The monitoring campaign conducted by Calamari et al. [4] showed that pollutant loads from Milan, carried by a tributary (Lambro River), contribute little to the contamination of the Po River, presumably due to the comparatively lower flow rate and load of the Lambro (mean flow rate equal to 5 m^3/s) than of the Po (about 1000 m^3/s at the mixing zone with the Lambro River).

Results from the same study by Calamari et al. [4] pro-

Table 2. Minimum and maximum daily loads of the investigated compounds in Italian and Catalonian full-scale WWTP effluents. The data are expressed in mg/day/1000 inhabitants

		Italy		Catalonia	
Class	Compound	Min.	Max.	Min.	Max.
Analgesics/Anti-inflammatories	Diclofenac	82	181	24	140
	Ibuprofen	ND	162	33	153
	Indomethacin	ND	28	ND	35
	Ketoprofen	5.6	93	2	94
	Mefenamic acid	ND	191	ND	13
	Naproxen	ND	68	5.7	347
	Propyphenazone	ND	12	4	23
Antibiotics	Azithromycin	15.2	47.7	5.6	7.9
	Ciprofloxacin	8.5	271	3.5	256
	Clarithromycin	ND	500	1.6	11
	Erythromycin	ND	161	9	17
	Lincomycin	0.5	183	ND	14
	Metronidazole	5.3	49	0.08	28
	Ofloxacin	4.9	268	ND	65
	Roxithromycin	ND	8	ND	5,4
	Spiramycin	9	418	–	–
	Sulfamethoxazole	ND	304	11	22
	Trimethoprim	ND	27	4	25
Antidiabetics	Glibenclamide	ND	16	1	6,1
Antihypertensives	Enalapril	ND	58	0,05	21
	Hydrochlorothiazide	50	745	21	345
Beta-blockers	Atenolol	38.1	966	122	126
	Metoprolol	52	63.4	ND	18
	Sotalol	33	93	12	29
	Timolol	1.8	3.3	ND	0.8
Diuretics	Furosemide	4.9	644	11	122
Lipid regulators	Bezafibrate	ND	79	1	74
	Clofibric acid	ND	18	ND	2
	Gemfibrozil	19	31	134	465
Psychiatric drugs	Carbamazepine	ND	422	15	122
	Diazepam	ND	2.3	0.06	0.8
	Lorazepam	15.7	34	1.5	18
Receptor antagonists	Ranitidine	6.7	266	3.5	56
Hormones	Estrone	ND	20	–	–
Beta-agonists	Salbutamol	2	8	0.3	2.1
Antineoplastics	Cyclophosphamide	ND	1	–	–

ND: non determinated.

vide several insights into the concentrations of veterinary vs. human pharmaceuticals. These authors found that the former were invariably lower, albeit with the exceptions of salbutamol, detected at Cremona, Casalmaggiore and Pieve in concentrations of 1.3–1.9 mg/l, and lincomycin. Salbutamol is used as bronchodilator in humans, but is also a popular, albeit illegal, anabolic agent for animals. The large amount of this drug detected in areas with a high density of livestock farming would appear to indicate a considerable contribution resulting from its illegal use, particularly as higher doses are needed to trigger anabolic activity than the bronchodilator effect. The high concentrations of lincomycin in the same area, despite a drop in its sales for human consumption, strongly suggest that it too is being used extensively in veterinary medicine.

Comparing the loads of antibiotics detected at various distances from the sources of the two rivers, Zuccato et al. [35] found that, in the Po River (flow rate of 600–1000 m^3/s), these totalled roughly 1.2 kg/day at about 200–300 km, 5.8 kg/day at 380 km and 4.2 kg/day at about 400 km. In the Arno River (average flow rate of 10 m^3/s), total loads increased substantially from source to mouth, reaching around 130 g/day, considerably lower than in the Po. Based on data collected by Zuccato et al. [35], the most abundant antibiotics detected in the Arno River were ciprofloxacin, clarithromycin and erythromycin (average concentration 20 ng/l). Veterinary antibiotics were generally undetectable.

