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RESEARCH ARTICLE

Survey of the occurrence of pharmaceuticals in Spanish finished drinking waters

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Abstract Fifty samples of finished drinking waters (FDWs) from Spain covering 12 million inhabitants were tested for 53 pharmaceuticals pertaining to 12 different Anatomical Therapeutic Chemical (ATC) classification system codes. The studied compounds are a combination of most commonly consumed pharmaceuticals with other barely reported in the literature. Five compounds, azithromycin, clarithromycin, erythromycin, sulfamethoxazole, and ibuprofen were tentatively identified by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) in some samples (2 to 15 %), but only ibuprofen and azithromycin could be confirmed when analyzed by liquid chromatography–high-resolution mass spectrometry (LC-HRMS) with a quadrupole-Orbitrap instrument. Concentration levels of ibuprofen in the positive samples ranged from 12 to 17 ng/L (n=6) while for azithromycin values from 5 to 9.5 ng/L (n=3) were found. Ibuprofen fragmentation behaviour in different mass spectrometry instrument configurations (triple quadrupole, quadrupole-ion trap, and quadrupole-Orbitrap) was evaluated.

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Keywords Pharmaceuticals · ATC code · FDW · LC-MS/MS · LC-HRMS

Introduction

Pharmaceuticals are one of the hottest topics in the environmental scientific literature (Khetan and Collins 2007). Since the mid-1990s, an exponential interest has emerged on their presence in numerous environmental compartments that has led USEPA to compile a pharmaceuticals and personal care products (PPCPs) literature database of more than 15,000 references covering origins, sources, occurrence, transport, fate, monitoring, and risk assessment among other aspects (Daughton and Scuderi 2013). Pharmaceuticals are released into the environment as trace pollutants mainly as a result of their excretion via urine and feces either metabolized or as parent compounds. Alternative routes for the entry of pharmaceuticals into the environment such as their release from skin during bathing and washing, disposal of unused, leftover medications, etc. have also been compiled (Daughton and Ruhoy 2009). The presence of pharmaceuticals in sewage effluents, groundwater, surface waters, and less frequently drinking waters has been extensively documented (Boxall et al. 2011; Daughton 2010; Hughes et al. 2013; Jones et al. 2005; Lapworth et al. 2012; Loos et al. 2010; Mompelat et al. 2009; Monteiro and Boxall 2010; Ontario 2010) and methodologies to prioritize compounds of interest have been developed (Besse and Garric 2008; De Voogt et al. 2009).

In relation to legislation of pharmaceuticals in the field of the water policy, the 3rd EPA drinking water contaminant candidate list CCL3 in the USA has included erythromycin and nitroglycerin. In Europe, three pharmaceuticals, diclofenac, 17-α-ethynilestradiol, and 17-β-estradiol were proposed to be added to the list of priority substances that are monitored and controlled in European Union surface

waters, but finally, they have been only included in the watch list of compounds that needs more data to support further prioritization.

Data from presence and concentration ranges in raw water sources (i.e., rivers and groundwater) provide information about targeted pharmaceuticals that are more prone to occur in drinking water, although the efficiencies of the treatments used in the drinking water treatment plants must be taken into account. Recently, pharmaceutical data sets collected from river systems around the world have been critically evaluated (Hughes et al. 2013). In this work, it is stated that most studies have been performed in the USA, Spain, China, Germany, Canada, and UK, and specifically in Europe, most of them have been undertaken in the Ebro and Llobregat (Spain) and Elbe and Rhine basins (Germany and Switzerland). An interesting finding related to the results from Spain is that the national mean for some compounds is much higher than the global mean of the ten most studied countries. For instance, Spain presents values exceeding 441 % of the global mean for blood lipid regulators, 213 % for other cardiovascular drugs, and 209 % for painkillers (Hughes et al. 2013) in raw waters.

The current state of knowledge of pharmaceuticals in Spanish rivers, which are the main raw source of the distributed drinking waters in the country is summarized in Table 1. Data available in the literature from positive and negative occurrence in finished drinking waters (FDW) in Spain and Europe are also included. Table 1 is restricted to the 75 compounds most frequently studied (out of the 220 compiled pharmaceuticals in Spain, Europe, and North America in FDW and Spanish rivers—Tables S1 and S2, respectively, of the Electronic supplementary material), where the corresponding references are included and uses the Anatomical Therapeutic Chemical (ATC) classification system codes as a framework to organize the data as suggested by Daughton (2010). Table 1 displays the number of publications were the pharmaceutical has been targeted, the positive occurrence data (expected for most raw source waters), the absence (expected for most FDW), and the range of the maximum values and the mean or median values if available, with their ranges.

Most of the Spanish data on pharmaceuticals came from studies carried out in the Llobregat river basin (NE Spain) (Farre et al. 2001; García-Galán et al. 2010; Huerta-Fontela et al. 2011; Köck-Schulmeyer et al. 2011; Kuster et al. 2008; López-Roldan et al. 2010; López-Serna et al. 2012; Boleda et al. 2011, 2013; Muñoz et al. 2009; Pedrouzo et al. 2007; Rodriguez-Mozaz et al. 2004a, b), in the Ebro River basin (NE Spain) (Ferreira da Silva et al. 2011; García-Galán et al. 2011; Gonçalves et al. 2011; Gros et al. 2006, 2007, 2008; López-Roldan et al. 2010; López-Serna et al. 2011; Pedrouzo et al. 2007), in Henares–Tagus–Jarama rivers (Central Spain) (Fernández et al. 2010; González-Alonso et al. 2010; Martínez Bueno et al. 2010; Valcárcel et al. 2011a, b, 2013) and less frequently, in other rivers of the country (Esteban et al. 2012; Iglesias et al. 2012; Martın et al. 2011; Rodil et al. 2012). The most studied compound classes are those related to the cardiovascular system (diuretics, β-blocking agents, and lipid modifying agents); the muscular–skeletal system (anti-inflammatory and antirheumatic products); the nervous system (analgesics, antiepileptics, psycholeptics, and psychoanaleptics); the genito-urinary system and sex hormones; the alimentary tract (acid-related disorders); the respiratory system and also anti-infectives (antibacterials), and X-ray contrast media, which is in agreement with the worldwide coverage of compound classes (Hughes et al. 2013). The ten most frequently identified compounds in Spanish rivers are ibuprofen, diclofenac, naproxen, clofibric acid, carbamazepine, sulfamethoxazole, trimethoprim, bezafibrate, atenolol, and gemfibrozil with concentration levels ranging from few ng/L to high μg/L. Their maximum levels represent the highest concentrations in river waters reported in the literature except for ibuprofen, naproxen and trimethoprim (Hughes et al. 2013). As regards Spanish FDW, quantitative data have been published for 29 pharmaceuticals among a total of 223 studied compounds (see Table S1). Table 1 displays 21 pharmaceuticals identified in Spanish FDW out of the 75 ranked; 48 compounds were never detected and 6 (enalapril, iomeprol, iopamidol and its transformation products, and iothalamic and ioxithalamic acids) were not studied in FDW. The most refractory compounds frequently reported in Spanish finished water (see the percentage of absence in Spanish FDW in Fig. S1) are (maximum concentration in brackets) iopromide (84 ng/L), ibuprofen (54 ng/L), venlafaxine (44 ng/L), atenolol and acetaminophen (23 ng/L), hydrochlorothiazide (7 ng/L), and carbamazepine (5.7 ng/L), some of them not included in the 75 (Table 1) most studied worldwide. Table 1 also displays quantitative data from European FDW for 32 pharmaceuticals out of 75 ranked (Table S1 provides quantitative data for 46 compounds out of 207 total targeted pharmaceuticals). The most refractory FDW compounds found in Europe are the X-ray contrast media group and their transformation products (see Table 1 and references cited herein). As examples, levels of iopamidol up to 270 ng/L, to 500 ng/L, and to 260 ng/L for iopromide transformation products were measured (Kormos et al. 2011). In Spain, only iopromide has been found. Other compounds commonly found in European FDW such as acetaminophen (maximum levels of 210 ng/L), carbamazepine (43 ng/L), and ibuprofen (28 ng/L) were also found in Spain whereas other pharmaceuticals such as phenazone (400 ng/L), clofibric acid (170 ng/L), salicylic acid (122 ng/L), propyphenazone (120 ng/L), sulfamethoxazole (25 ng/L), or diclofenac (18 ng/L) were practically not identified in Spanish FDW. On the contrary, venlafaxine and hydrochlorothiazide were absent or not studied in European FDWs. When comparing data from FDWs of Europe and North America, important differences are observed among the pharmaceuticals most frequently studied and encountered.

Table 1 Summary of occurrence data for the top 75 most frequently reported pharmaceutical compounds in Spanish rivers and finished drinking waters from Spain and rest of Europe (concentrations in ng/L)

