Occurrence of pharmaceuticals in hospital wastewaters and assessment of their associated environmental risk and hazard: a Spanish case study.

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G.I.D. en Toxicología Ambiental y Evaluación de Riesgos

Universidad Rey Juan Carlos

ICRAPHE
Paris, 8-9/9/2016

solutions

OUTLINE

- BACKGROUND
  - Hospital wastewaters as relevant sources of pharmaceuticals in the water cycle
  - Legislation
- OBJECTIVES
- METHODOLOGY
  - Sampling
  - Target compounds
  - Analysis
  - Environmental Risk Characterization
  - Environmental Hazard
- RESULTS AND DISCUSSION
- CONCLUSIONS

INTRODUCTION

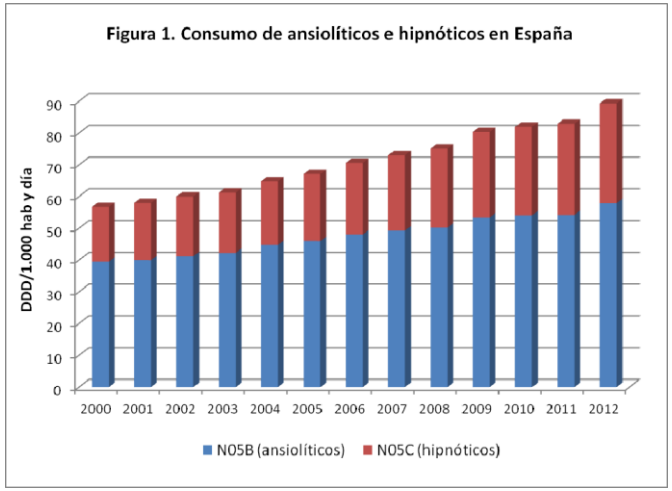
Current context

• Hospital wastewaters (HWWs) are a relevant source of pharmaceuticals (and their metabolites and transformation products) in the water cycle.

• However, to date, there are still important knowledge gaps with respect to the occurrence of various therapeutic groups in HWWs, the relative contribution of HWWs to the total load of pharmaceuticals entering wastewater treatment plants (WWTPs), and the associated environmental risks and hazard.

• These compounds are designed to have biologic activity and once in the environment they can provoke undesired effects in non-target organisms and become contaminants potentially hazardous, persistent and ubiquitous.

• Pharmaceutical spending has slowed down but consumption has increased (age and chronic diseases).



LEGISLATION

- No legal control over their discharge and/or environmental levels has been set up yet.

- **Decision 2015/495 – Watch List**

  → substances or groups of substances for which Union-wide monitoring data are to be gathered for the purpose of supporting future prioritisation exercises

  → substances for which the information available indicates that they may pose a significant risk, at Union level, to or via the aquatic environment, but for which monitoring data are insufficient to come to a conclusion on the actual risk posed.

Name of substance/group of substances	Max. MDL (ng/L)
17-Alpha-ethinylestradiol (EE2)	0.035
17-Beta-estradiol (E2), Estrone (E1)	0.4
Diclofenac	10
2,6-Ditert-butyl-4-methylphenol	3,160
2-Ethylhexyl 4-methoxycinnamate	6,000
Macrolide antibiotics*	90
Methiocarb	10
Neonicotinoids	9
Oxadiazon	88
Tri-allate	670

* Erythromycin , Clarithromycin, Azithromycin

Objectives

(i) to analyse the presence of 25 selected pharmaceuticals and one iodinated contrast media (ICM) in wastewater from a medium-size Spanish hospital

(ii) to compare the concentrations obtained with those reported in studies previously conducted in other areas, and

(iii) to preliminary characterise the environmental risk and hazard associated to the detected substances for aquatic ecosystems in order to set a list of “priority” pharmaceuticals to be considered in the potential up-grading of wastewater treatment technologies in hospitals or wastewater treatment plants (WWTPs) as well as in the adoption of future regulations concerning pharmaceuticals.

SAMPLING

. 5 HWW samples

- collected **daily** along five consecutive working days (1st week June 2013)
- every day three grab water samples were collected at 8 am, 4 pm and 8 pm and were combined to provide a final 12-h representative sample

. Hospital

- **medium-size university** hospital in Valencia Region (Spain)
- 1000 beds (total floor area of 260,000 m^2)
- wide range of medical specialities (311 wards & 39 operating rooms)
- service to 200,000 inhabitants
- average daily flow (June 2013) = 370 m^3 day^{-1}
- average water consumption (2013) = 500 L bed^{-1} day^{-1}.
- receiving WWTP (102,674 m^3 day^{-1}; 335,825 inhab.)