Loos et al. [19] investigated the occurrence of several common PhCs in other natural aquatic environments in Northern Italy, namely Lake Maggiore (Varese), rivers and mountain rivers, as well as in the tap water sourced from the lake. Lake Maggiore receives municipal, agricultural and industrial discharges, both directly and via its tributary rivers. Carbamazepine, gemfibrozil and bezafibrate were detected at almost the same concentrations in the tap water as in Lake Maggiore water, indicating that they are poorly removed by the sand filtration and chlorination used in the Lake Maggiore waterworks that produce some of the local drinking water. In the tap water produced from groundwater, lower levels of these substances were detected. The levels of bezafibrate detected in Lake Maggiore were in the same range as those found in rainwater samples collected nearby, specifically at concentrations up to 0.0008 µg/l.

Al Aukidy et al. [1], who compared the dilution effect in two case studies in which the dilution factors (corresponding to the ratio between the river flow rate and the WWTP effluent flow rate) differed, specifically 91 and 1, found that the concentrations of PhCs downstream of the point of treated effluent emission correlated strictly with the dilution in the mixing zone between the discharged effluent and the receiving water body. They determined that the hydrodynamic characteristics of the receiving water body thereby contributed to mitigating the risks posed by the presence of toxic compounds. The dilution capacity can therefore be considered of prime importance in reducing and controlling the toxicological effects of PhCs released into the environment.

Moreover, further degradation of residual PhCs can still occur in surface water bodies once the treated effluent leaves the WWTP. In fact, as mentioned above, if a substance is light-sensitive, photodecomposition may contribute to its further removal once in the environment. Phototransformation readily occurs in clear surface water, with the effectiveness of this process strictly correlating with the intensity and frequency of available light [2,18]. Nonetheless, this process may be affected by other variables, specifically pH, water hardness, location, season and latitude [17,33].

With regard to river sediments, among the investigated pharmaceuticals, some have also been detected in the river sediments examined in Italy, in particular erythromycin (400–630 ng/kg in the Lambro and Po rivers), ibuprofen (220 ng/kg in Lambro River), ranitidine (150–410 ng/kg in the Lambro and Po rivers), spiramycin (380–2900 ng/kg in the Lambro, Po and Adda rivers) and tylosin (130–2640 ng/kg in the Lambro and Po Rivers).

In Catalonia, the Llobregat River is a typical Mediterranean river, with a fluctuating flow and under severe pressure due to the industrial and agricultural activities as well as the dense population that characterize the region. In the Llobregat River basin (NE Spain) the mean annual precipitation is 3330 Hm^3 and the annual average discharge is 693 Hm^3. The average monthly flow registered since the year 2000 shows peaks of roughly 100 m^3/s and minimum values of 1 m^3/s (relative standard error: 124%). In addition, the Llobregat River receives the effluents discharged from more than 55 WWTPs; these effluents may contribute almost 100% of the total flow in some segments of the river, especially in periods of drought. Accordingly, high levels of organic contaminants are detectable along the river, in rising concentrations downstream of WWTPs and populated settlements.

In all monitoring studies to date, the PhCs detected in the Llobregat River closely match those identified by the Spanish National Health System as those most consumed. However, their concentrations vary widely, depending on the sampling time and hydrological conditions (water flow and consequently dilution factor).