Spain rivers						Spain FDW			Europe FDW		
TC code	Compound	Presence/ publ.[a]	Max[b] ranges	(Mean) and/or [median][c] ranges	References	Absence/ publ.	Max[b] ranges	References	Absence/ publ.	Max[b] ranges	References
Stomatological (A01), acid-related disorders (A02), antidiarrheals (A07), and antidiabetics (A10)											
A02BA01	Cimetidine	4/6	10.7–12	(0.1–10.7)	Boleda et al. (2011), Köck-Schulmeyer et al. (2011), Ferreira da Silva et al. (2011), López-Serna et al. (2011), and Gros et al. (2008, 2013)	2/2	nd	Boleda et al. (2011) and Gros et al. (2013)			
A02BA03	Famotidine	6/13	8.6–349	(0.1–14)	Boleda et al. (2011), Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2012), Muñoz et al. (2009), Ferreira da Silva et al. (2011), López-Serna et al. (2011), Gros et al. (2006, 2007, 2008), Martínez Bueno et al. (2010), and Valcárcel et al. (2011a, 2013)	4/4	nd	Boleda et al. (2011), Valcárcel et al. (2011a, 2013), and Gros et al. (2013)			
A02BC01	Omeprazole	4/4	1.6–222		Boleda et al. (2011, 2013), Martínez Bueno et al. (2010), and Valcárcel et al. (2011a)	5/5	nd	Boleda et al. (2011, 2013), Valcárcel et al. (2011a, 2013), and Pedrouzo et al. (2008)			
A02BA02	Ranitidine	15/15	4.9–570	(0.8–142)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2012), Muñoz et al. (2009), Ferreira da Silva et al. (2011), López-Serna et al. (2011), Gros et al. (2006, 2007, 2008, 2013), Martínez Bueno et al. (2010), and Valcárcel et al. (2011a), Pedrouzo et al. (2008)	6/7	0.6	Boleda et al. (2011, 2013), Valcárcel et al. (2011a, 2013), Pedrouzo et al. (2008), and Gros et al. (2013)	1/1	nd	Zuccato et al. (2000)
Cardiac (C01), diuretics (C03), calcium channel blockers (C08), and agents acting on the renin–angiotensin system (C09)											
C08DB01	Diltiazem	2/2	13	(4)	Huerta-Fontela et al. (2011) and Gros et al. (2013)	2/2	nd	Huerta-Fontela et al. (2011) and Gros et al. (2013)			
C09AA02	Enalapril*	4/5	3.10–6.84	(1.50–4.18)	Köck-Schulmeyer et al. (2011), López-Serna et al. (2012), Ferreira da Silva et al. (2011), López-Serna et al. (2011), and Gros et al. (2008)						
C03CA01	Furosemide	10/10	40–3,228	(9.2–174)	Köck-Schulmeyer et al. (2011), Huerta-Fontela et al. (2011), López-Serna et al. (2011, 2012), Ferreira da Silva et al. (2011), Gros et al. (2008, 2013), Martínez Bueno et al. (2010), and Valcárcel et al. (2011b, 2013)	4/4	nd	Huerta-Fontela et al. (2011), Valcárcel et al. (2011b, 2013), and Gros et al. (2013)	2/2	nd	Zuccato et al. (2000) and Vulliet et al. (2011)
C03AA03	Hydrochlorotiazide	11/11	11.9–17,589	(20–670)	Köck-Schulmeyer et al. (2011), López-Serna et al. (2011, 2012), Ferreira da Silva et al. (2011), Gros et al. (2008), Fernández et al. (2010), Martínez Bueno et al. (2010), Valcárcel et al. (2011b, 2013), and Gros et al. (2013)	3/5	7	Huerta-Fontela et al. (2011), Valcárcel et al. (2011b, 2013), and Gros et al. (2013)			

Table 1 (continued)

Spain rivers						Spain FDW			Europe FDW		
TC code	Compound	Presence/ publ.[a]	Max[b] ranges	(Mean) and/or [median][c] ranges	References	Absence/ publ.	Max[b] ranges	References	Absence/ publ.	Max[b] ranges	References
ß-blocking agents (C07)											
C07AB03	Atenolol	17/17	26–11,020	(7.4–2,789)	Köck-Schulmeyer et al. (2011), Huerta-Fontela et al. (2011), Kuster et al. (2008), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007, 2008, 2013), Fernández et al. (2010), Martínez Bueno et al. (2010), Valcárcel et al. (2011b, 2013), and Rodil et al. (2012)	2/5	6–23	Huerta-Fontela et al. (2011), Valcárcel et al. (2011b, 2013), Rodil et al. (2012), and Gros et al. (2013)	2/3	2	Zuccato et al. (2000), Vulliet et al. (2011), and De Jongh et al. (2012)
C07AB02	Metoprolol	14/15	5–1,600	(1–327)	Köck-Schulmeyer et al. (2011), Huerta-Fontela et al. (2011), López-Serna et al. (2012), Muñoz et al. (2009), Pedrouzo et al. (2007), Ferreira da Silva et al. (2011), López-Serna et al. (2011), Gross et al. (200, 2007, 2008, 2013), Fernández et al. (2010), Martínez Bueno et al. (2010), and Valcárcel et al. (2011b, 2013)	4/4	nd	Huerta-Fontela et al. (2011), Valcárcel et al. (2011b, 2013), and Gros et al. (2013)	2/4	14–26	Versteegh et al. (2007), Vulliet et al. (2011), De Jongh et al. (2012), and Stolker et al. (2004)
C07AA05	Propanolol	12/16	5–270	(2–54)	Köck-Schulmeyer et al. (2011), Huerta-Fontela et al. (2011), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Pedrouzo et al. (2007), Gros et al. (2006, 2007, 2008, 2013), Fernández et al. (2010), Martínez Bueno et al. (2010), Valcárcel et al. (2011b, 2013), Rodil et al. (2012), Martın et al. (2011), and Bourgin et al. (2013)	5/5	nd	Huerta-Fontela et al. (2011), Valcárcel et al. (2011b, 2013), Rodil et al. (2012), and Gros et al. (2013)	1/1	nd	Vulliet et al. (2011)]
C07AA07	Sotalol	14/14	13–1,820	(2.9–570)	Köck-Schulmeyer et al. (2011), Huerta-Fontela et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007, 2013), Martínez Bueno et al. (2010), Valcárcel et al. (2011b, 2013), and Bourgin et al. (2013)	3/4	3	Huerta-Fontela et al. (2011), Valcárcel et al. (2011b, 2013), and Gros et al. (2013)	1/1	nd	De Jongh et al. (2012)
Lipid-modifying agents (C10)											
C10AB02	Bezafibrate	17/18	10–15,060	(6–1,020)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Pedrouzo et al. (2007), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007, 2013), Fernández et al. (2010), Martínez	6/6	nd	Boleda et al. (2011, 2013),Valcárcel et al. (2011b, 2013), Rodil et al. (2012), and Gros et al. (2013)	4/8	1.9–32	Zuccato et al. (2000), Versteegh et al. (2007), Vulliet et al. (2011), De Jongh et al. (2012), Stolker et al. (2004), Stumpf et al. (1996), and Vieno et al. (2005)

Table 1 (continued)

Spain rivers						Spain FDW			Europe FDW		
TC code	Compound	Presence/ publ.[a]	Max[b] ranges	(Mean) and/or [median][c] ranges	References	Absence/ publ.	Max[b] ranges	References	Absence/ publ.	Max[b] ranges	References
					Bueno et al. (2010), Valcárcel et al. (2011b, 2013), Rodil et al. (2012), and Bourgin et al. (2013)						
C10AB01 (mlt)	Clofibric acid	18/20	4.9–7,910	(2–2,280)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), Kuster et al. (2008), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Pedrouzo et al. (2007), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007), Fernández et al. (2010), Martínez Bueno et al. (2010), Valcárcel et al. (2011b, 2013), Rodil et al. (2012), Martın et al. (2011), Bourgin et al. (2013), and Hernando et al. (2006)	6/7	40	Boleda et al. (2011, 2013), Kuster et al. (2008), Valcárcel et al. (2011b, 2013), Rodil et al. (2012), and Hernando et al. (2006)	0/7	32–170	Zuccato et al. (2000), Versteegh et al. (2007), Ternes (2001), Stolker et al. (2004), Stumpf et al. (1996), Heberer and Stan (1997), and Versteegh et al. (2003)
C10AB04	Gemfibrozil	17/17	3.80–7,780	(2.1–1,420)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007, 2013), Martínez Bueno et al. (2010), Valcárcel et al. (2011b, 2013), Martin et al. (2011), and Bourgin et al. (2013)	4/5	8	Boleda et al. (2011, 2013), Valcárcel et al. (2011b, 2013), and Gros et al. (2013)	1/2	0.8	Loos et al. (2007) and Togola and Budzinski (2008)
C10AB05	Fenofibrate	6/10	1.23–127	(0.2–82.1)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), López-Serna et al. (2011, 2012), Ferreira da Silva et al. (2011), Martínez Bueno et al. (2010), Valcárcel et al. (2011b), Valcárcel et al. (2013), Bourgin et al. (2013)	3/3	nd	Boleda et al. (2011) and Valcárcel et al. (2011b, 2013)	1/2	14–21	Versteegh et al. (2007) and Stolker et al. (2004)
none	Mevastatin	0/13	nd		Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007), Martínez Bueno et al. (2010), Valcárcel et al. (2011b), and Bourgin et al. (2013)	3/3	nd	Boleda et al. (2011) and Valcárcel et al. (2011b, 2013)			
C10AA03	Pravastatin	7/14	14.5–378	(8.57–65.1)	Boleda et al. (2011), Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007, 2013), Martínez Bueno et al. (2010), Valcárcel et al. (2011b, 2013)	4/4	nd	Boleda et al. (2011), Köck-Schulmeyer et al. (2011), Valcárcel et al. (2011b), Valcárcel et al. (2013), and Gros et al. (2013)	0/1	0.2	Vulliet et al. (2011)

Table 1 (continued)