0.5% contribution

(grit, fat and grease removal, decantation, activated sludge, coagulation, flocculation, filtration and disinfection with UV)

TARGET COMPOUNDS (26)

Therapeutic group	Compounds	CAS number	Molecular formula	MDL[1] (ng L $^{-1}$)	MQL[2] (ng L $^{-1}$)
ANALGESICS AND ANTI-INFLAMMATORIES (AAF, 7)	Acetaminophen	103-90-2	$C_8H_9NO_2$	7.6	25.3
	Diclofenac	15307-86-5	$C_{14}H_{11}Cl_2NO_2$	4.3	14.3
	Ibuprofen	15687-27-1	$C_{13}H_{18}O_2$	7.2	24.0
	Indomethacin	53-86-1	$C_{19}H_{16}ClNO_4$	3.0	9.9
	Ketoprofen	22071-15-4	$C_{16}H_{14}O_3$	0.6	2.2
	Naproxen	22204-53-1	$C_{14}H_{14}O_3$	5.2	17.6
	Propyphenazone	479-92-5	$C_{14}H_{18}N_2O$	1.5	4.8
ANTIBIOTICS (AB, 5)	Clarithromicyn	81103-11-9	$C_{38}H_{69}NO_{13}$	0.5	1.8
	Ofloxacin	82419-36-1	$C_{18}H_{20}FN_3O_4$	3.7	12.5
	Sulfadiazine	68-35-9	$C_{10}H_{10}N_4O_2S$	4.4	14.6
	Sulfamethazine	57-68-1	$C_{12}H_{14}N_4O_2S$	4.9	16.3
	Trimethoprim	738-70-5	$C_{14}H_{18}N_4O_3$	0.6	2.2
β -BLOCKERS (BBL, 4)	Atenolol	29122-68-7	$C_{14}H_{22}N_2O_3$	4.7	15.7
	Metoprolol	37350-58-6	$C_{15}H_{25}NO_3$	0.9	2.9
	Propanolol	525-66-6	$C_{16}H_{21}NO_2$	0.8	2.7
	Sotalol	3930-20-9	$C_{12}H_{20}N_2O_3S$	5.0	16.7
DIURETICS (DIU, 2)	Furosemide	54-31-9	$C_{12}H_{11}ClN_2O_5S$	0.7	2.2
	Hydrochlorothiazide	58-93-5	$C_7H_8ClN_3O_4S_2$	0.1	0.2
IODINATED CONTRAST MEDIA (ICM)	Iomeprol	78649-41-9	$C_{17}H_{22}I_3N_3O_8$	4.2	14.0
LIPID REGULATORS (LIR, 2)	Bezafibrate	41859-67-0	$C_{19}H_{20}ClNO_4$	0.4	1.2
	Fenofibrate	49562-28-9	$C_{20}H_{21}ClO_4$	3.8	12.5
PDE-V INHIBITORS (PVI)	Sildenafil	171599-83-0	$C_{22}H_{30}N_6O_4S$	1.0	3.2
PSYCHIATRIC DRUGS TREATMENT (PDT, 4)	Carbamazepine	298-46-4	$C_{15}H_{12}N_2O$	0.3	1.1
	Diazepam	439-14-5	$C_{16}H_{13}ClN_2O$	0.5	1.5
	Lorazepam	846-49-1	$C_{15}H_{10}Cl_2N_2O_2$	1.4	4.7
	Paroxetine	61869-08-7	$C_{19}H_{20}FNO_3$	0.6	2.0

[1] MDL: Method Detection Limit
[2] MQL: Method Quantification Limit

Selection based on:
- high consumption by population,
- feasibility of analysis,
- interest for environmental health.

ANALYTICAL METHOD

25 Pharmaceuticals

• Sample preparation (100 mL):

- Filtration (0.7 glass fiber + 0.45 µm nylon)
- Addition of Na_2EDTA to 0.1%

IOMEPROL

• Sample preparation (100 mL):

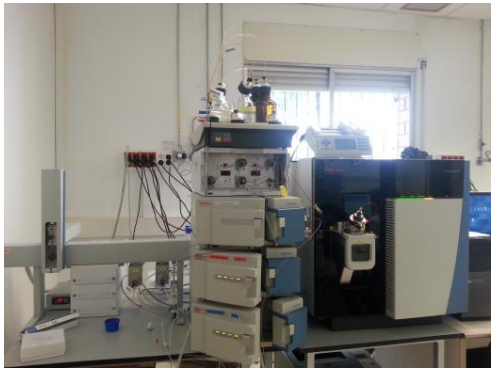
- Filtration (0.2 µm)
- Dilution with HPLC water (1:10)

• Solid phase extraction (SPE)

- Oasis HLB (200 mg, 6 mL, from Waters)
- Elution with 8 mL methanol
- Reconstitution with 1 mL of methanol/water 1/9 (v/v)
- Addition of isotopically labeled compounds for IS calibration (10 ng/mL)

• LC-MS/MS conditions*

- Column: Halo C-18 endcapped (50 mm × 2.1 mm, 2.7 µm)
- Mobile phase: gradient ACN/H20
  - ➢ with 0.1% HCOOH (PI) and 20mM of NH_4OAc (NI)
- Interfase: Electrospray
- Ion mode: PI (18 comp.) and NI (8 comp.)
- Acquisition mode: SRM (2 transitions per comp.)



Transcend LC-TSQ Vantage (Thermo, CA, U.S.A.).

*Gros et al. Anal. Chem. 2008, 81(3), 898-912 & Gros et al. J. Chromatogr. A 2012, 1248, 104-121.