Generally, the NSAIDs ibuprofen, ketoprofen acetaminophen and diclofenac; the lipid regulator gemfibrozil; beta-blockers atenolol, metoprolol and sotalol; the antibiotic trimethroprim, and the psychiatric drugs lorazepam and carbamazepine were the compounds detected at the highest concentrations in the Llobregat River. The concentrations in most of the samples analyzed were in the range of 10–300 ng/l (Fig. 7B) and the contamination load increased down-

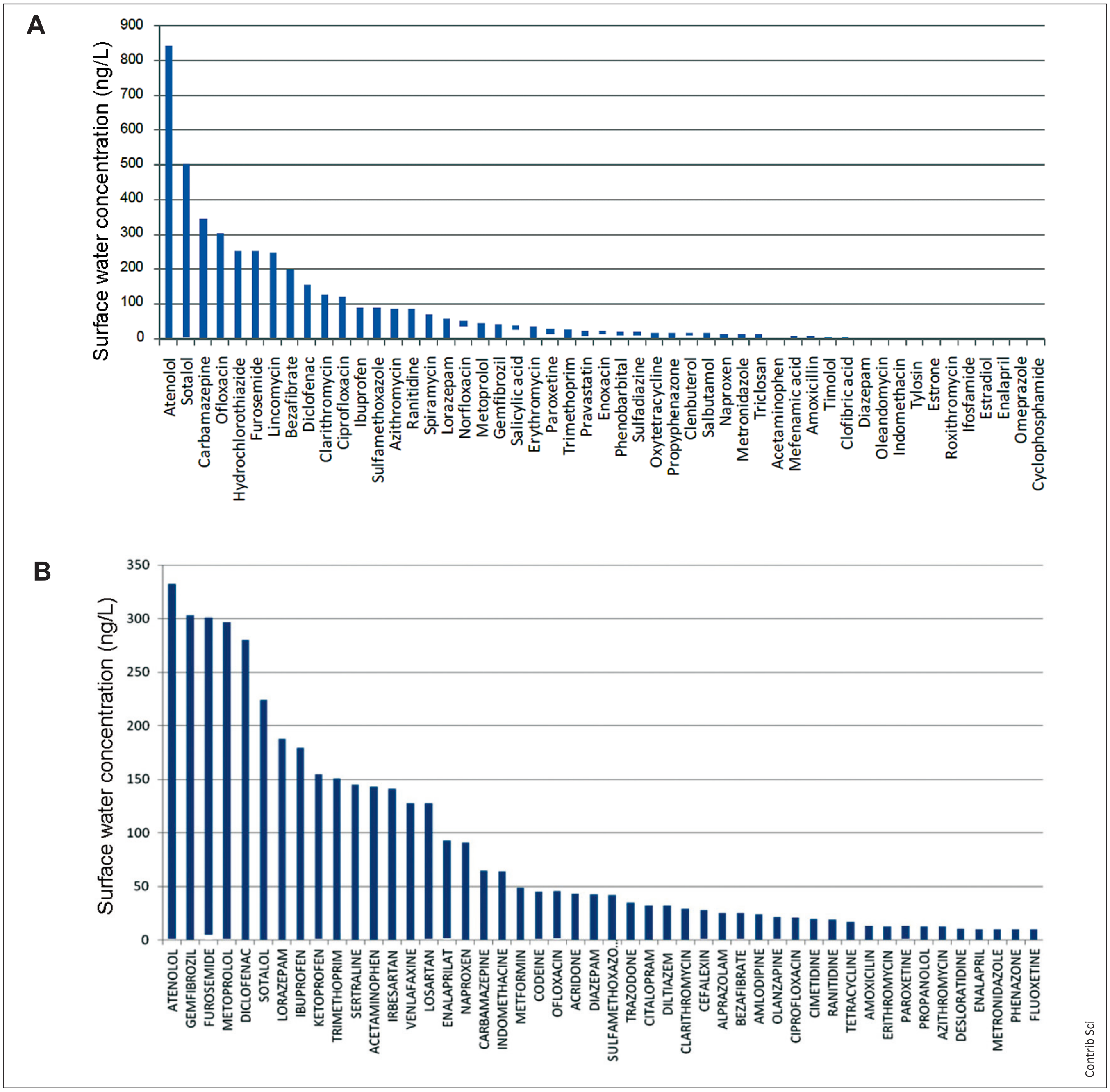

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Fig. 7. **(A)** Variability in the PhC concentration ranges in Italian surface waters. **(B)** Concentration ranges (ng/l) of some of the most representative PhCs measured in the Llobregat River at Sant Joan Despí (Barcelona).