Spain rivers						Spain FDW			Europe FDW		
TC code	Compound	Presence/ publ.[a]	Max[b] ranges	(Mean) and/or [median][c] ranges	References	Absence/ publ.	Max[b] ranges	References	Absence/ publ.	Max[b] ranges	References
Antifungals (D01), antipruritics (D04), antibiotics (D06), corticosteroids (C07), and antiseptics (D08)											
D01AE12, S01BC08	Salicylic acid	12/14	7–8,800	(1.8–333.2)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), López-Serna et al. (2011, 2012), Pedrouzo et al. (2007), Gros et al. (2008, 2013), Fernández et al. (2010), Valcárcel et al. (2011b, 2013), Valcárcel et al. (2013), Rodil et al. (2012), and Martın et al. (2011)	4/5	2	Boleda et al. (2011), Valcárcel et al. (2011b, 2013), Rodil et al. (2012), and Gros et al. (2013)	0/2	19–122	Versteegh et al. (2007) and Vulliet et al. (2011)
D08AE04	Triclosan	1/4	40		Boleda et al. (2011, 2013), Kuster et al. (2008), and Rodil et al. (2012)	3/3	nd	Boleda et al. (2011), Kuster et al. (2008), and Rodil et al. (2012)	2/2	nd	Vulliet et al. (2011) and Loos et al. (2007)
Sex hormones and modulators of the genital system (G03) and urologicals (G04)											
G03CA03	17β-Estradiol	0/7	nd		Köck-Schulmeyer et al. (2011), Kuster et al. (2008), Rodriguez-Mozaz et al. (2004a, b), López-Roldan et al. (2010), López-Serna et al. (2012), and Martın et al. (2011)	3/3	nd	Kuster et al. (2008) and Rodriguez-Mozaz et al. (2004a, b)	1/2	0.2–2.1	Loos et al. (2007) and Kuch and Ballschmiter (2001)
	Estradiol-17-glucuronide	0/5	nd		Kuster et al. (2008), Rodriguez-Mozaz et al. (2004a, b), López-Roldan et al. (2010), and López-Serna et al. (2012)	3/3	nd	Kuster et al. (2008) and Rodriguez-Mozaz et al. (2004a, b)			
	Estradiol-17-acetate	0/2	nd		Rodriguez-Mozaz et al. (2004a, b)	2/2	nd	Rodriguez-Mozaz et al. (2004a, b)			
G03CA04	Estriol	2/6	72–100	(26)	Huerta-Fontela et al. (2011), Rodriguez-Mozaz et al. (2004a), Rodriguez-Mozaz et al. (2004b), López-Roldan et al. (2010), López-Serna et al. (2012), and Martın et al. (2011)	3/4	11.6	Huerta–Fontela et al. (2011), Kuster et al. (2008), and Rodriguez-Mozaz et al. (2004a, b)	1/1	nd	Vulliet et al. (2011)
G03CA07	Estrone	7/8	0.68–22	(0.3–1.80)	Köck-Schulmeyer et al. (2011), Huerta-Fontela et al. (2011), López-Roldan et al. (2010), Kuster et al. (2008), Rodriguez-Mozaz et al. (2004a, b), López-Serna et al. (2012), and Martın et al. (2011)	5/5	nd	Huerta-Fontela et al. (2011), Kuster et al. (2008), Rodriguez-Mozaz et al. (2004a, b), and López-Roldan et al. (2010)	1/4	0.2–1.0	Vulliet et al. (2011), Hirsch et al. (2000), Loos et al. (2007), and Kuch and Ballschmiter (2001)
	Estrone 3-sulfate	4/6	0.33–7		Köck-Schulmeyer et al. (2011), Kuster et al. (2008), Rodriguez-Mozaz et al. (2004a, b), López-Roldan et al. (2010), and López-Serna et al. (2012)	2/3	0.5	Kuster et al. (2008) and Rodriguez-Mozaz et al. (2004a, b)			
G03CA01	17α-ethinyl estradiol	1/7	3.4	(2.5)	Huerta-Fontela et al. (2011), Kuster et al. (2008), Rodriguez-Mozaz et al. (2004a, b), López-Roldan et al. (2010), López-Serna et al. (2012), and Martın et al. (2011)	4/4	nd	Huerta-Fontela et al. (2011), Kuster et al. (2008), and Rodriguez-Mozaz et al. (2004a, b)	1/2	0.15–0.50	Kuch and Ballschmiter (2001) and Aherne and Briggs (1989)
Antibacterials (J01) and antivirals (J05)											
J01CA04	Amoxicillin	0/2	nd		Boleda et al. (2011) and Martínez Bueno et al. (2010)	1/1	nd	Boleda et al. (2011)			
J01FA10	Azithromycin	11/12	17.6–569	(1.7–71.7)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), López-	5/5	nd		1/1	nd	Vulliet et al. (2011)

Table 1 (continued)

Spain rivers						Spain FDW			Europe FDW		
TC code	Compound	Presence/ publ.[a]	Max[b] ranges	(Mean) and/or [median][c] ranges	References	Absence/ publ.	Max[b] ranges	References	Absence/ publ.	Max[b] ranges	References
					Serna et al. (2011, 2012), Muñoz et al. (2009), Gros et al. (2006, 2007, 2008, 2013) Martínez Bueno et al. (2010), and Valcárcel et al. (2011a)			Boleda et al. (2011, 2013), Valcárcel et al. (2011a, 2013), and Gros et al. (2013)			
J01DB01	Cefalexin	0/1	nd		Gros et al. (2013)	1/1	nd	Gros et al. (2013)			
J01MA02 (mlt)	Ciprofloxacin	7/8	23–224	(3.3–93)	Köck-Schulmeyer et al. (2011), López-Serna et al. (2012), López-Serna et al. (2011), Gros et al. (2008, 2013), Martínez Bueno et al. (2010), Valcárcel et al. (2011a), and Iglesias et al. (2012)	3/3	nd	Valcárcel et al. (2011a, 2013) and Gros et al. (2013)	1/1	nd	Zuccato et al. (2000)
J01FA09	Clarithromycin	11/11	36.9–1,727	(8.76–88.8)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), López-Serna et al. (2011, 2012), Ferreira da Silva et al. (2011), Gros et al. (2008, 2013), Martínez Bueno et al. (2010), and Valcárcel et al. (2011a, 2013)	5/5	nd	Boleda et al. (2011, 2013), Valcárcel et al. (2011a, 2013), and Gros et al. (2013)	1/1	nd	Bruchet et al. (2005)
J01FA01	Erythromycin	13/16	30–3,847	(1.2–175)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007, 2008, 2013), Martínez Bueno et al. (2010), Valcárcel et al. (2011a, 2013), and Pedrouzo et al. (2008)	4/6	2.0	Boleda et al. (2011, 2013), Valcárcel et al. (2011a, 2013), Pedrouzo et al. (2008), and Gros et al. (2013)	4/4	nd	Zuccato et al. (2000), Bruchet et al. (2005), De Jongh et al. (2012), and Stolker et al. (2004)
J01FF02	Lincomycin	3/3	17.9–644		Boleda et al. (2011, 2013) and Martínez Bueno et al. (2010)	2/2	nd	Boleda et al. (2011, 2013)	2/2	nd	Zuccato et al. (2000) and Bruchet et al. (2005)
J01XD01 (mlt)	Metronidazole	8/9	19–1,834	(0.4–44.9)	Köck-Schulmeyer et al. (2011), López-Serna et al. (2012), Ferreira da Silva et al. (2011), López-Serna et al. (2011), Gros et al. (2008), Martínez Bueno et al. (2010), Valcárcel et al. (2011a), Valcárcel et al. (2013), and Gros et al. (2013)	2/2	nd;	Valcárcel et al. (2013) and Gros et al. (2013)	2/2	nd	Vulliet et al. (2011) and Bruchet et al. (2005)
J01MA01	Ofloxacin	11/12	20–8,770	(7.3–2,110)	Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Gros et al. (2006, 2007, 2008, 2013), Martínez Bueno et al. (2010), and Valcárcel et al. (2013)	3/3	nd	Valcárcel et al. (2011a, 2013) and Gros et al. (2013)			
J01FA06	Roxithromycin	2/6		(0.32–0.5)	Boleda et al. (2011), Köck-Schulmeyer et al. (2011), López-Serna et al. (2011, 2012), Gros et al. (2008), and Pedrouzo et al. (2008)	2/2	nd	Boleda et al. (2011) and Pedrouzo et al. (2008)	2/2	nd	Vulliet et al. (2011) and Bruchet et al. (2005)
J01EC02	Sulfadiazine	8/10	6.4–2,978	(1.8–708.8)	Köck-Schulmeyer et al. (2011), García-Galán et al. (2010), López-	1/1	nd	Pedrouzo et al. (2008)			

Table 1 (continued)

Spain rivers						Spain FDW			Europe FDW		
TC code	Compound	Presence/ publ.[a]	Max[b] ranges	(Mean) and/or [median][c] ranges	References	Absence/ publ.	Max[b] ranges	References	Absence/ publ.	Max[b] ranges	References
					Serna et al. (2011, 2012), Ferreira da Silva et al. (2011), García-Galán et al. (2011), Gros et al. (2008), Martínez Bueno et al. (2010), and Iglesias et al. (2012)						
J01ED01	Sulfadimethoxine	5/5	7–43		Boleda et al. (2011, 2013), García-Galán et al. (2010, 2011), and Fernández et al. (2010)	2/2	nd	Boleda et al. (2011, 2013)			
J01EB03	Sulfamethazine	8/12	5–2,481.8	(2.6–112)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), García-Galán et al. (2010, 2011), López-Serna et al. (2011, 2012), Ferreira da Silva et al. (2011), Gros et al. (2008), Martínez Bueno et al. (2010), Iglesias et al. (2012), and Pedrouzo et al. (2008)	3/3	nd	Boleda et al. (2011, 2013) and Pedrouzo et al. (2008)	1/1	nd	Bruchet et al. (2005)
J01EC01	Sulfamethoxazole	17/19	23.7–11,920	(11–1,110)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), García-Galán et al. (2010, 2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Gros et al. (2006, 2007, 2008), Fernández et al. (2010), Martínez Bueno et al. (2010), Valcárcel et al. (2011a, b), Martın et al. (2011), Pedrouzo et al. (2008), and Gros et al. (2013)	5/6	0.5	Boleda et al. (2011, 2013), Valcárcel et al. (2011a, b), Pedrouzo et al. (2008), and Gros et al. (2013)	2/6	0.8–25	Versteegh et al. (2003, 2007), Vulliet et al. (2011), Bruchet et al. (2005), Stolker et al. (2004), and Loos et al. (2007)
J01AA07	Tetracycline	3/8	63.4–228	(1.2–86.9)	Boleda et al. (2013), Köck-Schulmeyer et al. (2011), López-Serna et al. (2011, 2012), Gros et al. (2008, 2013), Martínez Bueno et al. (2010), and Valcárcel et al. (2011a)	3/3	nd	Valcárcel et al. (2011a, b) and Gros et al. (2013)			
J01EA01	Trimethoprim	17/19	9–690	(4–140)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007, 2008, 2013), Fernández et al. (2010), Martínez Bueno et al. (2010), Valcárcel et al. (2011a, b), Martın et al. (2011), and Pedrouzo et al. (2008)	5/5	nd	Boleda et al. (2011), Valcárcel et al. (2011a, b), Pedrouzo et al. (2008), and Gros et al. (2013)	0/1	1.0	Vulliet et al. (2011)
Antineoplastic agents (L01) and endocrine therapy (L02)											
L01AB01	Cyclophosphamide	0/2	nd		Martínez Bueno et al. (2010) and Valcárcel et al. (2011a)	2/2	nd	Valcárcel et al. (2011a, 2013)	1/1	nd	Zuccato et al. (2000)
Antiinflammatory and antirheumatic products (M01)											
M01AB05	Diclofenac	19/21	35–18,740	(13–2,200)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), Kuster et	8/8	nd	Boleda et al. (2011, 2013), Kuster et al. (2008), Valcárcel et al.	3/8	0.2–18	Versteegh et al. (2007), Vulliet et al. (2011), Ternes (2001),