Main exp. cond. & method performance

Name	RT (min)	Polarity	Parent (m/z)	Product 1 (m/z)	CE 1 (eV)	Product 2 (m/z)	CE 2 (eV)	Recoveries ± RSD (%)	r^2	MDL (ng/L)	MQL (ng/L)
Negative ionization mode											
Bezafibrate	4.8	-	360.1	274.0	19	153.9	30	131 ±3	0.9987	0.4	1.2
Diclofenac	5.4	-	293.9	250.0	14	214.0	30	93 ±1	0.9976	4.3	14.3
Furosemide	4.4	-	328.9	204.9	22	285.0	14	117 ±6	0.9995	0.7	2.2
Hydrochlorothiazide	3.3	-	295.7	205.0	22	269.0	19	88 ±4	0.9969	0.1	0.2
Ibuprofen	5.3	-	205.0	161.4	7	-	-	86 ± 11	0.9909	7.2	24.0
Indomethazine	5.5	-	356.0	312.1	12	291.1	20	69 ±11	0.9911	3.0	9.9
Ketoprofen	4.6	-	252.9	209.4	9	-	-	128 ±7	0.9956	0.6	2.2
Naproxen	4.5	-	229.1	169.1	33	185.0	8	112 ±1	0.9995	5.2	17.6
Positive ionization mode											
Acetaminophen	2.5	+	152.0	110.0	14	65.0	30	122 ±12	0.9971	7.6	25.3
Atenolol	4.3	+	267.0	145.1	25	190.1	16	108 ±4	0.9998	4.7	15.7
Carbamazepine	10.5	+	237.0	194.1	19	193.1	33	62 ±6	0.9958	0.3	1.1
Clarithromycin	10.4	+	748.4	157.9	29	590.0	15	129 ±1	0.9995	0.5	1.8
Diazepam	11.0	+	284.9	193.1	30	154.0	26	111 ±1	0.9968	0.5	1.5
Fenofibrate	12.0	+	361.9	234.0	14	139.0	7	68 ±6	0.9972	3.8	12.5
Iomeprol	1.6	+	777.9	405.1	32	531.9	37	89 ±12	0.9974	4.2	14.0
Lorazepam	10.7	+	322.9	277.0	20	305.0	11	125 ±3	0.9962	1.4	4.7
Metoprolol	8.0	+	268.0	116.1	17	191.1	16	105 ±3	0.9993	0.9	2.9
Ofloxacin	7.2	+	361.9	318.1	19	261.1	29	117 ±8	0.9968	3.7	12.5
Paroxetine	10.3	+	330.0	192.1	19	70.1	30	60 ±7	0.9975	0.6	2.0
Propranolol	10.0	+	260.0	183.1	16	157.1	19	139 ±4	0.9959	0.8	2.7
Propyphenazone	10.6	+	231.0	189.1	19	56.0	33	75 ±1	0.9986	1.5	4.8
Sildenafil	10.5	+	475.2	283.1	37	58.0	35	88 ±12	0.9962	1.0	3.2
Sotalol	2.5	+	273.0	133.1	26	255.1	7	118 ±1	0.9999	5.0	16.7
Sulfadiazine	3.1	+	251.0	156.0	16	92.0	27	115 ±14	0.9990	4.4	14.6
Sulfamethazine	6.9	+	278.9	205.0	14	132.1	28	89 ±6	0.9977	4.9	16.3
Trimethoprim	6.8	+	291.0	230.1	22	261.1	24	61 ±8	0.9969	0.6	2.2

* Linearity: $r^2 > 0.99$ (0.5 (or LOQ if higher) - 500 ng/mL)

* Sensitivity: MDLs < 5 ng/L for most compounds

* Accuracy: absolute recoveries > 60%

* Repeatability: relative standard deviations < 15%

Environmental Risk Characterization

- **Hazard Quotient* = MEC/PNEC**
  - MEC = Measured Environmental Concentration

worst case scenario → max. conc. / 0.5 MQL

  - PNEC = Predicted no effect concentration

PNEC values were derived from the available aquatic toxicity data (NOEC, L(E)C50, QSAR, ECOSAR)** for three different species representative of different trophic levels (*algae, crustaceans and fish*), applying the pertinent Assessment Factors (AFs).

*European Commission 2003. Technical Guidance Document on Risk Assessment in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances, and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. Part II: Environmental Risk Assessment. Office for Official Publications of the European Communities, Luxembourg.

**EMEA 2006. Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. The European Agency for the Evaluation of Medicinal Products:Committee for Medical Products for Human Use; EMEA/CHMP/SWP/4447/00.