stream along the river. However, in some hot spots, such as the Rubí Creek and a canal receiving overspill from the most contaminated fractions of the river, the levels were occasionally much higher. For example, in their study of the occurrence of 28 multi-class pharmaceuticals in this area, López-Roldán et al. [20] detected the highest concentrations for the β-blockers metoprolol (8042 ng/l) and sotalol (788 ng/l), the antibiotic ofloxacin (1904 ng/l) and the lipid regulator gemfibrozil (1014 ng/l) at two sites (a canal receiving waters from the Anoia River and the Sant Feliu WWTP and Rubí Creek). However, the waters of these bodies have been diverted so that they reach the river at locations close to its mouth, downstream of the Sant Joan Despí WWTP inlet, to protect the quality of the source water.

García-Galán et al. [10] also investigated the Llobregat River focusing on the occurrence of sulfonamide antibiotics in its lower reaches. Sulfamethoxazole, sulfapyridine, sulfamethazine and sulfamethizole were the compounds most frequently detected, with maximum concentrations of 2482 ng/l for sulfamethazine and 4297 ng/l for sulfamethoxazole. However, median concentrations were <50 ng/l, except for some outlying values at the sampling site near the mouth of the Llobregat River.

Environmental risk posed by PhCs in effluent, surface water and drinking water

The risks posed by the occurrence of PhCs in water correlates with their potential adverse effects on aquatic organisms and are often evaluated by means of the risk quotient (RQ), a ratio of the maximum measured (or predicted) concentration of a compound and its predicted no-effect concentration in water. In the Po Valley, Al Aukidy et al. [1] assessed the RQ using the secondary effluent and corresponding surface water in two different case studies: (i) effluent from a large WWTP discharged into a receiving water body with a resulting dilution factor of 91, and (ii) effluent from a medium-sized WWTP discharging into a small receiving water body, resulting in a dilution factor of 1. They found that sulfamethoxazole, clarithromycin and azithromycin had the highest high RQs and were, therefore, the most critical compounds. In fact, according to the risk ranking system proposed by Hernando et al. [13], these compounds pose a high environmental risk (RQ > 1): sulfamethoxazole and clarithromycin in the two WWTP effluents investigated and in one receiving water body, and azithromycin in the effluent of one WWTP and its receiving canal B. Moreover, a medium risk (RQ in the range 0.1–1) was detected for sulfamethoxazole and clarithromycin in canal A, and azithromycin in effluent A.

According to Zuccato et al. [30], PhC concentrations measured in drinking water may give rise to human exposure in the ng /day range, corresponding to 3–4 orders of magnitude lower than those producing a pharmacological effect. Although risk arising from acute exposure can therefore be regarded as unlikely, the possible effects of life-long exposures remain to be determined.

The predicted no-effect concentrations of effluents and sludge are not the only factors that need to be taken into account, as there is another source of risk: antibiotic-resistant bacteria (ARB) and genes coding for antbiotic resistance (ARG). The levels of ARG and ARB have been found to be several orders of magnitude higher in raw WWTP influents than in treated effluents, but due to their high bacterial content, digested sludge also represents a significant route of environmental contamination [21]. As reported in the literature, the percentage of antibiotics showing resistance is generally higher in treated wastewater effluent than in river water, but the latter increases downstream of a WWTP [14]. WWTPs can therefore play a vital role in the elimination or spread of ARB and ARG, as the treatment systems and their operational conditions are likely to influence their fate [24]. However, treated effluents with trace amounts of ARGs and ARBs discharged into rivers or streams can undoubtedly add to environmental contamination. In a comparison of release loads of ARGs and ARBs, Munir et al. [21] showed that the land application of biosolids from WWTPs is, by far, the greatest source of entry into the natural environment. Further research is necessary to determine how to reduce the spread of these bacteria.