Table 1 (continued)

Spain rivers						Spain FDW			Europe FDW		
TC code	Compound	Presence/ publ.[a]	Max[b] ranges	(Mean) and/or [median][c] ranges	References	Absence/ publ.	Max[b] ranges	References	Absence/ publ.	Max[b] ranges	References
					al. (2008), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Pedrouzo et al. (2007), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007, 2008, 2013), Fernández et al. (2010), Martínez Bueno et al. (2010), Valcárcel et al. (2011b), Valcárcel et al. (2013), Rodil et al. (2012), Martın et al. (2011), and Hernando et al. (2006)			(2011b, 2013), Rodil et al. (2012), Gros et al. (2013), and Hernando et al. (2006)			Stolker et al. (2004), Stumpf et al. (1996), Loos et al. (2007), Vieno et al. (2005), and Togola and Budzinski (2008)
M01AE01	Ibuprofen	20/22	44–16,886	(46–1,370)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), Kuster et al. (2008), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Pedrouzo et al. (2007), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007, 2008, 2013), Fernández et al. (2010), Martínez Bueno et al. (2010), Valcárcel et al. (2011b, 2013), Rodil et al. (2012), Martın et al. (2011), Gros et al. (2013), and Hernando et al. (2006)	5/8	5–54	Boleda et al. (2011, 2013), Kuster et al. (2008), Valcárcel et al. (2011b, 2013), Rodil et al. (2012), Gros et al. (2013), and Hernando et al. (2006)	3/9	0.6–28	Zuccato et al. (2000), Versteegh et al. (2007), Vulliet et al. (2011), Ternes (2001), Stolker et al. (2004), Vieno et al. (2005), and Togola and Budzinski (2008)
M01AB01	Indomethacin	11/14	10–380	(6.8–160)	Boleda et al. (2011), Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007, 2013), Martínez Bueno et al. (2010), Valcárcel et al. (2011b, 2013), and Rodil et al. (2012)	4/5	6	Boleda et al. (2011), Valcárcel et al. (2011b, 2013), Rodil et al. (2012), and Gros et al. (2013)			
M01AE03	Ketoprofen	11/19	10.4–2,710	(3.2–790)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007, 2008), Fernández et al. (2010), Martínez Bueno et al. (2010), Valcárcel et al. (2011b, 2013), Rodil et al. (2012), Martın et al. (2011), and Hernando et al. (2006)	5/6	3	Boleda et al. (2011), Valcárcel et al. (2011b, 2013), Rodil et al. (2012), Gros et al. (2013), and Hernando et al. (2006)	1/3	0.9–3	Vulliet et al. (2011), Vieno et al. (2005), and Togola and Budzinski (2008)
M01AG01	Mefenamic acid	11/13	2.4–104	(2–20)	Boleda et al. (2011), Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007), Martínez Bueno et al. (2010),	3/3	nd	Boleda et al. (2011) and Valcárcel et al. (2011b, 2013)			

Table 1 (continued)

Spain rivers						Spain FDW			Europe FDW		
TC code	Compound	Presence/ publ.[a]	Max[b] ranges	(Mean) and/or [median][c] ranges	References	Absence/ publ.	Max[b] ranges	References	Absence/ publ.	Max[b] ranges	References
					Valcárcel et al. (2011b, 2013), and González-Alonso et al. (2010)						
M01AE02	Naproxen	19/21	50–3,140	(32.4–530)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Pedrouzo et al. (2007),. Ferreira da Silva et al. (2011), Gros et al. (2006, 2007, 2008, 2013), Fernández et al. (2010), Martínez Bueno et al. (2010), Valcárcel et al. (2011b, 2013), Rodil et al. (2012), Martın et al. (2011), and Hernando et al. (2006)	6/6	nd	Boleda et al. (2011, 2013), Valcárcel et al. (2011b), Rodil et al. (2012), Gros et al. (2013), and Hernando et al. (2006)	1/3	0.2–0.5	Vulliet et al. (2011), Vieno et al. (2005), and Togola and Budzinski (2008)
Anesthetics (N01) and analgesics (N02)											
N02BE01	Acetaminophen	17/17	30–2,813	(10–499.4)	Boleda et al. (2011, 2013), Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Pedrouzo et al. (2007), Ferreira da Silva et al. (2011), Gros et al. (2006, 2008, 2013), Fernández et al. (2010), Martínez Bueno et al. (2010), and Valcárcel et al. (2011b, 2013)	3/5	3.4–23	Boleda et al. (2011, 2013), Valcárcel et al. (2011b, 2013), and Gros et al. (2013)	1/4	33–210.1	Versteegh et al. (2007), Vulliet et al. (2011), and Togola and Budzinski (2008)
N02BB01	Phenazone (antypirine)	8/9	10.2–752	(1.8–40.3)	Köck-Schulmeyer et al. (2011), López-Serna et al. (2011, 2012), Ferreira da Silva et al. (2011), Martínez Bueno et al. (2010), Valcárcel et al. (2011b, 2013), Rodil et al. (2012), and Gros et al. (2013)	3/3	nd	Valcárcel et al. (2013), Rodil et al. (2012), and Gros et al. (2013)	0/5	20–400	Versteegh et al. (2007), Ternes (2001), De Jongh et al. (2012) Reddersen et al. (2002), and Zuhlke et al. (2004)
N02BB04	Propyphenazone	10/12	10–180	(2.6–90)	Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Gros et al. (2006, 2007, 2008), Martínez Bueno et al. (2010), Valcárcel et al. (2011b, 2013), and Rodil et al. (2012)	4/4	nd	Valcárcel et al. (2011b, 2013), Rodil et al. (2012), and Gros et al. (2013)	1/3	80–120	De Jongh et al. (2012) and Reddersen et al. (2002), Zuhlke et al. (2004)
Antiepileptics (N03), psycholeptics (N05),and psychoanaleptics (N06)											
N03AF01	Carbamazepine	19/19	6–67,715	(13–1,070)/ [82]	Köck-Schulmeyer et al. (2011), Huerta-Fontela et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Pedrouzo et al. (2007), Ferreira da Silva et al. (2011), Gros et al. (2006, 2007, 2008, 2013), Fernández et al. (2010), Martínez Bueno et al.	3/6	2–5.7	Huerta-Fontela et al. (2011), Valcárcel et al. (2011a, 2013), Esteban et al. (2012), Rodil et al. (2012), and Gros et al. (2013)	2/9	9.1–43	Versteegh et al. (2007), Vulliet et al. (2011), Ternes (2001), De Jongh et al. (2012), Stolker et al. (2004), Loos et al. (2007), Versteegh et al. (2003), Togola and Budzinski (2008), and Hummel et al. (2006)

Table 1 (continued)

Spain rivers						Spain FDW			Europe FDW		
TC code	Compound	Presence/ publ.[a]	Max[b] ranges	(Mean) and/or [median][c] ranges	References	Absence/ publ.	Max[b] ranges	References	Absence/ publ.	Max[b] ranges	References
					(2010), Valcárcel et al. (2011a, 2013), González-Alonso et al. (2010), Rodil et al. (2012), and Martın et al. (2011)						
N03AF01 (mlt)	Carbamazepine epoxide	5/5	14–282	(10.5–54)	Huerta-Fontela et al. (2011), Martínez Bueno et al. (2010), Valcárcel et al. (2011a, 2013), and Gros et al. (2013)	3/4	2	Huerta-Fontela et al. (2011), Valcárcel et al. (2011a, 2013), and Gros et al. (2013)	1/1	nd	De Jongh et al. (2012)]
N06AB04	Citalopram	5/5	10–160	(2.2)/[43]	Martínez Bueno et al. (2010), Valcárcel et al. (2011a, 2013), González-Alonso et al. (2010), and Gros et al. (2013)	4/4	nd	Valcárcel et al. (2011a, 2013), Esteban et al. (2012), and Gros et al. (2013)			
N05BA01	Diazepam	8/10	2.68–90	(2.68–14.9)	Köck-Schulmeyer et al. (2011), Huerta-Fontela et al. (2011), López-Serna et al. (2011, 2012), Ferreira da Silva et al. (2011), Gros et al. (2008, 2013), Martínez Bueno et al. (2010), and Valcárcel et al. (2011a, 2013)	4/4	nd	Huerta-Fontela et al. (2011), Valcárcel et al. (2011a, 2013), and Gros et al. (2013)	3/4	19.3–23.5	Zuccato et al. (2000), Togola and Budzinski (2008), and Hummel et al. (2006), and Hass et al. (2012)
N06AB03	Fluoxetine	6/13	3–66.1	(2–10.87)/ [14]	Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Gros et al. (2006, 2007, 2008, 2013), Fernández et al. (2010), Martínez Bueno et al. (2010), Valcárcel et al. (2011a), and González-Alonso et al. (2010)	4/4	nd	Valcárcel et al. (2011a, 2013), Esteban et al. (2012), and Gros et al. (2013)	1/2	10	Versteegh et al. (2007) and Vulliet et al. (2011)
N05BA06	Lorazepam	6/7	19–53.1	(11–41.3)	Köck-Schulmeyer et al. (2011), López-Serna et al. (2011, 2012), Ferreira da Silva et al. (2011), Gros et al. (2008), González-Alonso et al. (2010), and Gros et al. (2013)	1/2	562	Esteban et al. (2012) and Gros et al. (2013)	1/1	nd	Vulliet et al. (2011)
N06AB03 (mlt)	Norfluoxetin	0/2	nd		González-Alonso et al. (2010) and Gros et al. (2013)	1/1	nd	Gros et al. (2013)	1/1	nd	Vulliet et al. (2011)
N06AB05	Paroxetine	3/12	40–225	(0.4–212.5)	Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Gros et al. (2006, 2007, 2008. 2013), Martínez Bueno et al. (2010), Valcárcel et al. (2011a), and González-Alonso et al. (2010)	3/3	nd	Valcárcel et al. (2011a, 2013) and Gros et al. (2013)			
N03AB02	Phenytoin	2/2	107.4–140	(56)	Huerta-Fontela et al. (2011) and Fernández et al. (2010)	0/1	10	Huerta-Fontela et al. (2011)			
N06AX16	Venlafaxine	6/6	45–1,003	(12–26.6)/ [57]	Huerta-Fontela et al. (2011), Martínez Bueno et al. (2010), Valcárcel et al. (2011a, 2013), González-Alonso et al. (2010), and Gros et al. (2013)	3/5	9–44	Huerta-Fontela et al. (2011), Valcárcel et al. (2011a, 2013), Esteban et al. (2012), and Gros et al. (2013)	1/1	nd	De Jongh et al. (2012)