Ecotoxicological data (mg/L)

Compound	Algae	Cladocerans	Fish	Selected	Data	AF	PNEC	References
AAF								
Acetaminophen	*134*[1]	*2.04*	*>160*	2.04	EC50	1000	2.04E-03	Dave and Herger, 2012; Henschel et al., 1997; Kim et al., 2007;
Diclofenac	**10**[2]	**10**	**0.0005**	0.0005	NOEC	10	5.00E-05	Ferrari et al., 2003; Hoeger et al., 2005; Quinn et al., 2011
Ibuprofen	**2**	**20**	**0.0001**	0.0001	NOEC	10	1.00E-05	Han et al., 2006; Han et al., 2010; Yamamoto et al., 2007
Indomethacin	**2.9**	*16.14*	*44*	2.9	NOEC	100	2.90E-02	Kim et al., 2009; Yamamoto et al., 2007
Ketoprofen	*2*	*2.3*	32*[3]	2	EC50	1000	2.00E-03	Harada et al., 2008; Sanderson et al., 2003
Naproxen	*3.7*	0.33	*52*	0.33	EC50	1000	3.30E-04	Harada et al., 2008; Isidori et al 2005a; Straub and Stewart, 2007
Propyphenazone	1*	3.5*	0.8*	0.8	EC50	1000	8.00E-04	Sanderson et al., 2003
ABI								
Clarithromicyn	0.002	**0.0031**	*>100*	0.002	EC50	100	2.00E-05	Isidori et al., 2005b; Kim et al., 2009; Yamashita et al., 2006
Ofloxacin	**0.005**	3.13	**>16**	0.005	NOEC	50	1.00E-04	Ferrari et al., 2004; Isidori et al., 2005b
Sulfadiazine	*0.135*	1.884*	1516.102*	0.135	EC50	1000	1.35E-04	Holten-Lutzhoft et al., 1999; ECOSAR (This study)
Sulfamethazine	**1**	**1.563**	*>100*	1	NOEC	50	2.00E-02	De Liguoro et al., 2009; Kim et al., 2007; Yang et al., 2008
Trimethoprim	**16**	**3.12**	**25**	3.12	NOEC	10	3.12E-01	De Liguoro et al., 2012; Yang et al., 2008
BBL								
Atenolol	**10**	*33.4*	**1**	1	NOEC	50	2.00E-02	Fraysse and Garric, 2005; Winter et al., 2008; Yamamoto et al., 2007;
Metoprolol	*7.3*	**6.15**	*>100*	6.15	NOEC	100	6.15E-02	Cleuvers, 2003; Dzialowski et al., 2006; Hugget et al., 2002
Propanolol	**0.10**	**0.001**	**0.0005**	0.0005	NOEC	10	5.00E-05	Hugget et al., 2002; Yamamoto et al., 2007;
Sotalol	26.386*	*>300*	616.625*	26.386	EC50	1000	26.39E-03	Hernando et al., 2004; ECOSAR (This study)
DIU								
Furosemide	*142*	**0.156**	*497*	0.156	NOEC	100	1.56E-03	Christensen et al., 2009; Isidori et al., 2006
Hydrochlorothiazide	*34.35*	477*	2428.571*	34.35	EC50	1000	34.35E-03	Fernandez et al., 2010; Ginebreda et al., 2012; ECOSAR (This study)
ICM								
Iomeprol	881.051*	271000*	49277.332*	881.051	EC50	1000	88.11E-02	ECOSAR (This study)
LIR								
Bezafibrate	60	**0.023**	5.3*	0.023	NOEC	100	2.30E-04	Isidori et al., 2007; Sanderson et al., 2003
Fenofibrate	**3.12**	**0.039**	0.8*	0.039	NOEC	50	7.80E-04	Isidori et al., 2007; Sanderson et al., 2003
PVI								
Sildenafil	13445.509*	1014.658*	2.99E05*	1014.658	EC50	1000	1.015	ECOSAR (This study)
PDT								
Carbamazepine	**6.4**	**0.025**	**25**	0.025	NOEC	10	2.50E-03	Ferrari et al., 2003; Yamamoto et al., 2007
Diazepam	*16.5*	*4.2*	*12.7*	4.2	EC50	1000	4.20E-03	Calleja et al., 1993; Nunes et al., 2005
Lorazepam	1.683*	12.8*	43.467*	1.683	EC50	1000	16.83E-04	Ginebreda et al., 2012; ECOSAR (This study)
Paroxetine	*0.14*	**0.22**	3.293*	0.14	EC50	100	1.40E-03	Christensen et al., 2007; Henry et al., 2004; ECOSAR (This study)

[1] Values in italics represent Short Term L(E)C50.
[2] Values in bold represent Long Term NOEC.
[3] Values with * represent predicted QSAR values.
[4] Underlined values represent Chronic Toxicity L(E)C50.

AF = 1000 (at least one short-term L(E)C50)
AF = 100 (one long-term NOEC for either algae, crustaceans or fish)
AF = 50 (two long-term NOEC for two different trophic levels)
AF = 10 (three long long-term NOECs)

Mendoza A. et al. (2015) Environmental Research 140: 225-241

Environmental Risk Characterization

- **Individual compounds**
  - HQ < 0.1 → insignificant risk (no adverse effect expected)
  - HQ = 0.1-1 → low risk (potential adverse effects)
  - HQ = 1 – 10 → moderate risk (probable adverse effect)
  - HQ > 10 → high risk

- **Mixtures (therapeutic groups)**

  TUs (Toxic Units) = ∑ HQ

  for each compound within a given therapeutic group in each sample assuming that they possess a similar toxicological mode of action.