Best strategies for managing and treating hospital effluents (Case Study)

Hospital effluents are one of the main sources of PhCs released into the environment, not only because of the treatments performed and pharmaceuticals administered and excreted within these facilities, but also due to the research and laboratory activities they house. Indeed, hospital effluents contain a wide spectrum of toxic substances, including medicines and their metabolites, chemicals, heavy metals, disinfectants sterilization agents, radioactive markers, and iodinated contrast agents used for diagnosis, which are generally present at concentrations of µg/l. According to a recent investigation carried out in Italy and elsewhere, these wastewaters should be earmarked for special consideration. In fact, the concentrations of common PhCs in hospital effluents, including antibiotics, analgesics, anti-inflammatory drugs and iodinated contrast agents, are several orders of magnitude higher than in raw urban wastewater, as noted by Verlicchi et al. [32]. In legal terms, however, currently there is no distinction made between urban and hospital wastewaters, and, despite their potentially hazardous loads, hospital effluent are generally discharged directly into the public sewage network and conveyed for co-treatment at the nearest municipal WWTP. In response to this problem, guidelines for the management and treatment of hospital effluents were recently drawn up by an Italian research group from the Uni-

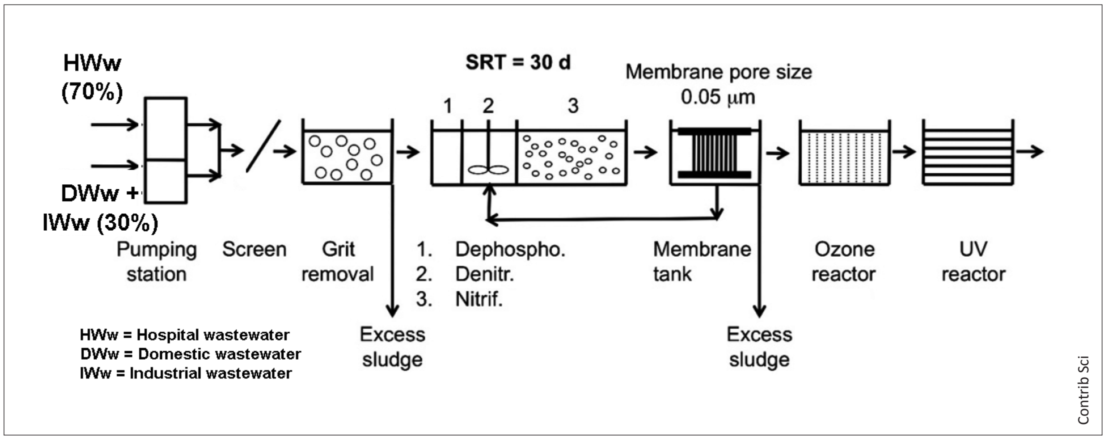

Fig. 8. Schematic of the new WWTP plant treating the effluent from the 900-bed hospital near Ferrara (in operation since July 2011).

versity of Ferrara Department of Engineering [25,30], based on their experience of a purpose-built WWTP designed to treat the effluents from a new hospital complex (900 beds) in Ferrara, in addition to a small amount of urban wastewater. This plant has been in operation since July 2011 and consists of a multi-barrier system, including advanced biological treatment (a membrane bioreactor), and advanced oxidation processes (ozonation followed by UV irradiation) to enhance the removal of the different micro-pollutants by biological, chemical and physical means and to guarantee good separation between the solid and liquid phases. A schematic of the completed WWTP is shown in Fig. 8.

Conclusions

Even if a treated effluent is discharged into a receiving body characterized by a high flow rate, PhC concentrations do not appear to be reduced to an acceptable environmental risk level. Hence, further measures are needed, including source control of the most critical compounds and enhancement of PhC removal by appropriately upgrading existing WWTPs. In this regard, although natural processes are often effective in removing many micro-pollutants, some effluent-derived contaminants seem to be resistant to biodegradation. These persistent polar pollutants require further study aimed at limiting the risks they pose to the environment and to human healt.

Competing interests. None declared.

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