Table 1 (continued)

Spain rivers						Spain FDW			Europe FDW		
TC code	Compound	Presence/ publ.[a]	Max[b] ranges	(Mean) and/or [median][c] ranges	References	Absence/ publ.	Max[b] ranges	References	Absence/ publ.	Max[b] ranges	References
Veterinary: antibacterials for systemic use (QJ01), anesthetics (QN01), and antiprotozoals (QP51)											
QJ01FA90	Tylosin	4/7	0.77–1.6	(0.6–0.77)	Boleda et al. (2011), Köck-Schulmeyer et al. (2011, López-Serna et al. (2011, 2012), Ferreira da Silva et al. (2011), Gros et al. (2008), and Pedrouzo et al. (2008)	2/2	nd	Boleda et al. (2011, 2013)	2/3	1.7	Zuccato et al. (2000), Vulliet et al. (2011), and Bruchet et al. (2005)
Obstructive airway disease (R03), cough (R05), and antihistaminic (R06)											
R05DA04	Codeine	7/7	19–3,141	(5.6–110)	Köck-Schulmeyer et al. (2011), López-Serna et al. (2011, 2012), Gros et al. (2008, 2013), Martínez Bueno et al. (2010), and Valcárcel et al. (2011b)	3/3	nd	Valcárcel et al. (2011b, 2013) and Gros et al. (2013)			
R06AX13	Loratadine	7/11	3–201.6	(0.3–45.5)	Köck-Schulmeyer et al. (2011), López-Roldan et al. (2010), López-Serna et al. (2011, 2012), Muñoz et al. (2009), Gros et al. (2006, 2007, 2008, 2013), Martínez Bueno et al. (2010), and Valcárcel et al. (2011a)	3/3	nd	Valcárcel et al. (2011a, 2013) and Gros et al. (2013)			
R03AC02	Salbutamol	7/10	1–28	(0.03–4.9)	Köck-Schulmeyer et al. (2011), Huerta-Fontela et al. (2011), López-Serna et al. (2011, 2012), Ferreira da Silva et al. (2011), Gros et al. (2008), Martínez Bueno et al. (2010), Valcárcel et al. (2011a, 2013), and Rodil et al. (2012)	5/5	nd	Huerta-Fontela et al. (2011), Valcárcel et al. (2011a, 2013), Rodil et al. (2012), and Gros et al. (2013)	2/2	nd	Zuccato et al. (2000) and Togola and Budzinski (2008)
X-ray contrast media (V08)											
V08AA01	Diatrizoic acid	2/2	58.8–84		Boleda et al. (2011, 2013)	2/2	nd	Boleda et al. (2011, 2013)	0/5	32–149	Ternes (2001), Bruchet et al. (2005), Wenzel et al. (2003), Hirsch et al. (2000), and Seitz et al. (2006)
V08AB02	Iohexol	2/2	71.4–341		Boleda et al. (2011, 2013)	2/2	nd	Boleda et al. (2011, 2013)	0/5	5–57	Kormos et al. (2011), Versteegh et al. (2007), Bruchet et al. (2005), Seitz et al. (2006), and Kormos et al. (2009)
V08AB10	Iomeprol	–							0/4	12–92	Kormos et al. (2011), Wenzel et al. (2003), Seitz et al. (2006), and Kormos et al. (2009)
V08AB04	Iopamidol	0/1	nd		Martínez Bueno et al. (2010)				0/7	60–270	Kormos et al. (2011), Ternes (2001), Bruchet et al. (2005), Wenzel et al. (2003), Hirsch et al. (2000), Seitz et al. (2006), and Kormos et al. (2009)
V08AB05	Iopromide	3/3	58–505		Boleda et al. (2011), Martínez Bueno et al. (2010), and Gros et al. (2013)	1/3	17.2–84	Boleda et al. (2011, 2013) and Gros et al. (2013)	1/7	21–86	Kormos et al. (2011), Versteegh et al. (2007), Ternes (2001), Bruchet et al. (2005), Wenzel et al. (2003), Hirsch et al. (2000), and Seitz et al. (2006)

Table 1 (continued)

Spain rivers						Spain FDW			Europe FDW		
TC code	Compound	Presence/ publ.[a]	Max[b] ranges	(Mean) and/or [median][c] ranges	References	Absence/ publ.	Max[b] ranges	References	Absence/ publ.	Max[b] ranges	References
V08AB05	Iopromide (tp's)[a]	–							0/1	260	Kormos et al. (2011)
V08AA04	Iothalamic acid	–							1/2	10	Bruchet et al. (2005) and Hirsch et al. (2000)
V08AA05	Ioxitalamic acid	–							1/2	12	Bruchet et al. (2005) and Wenzel et al. (2003)

(tp's)[a] transformation products, *mlt* metabolite

[a] Absence/no. of publications is referred to the frequency of absence of a determined pharmaceutical respect to the number of publications revised

[b] Maximum is referred to the range of the maximum values reported by all references for each pharmaceutical

[c] Mean and/or median is referred to the range of mean or median values (if available) reported by all references for each pharmaceutical

Data compiled in North America FDW which are included in Table S1 (Electronic supplementary material) show that ibuprofen (1,350 ng/L) and its methyl ester (4,950 ng/L), carbamazepine (258 ng/L), erythromycin (155 ng/L), meprobamate (43 ng/L), which has not been studied in Europe, roxithromycin (41 ng/L), phenytoin (32 ng/L), and sulfamethoxazole (20 ng/L) are among the most studied refractory compounds (see Table S1 and references cited herein). Among them, only ibuprofen and carbamazepine have been frequently studied and found in Spain and the rest of Europe.

The aim of this paper is to evaluate the occurrence of pharmaceuticals in tap waters from Spain in a national survey. The compounds to be studied were selected among the most commonly consumed pharmaceuticals, and other pharmaceuticals much less frequently studied in the literature have also been added. These last compounds were included with the objective of expanding the knowledge, to cover a high number of pharmaceutical classes and to assess the potential of these compounds to survive potabilization processes. As indicated by Daughton (2003), the compilation of potential negative data and a more comprehensive characterization of those pharmaceuticals not currently monitored are essential for ensuring a holistic assessment of risk. Data obtained from the national survey in a country with high consumption levels for most of the therapeutic classes and national FDW average concentrations above the global values can provide a better understanding of the presence and behavior of pharmaceuticals in drinking water treatment plants. Analyses were carried out using ultra-performance liquid chromatography coupled to tandem mass spectrometry (UHPLC-MS/MS) whereas high-resolution mass spectrometry (HRMS) with an Orbitrap analyzer, which has been proved to be suitable for trace detection (Fedorova et al. 2013), has been used to evaluate false positives.

Material and methods

The group of pharmaceuticals analyzed comprises compounds from the following therapeutic classes: stomatological (ATC code, A01); acid-related disorders (A02); antidiarrheals (A07); lipid-modifying agents (C10); antifungals (D01); antiseptics (D08); urological (G04), antibacterials (J01); anti-inflammatory and antirheumatic (M01); psycholeptics (N05); antibacterials for systemic use (QJ01), X-ray contrast media (V08); and several metabolites. Figure S1 (Electronic supplementary material) displays the chemical structures of the individual compounds of each group.

Standards and reagents

Individual standard solutions of target compounds and selected deuterated compounds were obtained from Cerilliant

(Austin, TX, USA), LGC Standards (Middlesex, UK), Aldrich Chemical (St. Louis, MO, USA), and Toronto Research Chemicals (North York, Canada).

Analytical-grade ammonium acetate, ammonium formate, and formic acid used for the LC mobile phase were obtained from Sigma Chemical (St. Louis, MO, USA). HPLC-grade methanol and acetonitrile were provided by Aldrich Chemical. Methanol Purge&Trap grade used for the preparation of standard working solutions was obtained from Riedel-de-Haën (Germany). Water was purified in an Elix-MilliQ system (Millipore Corp., Bedford, MA, USA). Mobile phases were filtered through a 0.22-μm nylon filter (Whatman, England).

Sample collection

FDW samples from 43 Spanish cities (total 50 samples) were collected directly from the tap between fall 2008 and summer 2009. One-liter propylene bottles containing sodium thiosulfate, wrapped in aluminum foil and kept refrigerated (4 °C) until analysis were used. Stability of the samples was checked in order to ensure the reliability of the results.

Analytical methodology

The studied pharmaceuticals were analyzed using a previously reported SPE-LC-MS/MS method (Boleda et al. 2013). Briefly, 200 mL of water (1 % methanol) were enriched by SPE on Oasis-HLB cartridges (200 mg, 6 mL, Waters, Milford, MA, USA) at a flow rate of 10 mL/min. The cartridges were washed with 3 mL of water with 5 % aqueous MeOH and dried with nitrogen (5 min). Analytes were eluted using 8 mL of methanol, and the extract was evaporated to dryness and reconstituted in 500 μL of methanol/water solution (20:80). The final extract was filtered through 0.2 μm and was spiked with 10 μL of the mixed deuterated compounds solution (10 ng/μL). Quantitation was performed by external calibration using these deuterated compounds as internal standards and applying the recoveries obtained during method validation (Boleda et al. 2013).