ENVIRONMENTAL HAZARD

The environmental hazard of a substance:

- derives from its inherent environmentally damaging characteristics in terms of persistence, bioaccumulation and toxicity
- expresses its inherent capacity to adversely affect the environment

PBT index

- adapted from the method originally formulated by the Stockholm County Council*
- each of the characteristics of persistence, bioaccumulation and toxicity is assigned a numerical value (0 or 3), and the sum of these values constitutes the PBT index for the substance.
- the PBT value can therefore be equal to 0, 3, 6 or 9
- the higher the value the greater the potential of the substance to danger the environment.

Wennmalm Å and Gunnarsson B. Drug Inf. J. 2005, 39, 291-7.

PBT index

Persistence:

- ability of a substance to resist degradation in the aquatic environment (according to the OECD's test guidelines (OECD, 1992; test 301)
- P = 0 (readily biodegradable comp.); P = 3 (not readily biodegradable comp.)

Bioaccumulation:

- accumulation in the adipose tissue of aquatic organisms (according to the OECD's test guidelines (OECD, 1995, 2004; tests 107 and 117)
- B = 0 (log Kow < 3); B = 3 (log Kow > 3)

Toxicity:

- potential of a substance to poison aquatic organisms (based on the compiled aquatic toxicity data, the lowest value among the three groups)
- T = 3 (long-term NOEC < 0.01 mg L^{-1} or short-term L(E)C50 < 0.1 mg L^{-1})*

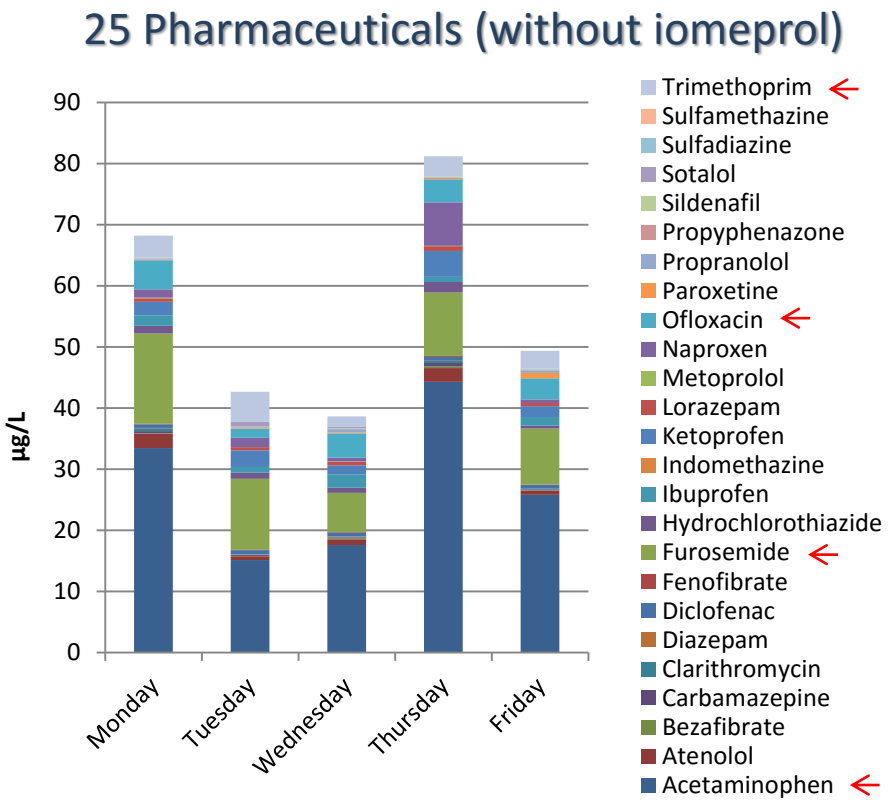
Mendoza A. et al. (2015) Environmental Research 140: 225-241

*European Commission 2003. Technical Guidance Document on Risk Assessment. Office for Official Publications of the European Communities, Luxembourg.

RESULTS - MECs

- Twenty-four out of the twenty-six compounds analysed were quantified (indomethacin (AAF) < MQL, sulfamethazine (AB) < MDL)
- Individual conc. = 5 ng/L - 2 mg/L
- The highest conc. corresponded to :
  - iomeprol (ICM) = 424-2093 µg/L
  - acetaminophen (AAF) = 15-44 µg/L
  - furosemide (DIU) = 6-15 µg/L
  - ofloxacin (AB)
  - trimethoprim (AB)

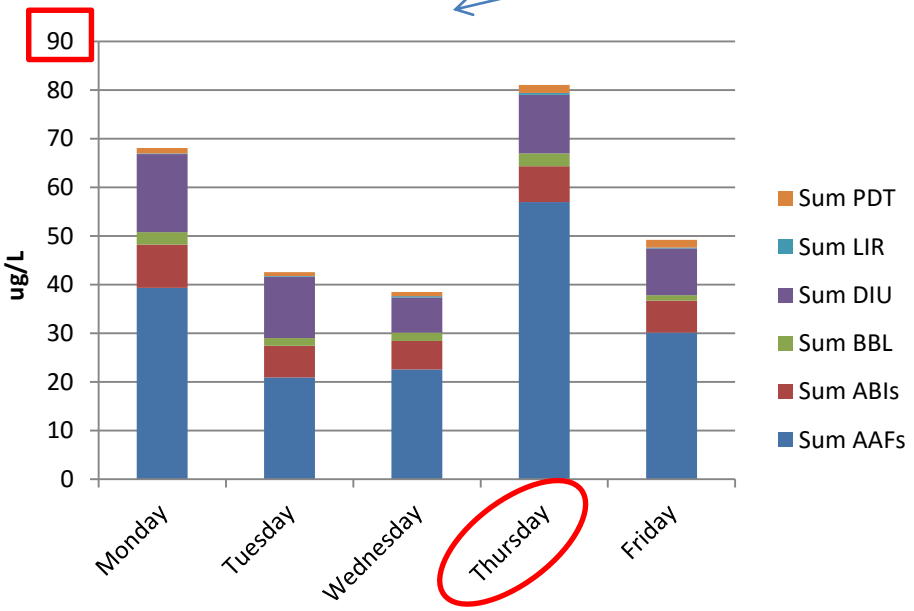
  (2-5 µg/L)
- The lowest concentrations corresponded to:
  - propyphenazone (AAF) = 5-44 ng/L)



RESULTS - MECs

Cumulative concentrations of pharmaceuticals
(grouped by therapeutic class)

without iomeprol



with iomeprol

- The **mass load of pharmaceuticals** discharged by the hospital was on average **598 mg bed^{-1} day^{-1} (> 0.5 Kg day^{-1}).**

- Knowledge on the concentration of pharmaceuticals HWWs is **important** because it cannot actually be calculated from the **prescription data: outpatient** surgery is relevant and the pharmaceuticals administered to the patients at the facility may easily be excreted at home.

RESULTS – Comparison other studies

- **Differences** in terms of concentrations of the analysed compounds have been observed in all the therapeutic groups when comparing the results obtained in this and other recent studies carried out in hospitals with different characteristics from diff. geographical areas and in diff. seasons.
- **Three factors** have been analysed as potential reasons for these divergences: differences in pharmaceutical prescriptions (among countries and among practitioners), diverse characteristics of the hospitals (size of the facilities in terms of number of beds and population served, average daily flow rate, water consumption and medical specialities available), and finally season in which the study is conducted.
- **Concentrations** depend on prescription, but also other factors, such as average flow rate, water consumption, season, number of beds, specialities in the hospital, etc.
- **Pharmaceutical mass loads** were calculated and compared among studies with aspects such as the type and size of the monitored hospitals.

Comparison with other hospitals - AAFs

- one of the most widely used therapeutic groups in Spain
- ↑ consumption in Spain: 38.7 (2000) → 49 (2012) DDD per 1000 people (+ 26.5%)
- conc.: acetaminophen is the most abundant
- load: the size of the hospital appears to be a determinant factor when comparing different hospitals from the same country, with smaller hospitals having higher mass loads
- inverse relationship found between the size of the facilities and the rate of water consumption per day and bed.

THERAPEUTIC GROUP	COMPOUNDS	Australia[1]	France[2]	Italy[3]	Korea[4]	Mexico[5]	Norway[6]	Portugal[7]	Spain[8]	Sweden[9]	Taiwan[10]
AAF	Acetaminophen	N.A.[11]	56111 (F) 98846 (M)	4500 (HAS) 4100 (HBS) 2500 (HBW)	N.D.[12]	N.A.	58372 (UH) 329852 (RH)	27700 (UH) 24687 (GH) 18235 (PH) 9211 (MH)	5020	N.A.	36950 62250
	Diclofenac	N.A.	11 (F) <1 (M)	300 (HAS) 220 (HBS) 510 (HBW)	161	N.A.	819 (UH) 2737 (RH)	80.8 (UH) <MQL (GH) 46.6 (PH) 47 (MH)	1400	N.A.	286 328 (Max 70000)
	Ibuprofen	N.A.	1614(F) 1729 (M)	1700 (HAS) 600 (HBS) 2600 (HBW)	N.A.	N.A.	499 (UH) 2440 (RH)	1965 (UH) 3082 (GH) 7090 (PH) 7728(MH)	19770	N.A.	282 119
	Indomethacin	N.A.	N.A.	2500 (HAS) 2200 (HBS) 530 (HBW)	N.A.	N.A.	N.A.	<MDL (UH) <MQL (GH) N.D. (PH) <MDL (MH)	N.A.	N.A.	N.A.
	Ketoprofen	N.A.	401 (F) 143 (M)	5000 (HAS) 1100 (HBS) 1400 (HBW)	N.A.	N.A.	N.A.	99.3 (UH) 1107 (GH) 124 (PH) 146 (MH)	N.A.	N.A.	N.D.
	Naproxen	N.A.	N.A.	2300 (HAS) 410 (HBS) 4900(HBW)	309	N.A.	N.A.	1837 (UH) 608 (GH) 674 (PH) 504 (MH)	N.A.	N.A.	470 698
	Propyphenazone	N.A.	N.A.	11 (HAS) <LOD (HBS) 38 (HBW)	N.A.	N.A.	N.A.	<MQL (UH, GH, PH, MH)	N.A.	N.A.	N.A.