LC-MS/MS procedure

Compounds were analyzed by UHPLC-MS/MS with a Waters Acquity ultra-performance™ liquid chromatograph system (Waters Corp. USA), coupled to a Quattro Micro™ triple quadrupole mass spectrometer (Micromass, Waters Corp., USA) with an electrospray ionization source Z-spray™ working in positive or in negative ionization mode, as described in the previously reported SPE-LC-MS/MS method (Boleda et al. 2013). Briefly, an Acquity BEH C18 column (100 mm×2.1 mm i.d., 1.7 μm particle size; Waters Corp. USA) was used; the sample volume injected was 10 μL, and the acquisition was performed in selected reaction monitoring (SRM) mode, using the Quanlynx™ software.

For those compounds analyzed in positive ESI mode, the separation was performed with a ternary mobile phase at a flow rate of 0.4 mL/ min. Solvent A, acetonitrile/methanol (2:1); solvent B, 6.5 mM ammonium acetate/acetic acid (pH 5.2). For compounds analyzed in negative ESI mode, a binary mobile phase, solvent A, methanol and solvent B, 6.5 mM ammonium acetate/acetic acid (pH 5.2) at a flow rate of 0.4 mL/ min was used (Boleda et al. 2013). Transitions, optimized MS/MS conditions, and allowed tolerances are summarized in Table S3 of the Electroni supplementary material.

UHPLC-HRMS procedure

Samples analyzed according to the procedure described above exhibiting presence of pharmaceuticals were subjected to liquid chromatography–high-resolution mass spectrometry (LC-HRMS) analysis using an Accela 1000 UHPLC pump (Thermo Fisher Scientific, CA, US) coupled to a Q-Exactive quadrupole-Orbitrap mass spectrometer (Thermo Fisher Scientific, US) equipped with a heated electrospray (H-ESI II) source working in positive and negative modes. Analytical column and mobile phase used in this system were the same as indicated above. Chromatographic separation was performed at a flow rate of 300 μL/ min with the following gradient elution: 0 min, 20 % A; 0–2.0 min, 20–50 % A; 2.0–6.67 min, 50–60 % A; 6.67–8.0 min, 60–90 % A; 8.0–10.67 min, 90–100 % A; 10.67–12.0 min. 100 % A and then returning to initial conditions.

Targeted-SIM (t-SIM) and targeted-MS/MS (t-MS2) modes were used for the acquisition of samples. In t-SIM mode, a quadrupole isolation width of 4 *m/z* and a scanning range from *m/z* 100 to *m/z* 1,000 at a mass resolving power of 70,000 FWHM (at *m/z* 200) were used. In t-MS2, ions selected (1 *m/z* window) were sent to the high-collision dissociation (HCD) cell for their fragmentation, and product ions were scanned in the Orbitrap at a mass resolving power of 17,500 FWHM (at *m/z* 200) in the range of 100 to 1,000 *m/z*. H-ESI II source conditions in positive mode were fixed as follows: spray voltage at +3.0 kV, sheath gas flow at 40 arbitrary units (au), auxiliary gas flow at 10 au, ion sweep gas at 0 au, heated capillary temperature at 320 °C, vaporizer temperature at 400 °C, S-lens frequency of 50 %. For H-ESI II in negative mode, the conditions were fixed as follows: spray voltage at −3.0 kV, sheath gas flow at 50 au, auxiliary gas flow at 0 au, ion sweep gas flow at 0 au, heated capillary temperature at 320 °C, vaporizer temperature at 400 °C, and S-lens frequency of 40 %. Nitrogen (>99.8 %) was used as desolvation and nebulization gas, as well as collision gas. The optimal HCD-normalized collision energies were: ibuprofen, 25 %; sulfametoxazole, 38 %; clarithromycin, 16 %; azithromycin,

30 %; and erythromycin, 22 %. Data were acquired and processed using the Xcalibur *v* 2.1 software package and Exact Finder *v* 2.0 for isotopic pattern score calculation, both from Thermo Fisher Scientific (CA, USA).

Validation and uncertainty estimation

A full validation of the method and an estimation of measurement uncertainty associated with quantitative results is given elsewhere (Boleda et al. 2013). Briefly, recoveries at a concentration of 100 ng/L were >80 % for 79 % of the studied compounds and the expanded relative uncertainties ranged from 6 to 23 % being the uncertainty associated with reproducibility in the main contribution. Limits of quantification for the studied pharmaceuticals were determined as described elsewhere (Boleda et al. 2013) and ranged from 0.2 to 30 ng/L (see Table S3).

Results and discussion

Analysis of pharmaceuticals in FDW from Spanish cities

In Spain, 66 % of the distributed water comes from surface waters and 34 % from groundwater. However, several cities along the Mediterranean coast are water deficient and use brackish or seawater as the main raw water source for potabilization processes. Spanish DWTPs employ a wide array of combinations of treatment steps but the most common consists of preoxidation with chlorine followed by coagulation, flocculation, and sedimentation; sand filtration; and post-chlorination. This is the process followed by 15 DWTPs which FDW have been analyzed. Alternative disinfectants (ClO_2) are still scarcely used as well as granular-activated carbon (GAC) or ozonization treatments which are restricted to those locations with low raw water quality. In our study, 14 DWTPs used some of the following potabilization processes: (a) Pre-oxidation (mainly Cl_2; ClO_2), coagulation, flocculation and sedimentation, sand filtration, O_3 (and/or) GAC, and post-chlorination, (b) pre-ozonation, coagulation, flocculation and sedimentation, ozonation, sand filtration, and post-chlorination. For brackish waters or seawater (3 DWTPs), the most common treatment applied consists of optional pre-oxidation (Cl_2), coagulation, flocculation and sedimentation, ultrafiltration (UF), desalination by reverse osmosis (RO), and final post-chlorination. For eight samples, no information about DWTP treatment was available.

FDW from the most important and populated Spanish cities which represent more than 12 million inhabitants were monitored at least once. For those larger cities which were monitored several times, results were averaged.

A summary of the occurrence of pharmaceuticals in Spanish FDW is shown in Table 2. Only five compounds out of 54 targeted (Fig. S1) were detected at measurable levels by LC-MS/MS (triple quadrupole system).

Pharmaceuticals of the alimentary tract and metabolism (ATC code: A)

This is one of the classes of pharmaceutical ingredients compiled by Daughton (2010) not reported to occur in drinking water. Nine compounds and two metabolites pertaining to three different ATC A classes (stomatological, acid-related disorders, and antidiarrheals) were monitored. None of them were found in FDW above their LOQs. Among them, miconazole, prednisone, chlorhexidine, and 5-desmethyl omeprazole are seldom studied and even less reported in Spanish rivers or FDWs (see Tables S1 and S2). Some representative compounds of this group such as ranitidine, famotidine, cimetidine, omeprazole, 4-hydroxy-omeprazole, and lansoprazole are currently monitored and identified in Spanish rivers (see Table S2 and references cited herein). However, they have been scarcely studied in Spanish (Boleda et al. 2011, 2013; Pedrouzo et al. 2008; Valcárcel et al. 2011a, 2013), European and American FDW (Stackelberg et al. 2004; Zuccato et al. 2000). In fact, of all compounds monitored in this group, only ranitidine has been identified once, at 0.6 ng/L, in finished waters of Spain (Gros et al. 2013). The absence of the targeted pharmaceuticals in the FDW studied in this survey can be attributed to that some of them contain primary and secondary amines in their chemical structures (ranitidine, famotidine, cimetidine, and chlorhexidine), which are prone to easily react with chlorine by electrophilic substitution (Deborde and von Gunten 2008) leading to the formation of nitrosamines and with ozone (e.g., omeprazole and metabolites and lansoprazole) to yield different disinfection by-products (von Gunten 2003; Boix et al. 2013). Carbadox, another compound of this group, which was neither identified in North-American (Kleywegt et al. 2011; Stackelberg et al. 2004) nor Spanish FDWs (Boleda et al. 2011, 2013), reacts with aqueous chlorine under typical drinking water treatment conditions to yield non-chlorinated, hydroxylated, and larger molecular weight by-products (Shah et al. 2006), which can preclude its presence in final treated water.

Pharmaceuticals of the cardiovascular system (ATC code: C)

Eight compounds of this group (bezafibrate, clofibric acid, fenofibrate, gemfibrozil, mevastatin, pravastatin, atorvastatin, and simvastatin) were analyzed. All FDW of this study presented concentration levels below the LOQ for the targeted pharmaceuticals of the cardiovascular system, although the studied compounds except mevastatin are currently found in Spanish rivers (see Table 1; Table S2) and worldwide (Hughes et al. 2013).

Table 2 Pharmaceuticals in Spanish finished drinking water (n=50)

ATC code	Pharmaceutical	LOQ	%U[a]	N>LOQ[b]	Max	Mean	90 % percentile[c]	HRMS confirmation
M01AE01	Ibuprofen	10	8.1	6	18.5	<LOQ	11.3	6/6
J01FA10	Azithromycin	0.9	10.9	5	9.5	0.9	2.2	3/5
J01FA09	Clarithromycin	0.2	8.8	5	2.2	0.2	0.7	0/5
J01FA01	Erythromycin	0.2	8.8	8	1.5	0.2	1.1	0/8
J01EC01	Sulfamethoxazole	1	9.8	1	1.4	<LOQ	<LOQ	0/1

Summary of rates of detection; maximum level, mean, 90th percentiles, and number of samples confirmed by HRMS. All values are expressed in nanograms per liter. *Pharmaceuticals not identified in any sample*: acetaminophen, amobarbital, amoxicillin, bezafibrate, butalbital, carbadox, chlorhexidine, chlorotetracycline, cimetidine , clofibric acid, diatrizoic acid, diclofenac, famotidine, fenofibrate, fenoprofen, gemfibrozil, hexobarbital, indomethacine, iopromide, iohexol, ketoprofen, lansoprazole , lincomycin, mefenamic acid, mevastatin, miconazole, naproxen, ofloxacin, olaquindox, omeprazole, oxytetracycline, pentobarbital, phenobarbital, pravastatin, prednisone, ranitidin, roxithromycin, salicylic acid, secobarbital, sildenafil, simvastatin, sulfadimethoxine, sulfamethazine, sulfamethoxazole, tetracycline, triclosan, trimethoprim, tylosin, 4-hydroxy omeprazole, 5-*O*-desmethyl omeprazole, and *N*-desmethyl sildenafil. Mean, and percentile are based on all samples analyzed and calculated using LOD/2 for < LOD values and LOQ/2 for < LOQ values