Comparison with other hospitals - ABs

- one of the groups with highest loads coming from hospitals
- important because of its role in the introduction of microorganisms multi-resistant to antibiotics into public wastewaters
- conc.: variable among studies, but ofloxacin (80% excretion rate) and trimethoprim (60% excretion rate and persistent) more abundant
- load: clear seasonal use (higher in winter)

THERAPEUTIC GROUP	COMPOUNDS	Australia[1]	France[2]	Italy[3]	Korea[4]	Mexico[5]	Norway[6]	Portugal[7]	Spain[8]	Sweden[9]	Taiwan[10]
ABI	Clarithromicyn	N.A.	N.A.	60 (HAS) 58 (HBS) 11000 (HBW)	N.A.	N.A.	N.A.	62.6 (UH) 7.56 (GH) 135 (PH) 32.5 (MH)	N.A.	N.A.	721
	Ofloxacin	N.A.	N.A.	19000 (HAS) 3700 (HBS) 31000 (HBW)	N.A.	25500 (H1) 34500 (H2) 35500 (H3)	N.A.	12222 (UH) 7303 (GH) 104 (PH) <MDL (MH)	N.A.	200-7600	1088
	Sulfadiazine	N.A.	N.A.	32 (HAS) 100 (HBS) 330 (HBW)	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	50
	Sulfamethazine	N.A.	N.A.	7 (HAS) <LOD (HBS) 23 (HBW)	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.D. N.D.
	Trimethoprim	300	N.A.	1200 (HAS) 650 (HBS) 180 (HBW)	29 (Maximum 95100)	2900 (H2) 5000 (H1)	4302 (UH) 3896 (RH)	1849 (UH) 528 (GH) 337 (PH) 13.5 (MH)	25	600-7600	1040

Study carried out in August 2009 (S, summer) and in March 2010 (W, winter). Hospital A (HA), 300 beds, 5,000 population (seven times higher in summer); Hospital B (HB), 900 beds, 135,000 population.

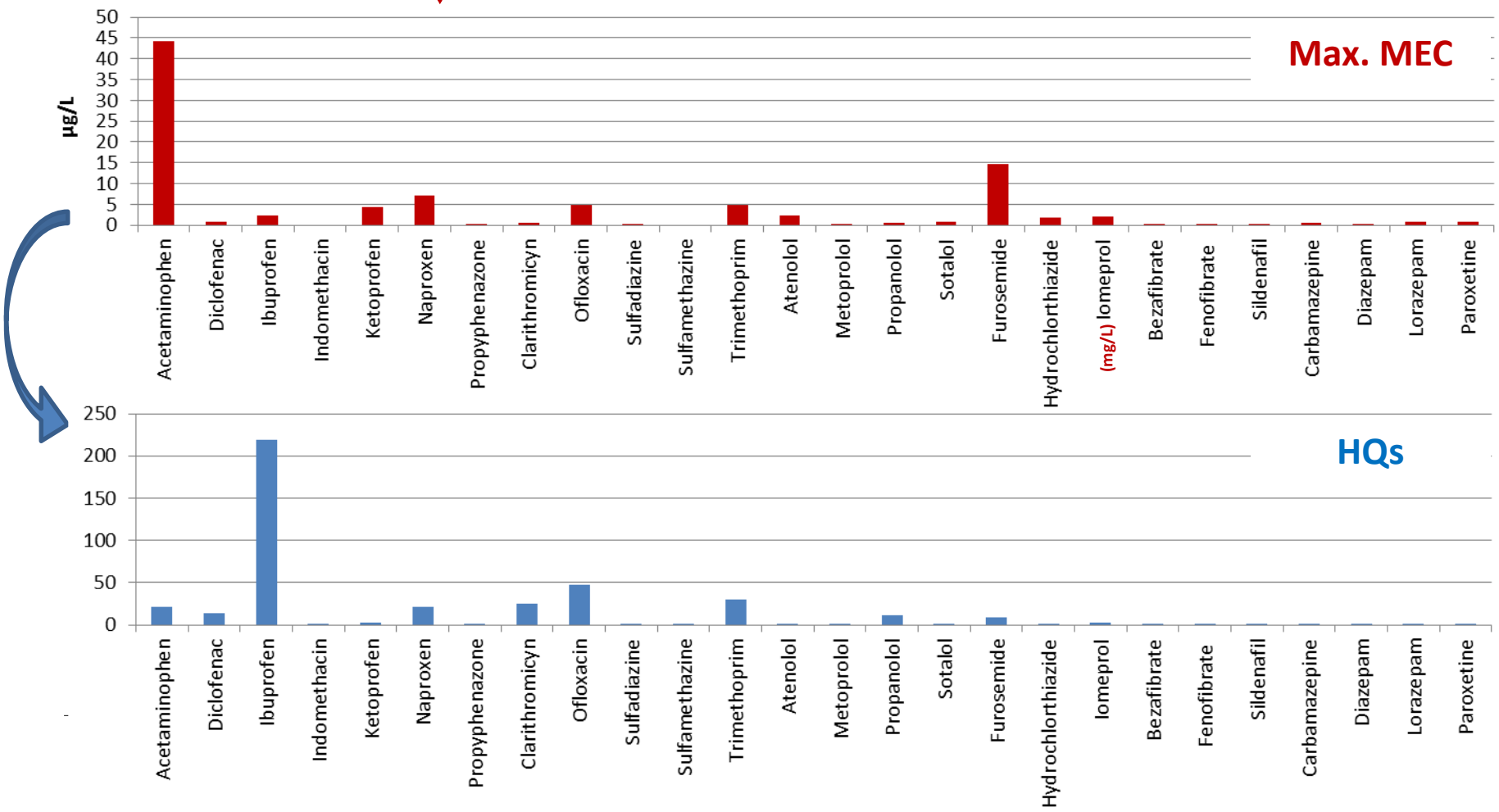
Comparison with other hospitals – other classes