[a] %U expanded uncertainty in drinking water (Boleda et al. 2013)

[b] Number of samples with concentration levels > LOQ

[c] Percentile calculation according to NIST

Some compounds from this group, bezafibrate, clofibric acid, and gemfibrozil have been extensively found in FDW (Daughton 2010; Mompelat et al. 2009; Monteiro and Boxall 2010), but only the latter two compounds have been sporadically identified in Spanish-treated waters at maximum concentrations of 40 and 8 ng/L, respectively (Gros et al. 2013; Rodil et al. 2012). Other less studied compounds, atorvastatin and mevastatin have not been reported to occur in any FDW but fenofibrate was found in Dutch FDWs (see Table S1) (Versteegh et al. 2007). Clofibric acid does not react with chlorine (Quintana et al. 2010) although reactivity with chlorine dioxide (Huber et al. 2005) has been reported; it is poorly reduced (<40 %) with ozone and has a low adsorption capacity in carbon filters (Ternes et al. 2002) that makes it a recalcitrant compound and the most reported compound of this group in drinking waters (Daughton 2010). Maximum concentration ranges from 32 to 170 ng/L, in European FDW, and median values of 0.9–1.1 ng/L in American FDW, have been reported (see Table 1 and references cited herein). However, we were unable to find it at concentrations above its LOQ in line with the usual absence of colofibric acid in Spanish FDW (see Table 1). The high reactivity of gemfibrozil with chlorine (Bulloch et al. 2012; Krkosek et al. 2011; Westerhoff et al. 2005) and also its moderate reactivity with chlorine dioxide (Boleda et al. 2011) can explain their absence in the drinking waters analyzed. Bezafibrate, also not detected, reacts with ozone (Huber et al. 2003; Westerhoff et al. 2005), although it does not react with chlorine dioxide (Huber et al. 2005). It has been reported that pravastatin and simvastatin are eliminated by dioxychlorination in DWTPs (Boleda et al. 2011); both compounds have not been identified neither in Spain and Europe (see Table 1; Table S1) nor in USA drinking waters (Benotti et al. 2009).

Pharmaceuticals of the dermatological and genito-urinary system (ATC codes: D and G)

Two dermatological compounds, salicylic acid, triclosan, and sildenafil and its main metabolite *N*-desmethyl sildenafil of the urological ATC code G04 group were monitored. None of the four compounds was identified in the studied FDW. Salicylic acid is consistently found in Spanish river waters, but it has been scarcely found in FDWs (see Table 1), which can be related to the formation of mono- and dichloroderivatives of salicylic acid under chlorination conditions (Quintana et al. 2010). In Europe, maximum values of 122 ng/L in the Netherlands (Versteegh et al. 2007) and 19 ng/L in a French national survey (Vulliet et al. 2011) have been reported. Triclosan which is significantly oxidized by chlorine and ozone (Giri et al. 2010; McAvoy et al. 2002; Snyder 2008) has been frequently reported at concentrations below the LOQ in Spanish and European FDWs (see Table 1). Sildenafil which has been identified in wastewaters (Nieto et al. 2010) and surface waters is substantially removed by dioxychlorination (78 %) and fully eliminated after ozonation (Boleda et al. 2011). No previous data is available for its metabolite in the aquatic environment.

Pharmaceuticals of the anti-infectives for systemic use group (ATC codes: J and QJ)

The presence of pharmaceuticals of the J and QJ (for veterinary use) ATC codes has been extensively reported in Spanish (see Table 1; Table S2 and references cited herein) and worldwide rivers (Hughes et al. 2013) and in the aquatic environment (Kümmerer 2009a, b). Erythromycin, with maximum concentrations of 2 ng/L in Spanish (Boleda et al. 2011) and

155 ng/L in North-American FDW (Kleywegt et al. 2011) and sulfamethoxazole with maximum levels of 0.5 ng/L (Gros et al. 2013), 25 ng/L (Versteegh et al. 2007), and 20 ng/L (Snyder et al. 2007) in Spanish, European, and North-American FDW, respectively, are among the compounds of this group most frequently reported to occur worldwide in FDWs (Daughton 2010). On the contrary, amoxicillin, azithromycin, lincomycin, roxithromycin, sulfadimethoxine, tetracycline, trimethoprim, and tylosin, which are extensively studied in rivers (see Table 1) were not found in Spanish FDWs, and they are very rarely reported in American (i.e., roxithromycin and trimethoprim) and European FDWs (see Table 1; Table S1).

Azithromycin, clarithromycin, erythromycin, and sulfamethoxazole out of 14 targeted compounds of the J group and 2 of the QJ group were tentatively identified and confirmed (two SRM transitions and ion ratios tolerances) by UHPLC-MS/MS (triple quadrupole system) in five, five, eight, and one samples, respectively. Maximum concentrations ranged from 1.4 ng/L, for sulfamethoxazole to 9.5 ng/L, for azithromycin. Erythromycin was the pharmaceutical most frequently identified; 8 positive samples out of the 50 studied although with a low maximum level, 1.5 ng/L. To obtain alternative confirmation of the presence of the detected compounds, the positive samples were analyzed by UHPLC-HRMS using a quadrupole-Orbitrap instrument. t-SIM mode with a quadrupole isolation width able to include information from the isotopic cluster was used. Three of the five samples that resulted positive in azytromycin with the triple quarupole instrument could be confirmed with the quadrupole-Orbitrap t-SIM mode, obtaining mass accuracies ranging from −0.75 to −1.1 ppm for the protonated molecule. The fit for the isotopic pattern was scored in those positive samples and all of them were higher than 82 %. These results allowed confirming the presence of azytromycin in the three samples although the sensitivity of the MS/MS (t-MS2) mode was not enough for additional confirmation. The samples containing clarythromycin, erythromycin and sulfamethoxazole could not be confirmed by UHPLC-HRMS because of the low concentration level of these compounds in the samples.

The behavior of sulfamethoxazole and erythromycin in simulated drinking water treatments indicated that they are removed (>90 %) when chlorination and/or ozonation takes place (Westerhoff et al. 2005). Moreover, for those drinking water treatments using chlorine dioxide and/or ozone, the former reacts faster than chlorine with sulfonamide (i.e., sulfamethoxazole) and macrolide antibiotics (i.e., reacts at the tertiary amino group of roxithromycin) (Deborde and von Gunten 2008) and ozone has proved to be effective to oxidize a wide variety of antibiotics (Dodd et al. 2006; Huber et al. 2003). On the contrary, olaquindox did not react with chlorine (Shah et al. 2006).

Although the removal of antibiotics in conventional water treatment processes has been described (Adams et al. 2002), the data compilation of occurrence in worldwide FDW shows that the anti-infectives for systemic use are the second largest group of pharmaceuticals most frequently reported in FDW after those belonging to the nervous system (Daughton 2010).

Pharmaceuticals of the musculo-skeletal and nervous system (ATC codes: M and N)

Seven anti-inflammatory and antirheumatic (M01), one analgesic (N02) and six psycholeptic (N05) compounds were analyzed (see Fig. S2). Whereas compounds from the M01 and N02 groups are by far the most worldwide analyzed group of pharmaceuticals in FDWs and rivers (Daughton 2010; Hughes et al. 2013), much less information is reported about the presence of the barbiturate N05 compounds in the aquatic environment (Boleda et al. 2011; Peschka et al. 2006; Phillips et al. 2010) despite of their wide prescription. From the M01 group, ibuprofen has been the most profusely pharmaceutical determined in Spanish (max. 54 ng/L), European (max. 28 ng/L), and North-American (max. 1,350 ng/L) FDWs (Loraine and Pettigrove 2006; Boleda et al. 2013; Versteegh et al. 2007). This is in agreement with its low reactivity; ibuprofen reacts with chlorine and ozone in a moderate extent (<60 and 80 %) (Giri et al. 2010; Westerhoff et al. 2005), and no reactivity has been observed with chlorine dioxide (Huber et al. 2005; Von Gunten et al. 2006).

Ibuprofen was detected in six samples by UHPLC-MS/MS (triple quadrupole system) with a concentration range from 12 to 17 ng/L. However, the identification of this compound presented some problems since only one abundant ion (*m/z* 161) was observed in the triple quadrupole product ion mass spectrum (Fig. 1a) reducing the number of identification points needed for a suitable confirmation in UHPLC-MS/MS at low mass resolution. To confirm the presence of ibuprofen in these samples, UHPLC-MS/HRMS (quadrupole-Orbitrap) was used. When the triple-quadrupole-positive samples were analyzed by the t-SIM mode, good mass accuracies ranging from −0.65 to 0.67 ppm for the deprotonated molecule of ibuprofen were obtained and the fit for the isotopic pattern scores were always above 97 %. However, when acquiring the product ion mass spectrum, for the precursor ion *m/z* 205 (Fig. 1b), two product ions were obtained. The base peak was the ion at *m/z* 159 while the ion at *m/z* 161 showed only a relative abundance of 51 %. Both ions have been described in the literature as product ions of ibuprofen. In general, product ion at *m/z* 161 is generated in triple-quadrupole instruments (Gracia-Lor et al. 2010; Gros et al. 2006; Marchese et al. 2003; Nebot et al. 2007), whereas in ion trap analyzers, the main product ion is that at *m/z* 159 (Bandu et al. 2004; Grujić et al. 2009), suggesting that tandem in time, trapping, and storing the ions, favors the loss of 46 U (CH_2O_2)

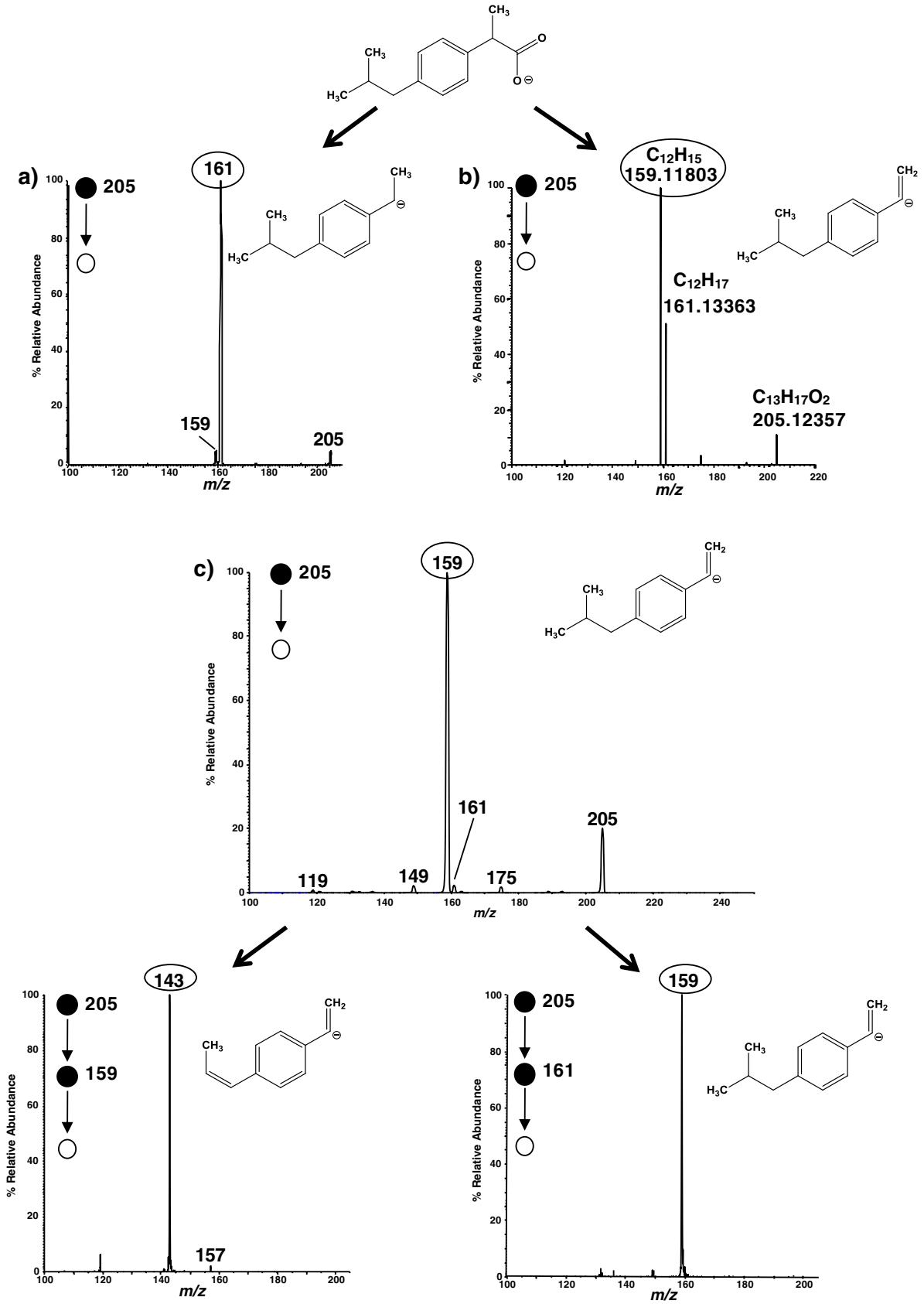

Fig. 1 Product ion mass spectra of ibuprofen: **a** triple quadrupole, **b** quadrupole-orbitrap, and **c** QTRAP instruments

instead of 44 U (CO_2), which is observed in the tandem in space of triple-quadrupole systems. The presence of the product ion at *m/z* 159 in the product ion spectrum of ibuprofen has also been observed when using hybrid instruments that allow trapping product ions before being released into the second mass analyzer (Marchese et al. 2003; Martínez Bueno et al. 2007). As an example in Fig. 1c, the product ion spectrum obtained in a triple-quadrupole-linear ion trap mass spectrometer (QTRAP Applied Biosystems, USA) is depicted to be working in enhanced product ion mode (EPI) (product ions are accumulated in the ion trap before the final *m/z* scan) where the ion at *m/z* 159 is the base peak of the mass spectrum. The MS^3 spectra obtained in the ion trap for both MS/MS product ions (Fig. 1c) showed that the ion at *m/z* 159 could originate from the product ion *m/z* 161 by the loss of two H. The formation of an additional double bond conjugated with the benzene ring (Fig. 1) could generate a product ion of high stability. The formation of the ion at *m/z* 159 in instruments with ion storage technology can be explained if it is regarded as a multistep process that involves the consecutive losses of CO_2 and 2H with a second step so slow that the ion can only be observed in instruments where the time to detect ions is long enough to allow this loss to take place. When working in tandem at HRMS, mass accuracies ranging from −0.15 to 0.35 ppm were obtained for the ibuprofen product ion at *m/z* 159 in the positive samples. The results obtained in HRMS in both acquisition modes (t-SIM and t-MS2) allowed to confirm the presence of this compound in these samples.

Diclofenac, naproxen, and indomethacine have not been found at measurable levels in the studied samples. The oxidation of these acidic pharmaceuticals with chlorine (Acero et al. 2010; Boyd et al. 2005; Deborde and von Gunten 2008; Quintana et al. 2010; Simazaki et al. 2008); chlorine dioxide (Hey et al. 2012; Huber et al. 2005) and ozone (Benitez et al. 2009; Giri et al. 2010; Vogna et al. 2004) has been already reported. These reactivities can explain their absence in the analyzed samples and the usual negative report data encountered in Spanish, American and also, although at much less frequently, in European FDWs (see Table 1). On the contrary, fenoprofen does not show significant elimination during chlorination (Quintana et al. 2010; Simazaki et al. 2008), dioxychlorination (Huber et al. 2005), or ozonation practices (Giri et al. 2010; Nakada et al. 2007). Ketoprofen and mefenamic acid react too slowly with chlorine to be significantly transformed during potabilization processes (Pinkston and Sedlak 2004; Quintana et al. 2010) and also exhibited either moderate removal or recalcitrance towards ozone degradation (Antoniou et al. 2013; Nakada et al. 2007). These three compounds which are often present in Spanish River waters were not identified in this survey but they are also seldom reported to occur globally in FDW (see Table 1). Another compound not identified was acetaminophen, an analgesic from the NO_2 group, which is easily oxidized with ozone (Rosal et al. 2010) and reacts extensively with chlorine to yield several transformation products, such as *N*-acetyl-*p*-benzoquinone imine and 1,4-benzoquinone (Bedner and MacCrehan 2006). Therefore, its presence in worldwide FDW is scarce (Table 1; Table S1), for instance, acetaminophen was only identified in one sample out of 44 corresponding to 22 European DWTPs monitored over 2 years (Versteegh et al. 2007). Among the psycholeptic compounds (NO_5 group), barbiturates are seldom monitored in FDW (see Table 1). Chlorination and recalcitrance to ozonation of phenobarbital have been described (Giri et al. 2010; Swindyard et al. 1963). Barbital, pentobarbital, and phenobarbital have been reported to occur more frequently in Dutch FDWs produced from bank filtrate than in those produced from surface water (Van der Aa et al. 2010). Full removal of phenobarbital was observed in a Spanish DWTP after ozonation in a conventional treatment line and also after reverse osmosis in an advanced parallel treatment line (Boleda et al. 2011).

Pharmaceuticals of the various group (ATC code: V)

Three compounds of the X-ray contrast media (group V08), diatrizoic acid, iohexol, and iopromide, were monitored. In Spanish rivers, only diatrizoic acid (max. 84 ng/L) and iohexol (max. 341 ng/L) have been reported (Boleda et al. 2011, 2013). Few studies about the presence of these compounds in FDWs have been carried out in Spain (Boleda et al. 2011, 2013) and North America (Snyder et al. 2007; Trenholm et al. 2006). Iopromide is the sole compound identified in both Spanish and North-American FDW with maximum concentrations of 84 and 31 ng/L, respectively (Boleda et al. 2011, 2013; Snyder et al. 2007). By contrast, at the European FDW level, X-ray contrast media compounds and their transformation products have been extensively monitored and are frequently encountered in FDW (Bruchet et al. 2005; Hirsch et al. 2000; Kormos et al. 2009, 2011; Seitz et al. 2006; Ternes 2001; Wenzel et al. 2003). For instance, transformation products of iomeprol and iopromide reached maximum values of 500 and 260 ng/L, respectively (Kormos et al. 2011) whereas monitored maximum concentrations of their parent compounds were 92 and 86 ng/L (Seitz et al. 2006; Ternes 2001). Iodinated X-ray compounds exhibited removals (<60 %) during chlorination, 64 % after ozonation, and 30 % elimination by powdered activated carbon in simulated DWTP conditions (Westerhoff et al. 2005), which is in agreement with the average removal of 70 % of nonionic X-ray found in a German DWTP (Seitz et al. 2006). Despite these antecedents and the relatively poor behavior of these compounds with the most common oxidants used in DWTPs, no X-ray compounds were identified in our survey, suggesting their absence in the raw waters used for potabilization

Conclusions

Fifty-three pharmaceuticals pertaining to 12 different ATC codes were analyzed by LC-MS/MS in 50 FDW samples from a national survey in Spain. The presence of the selected compounds in FDW was very scarce. Only few pharmaceuticals, one anti-inflamatory, ibuprofen, in 12 % of the samples and four anti-infectives, azithromycin, and clarithromycin in 10 % of the samples, erythromycin in 16 % of the samples, and sulfamethoxazole in 2 % of the samples, were detected at low concentration levels. To confirm the presence of these compounds, positive samples were tested by LC-HRMS using a quadrupole-Orbitrap instrument. Among the four anti-infectives detected by LC-MS/MS, only azithromycin could be confirmed by LC-HRMS, which was confirmed in three samples at concentration levels of 5 to 9.5 ng/L. The presence of ibuprofen with concentration ranges from 12 to 17 ng/L was confirmed by LC-HRMS in all positive samples. As regards the MS fragmentation patterns of the compounds studied, it was demonstrated that the most intense product ions of ibuprofen are dependent of instrument configuration: *m*/*z* 159 is mainly detected in instruments with ion storage capabilities while *m*/*z* 161 is observed in triple quadrupole instruments.

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