- BBLs (atenolol, metoprolol, propanolol, sotalol):
  - widely used to lower hypertension, relieve chest pain and prevent heart attacks
  - profile dominated by atenolol in all studies (excretion rate > 70%)
  - winter > summer
- DIUs (furosemide and hydrochlorothiazide):
  - similar results in other studies
  - small hospitals > large hospitals
  - both furosemide and hydrochlorothiazide have excretion rates > 75%
- LIRs (bezafibrate, fenobibrate):
  - differences among studies
  - no clear trends
- PDE-V inhibitors (sildenafil):
  - treatment of erectile disfunction (viagra) and pulmonary hypertension
  - found in all samples
  - no other data for comparison
- PDTs (carbamazepine, diazepam, lorazepam, paroxetine):
  - differences among studies
  - differences in prescription (dosages and duration)
- ICM (iomeprol):
  - most frequently used pharmaceuticals in hospitals (for diagnosis)
  - iomeprol > other ICM

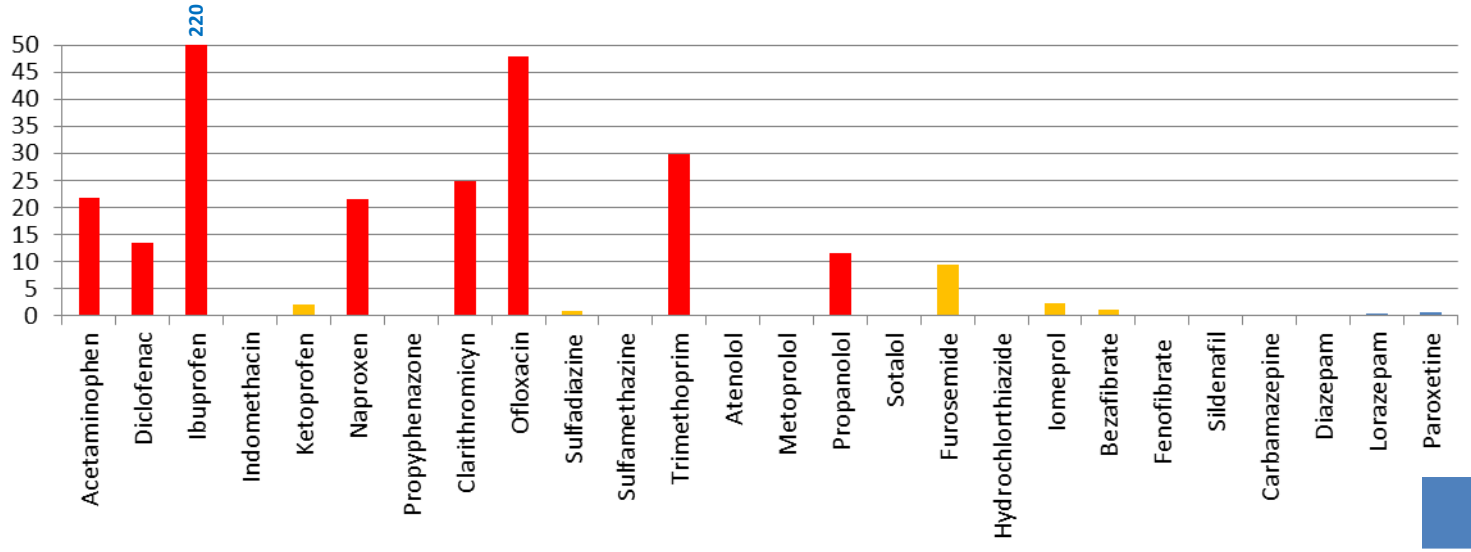
ERA results – Hazard Quotients

HQ = MEC/PNEC ← lowest ecotoxicological value

highest level detected ← worst possible case scenario



ERA results – Hazard Quotients



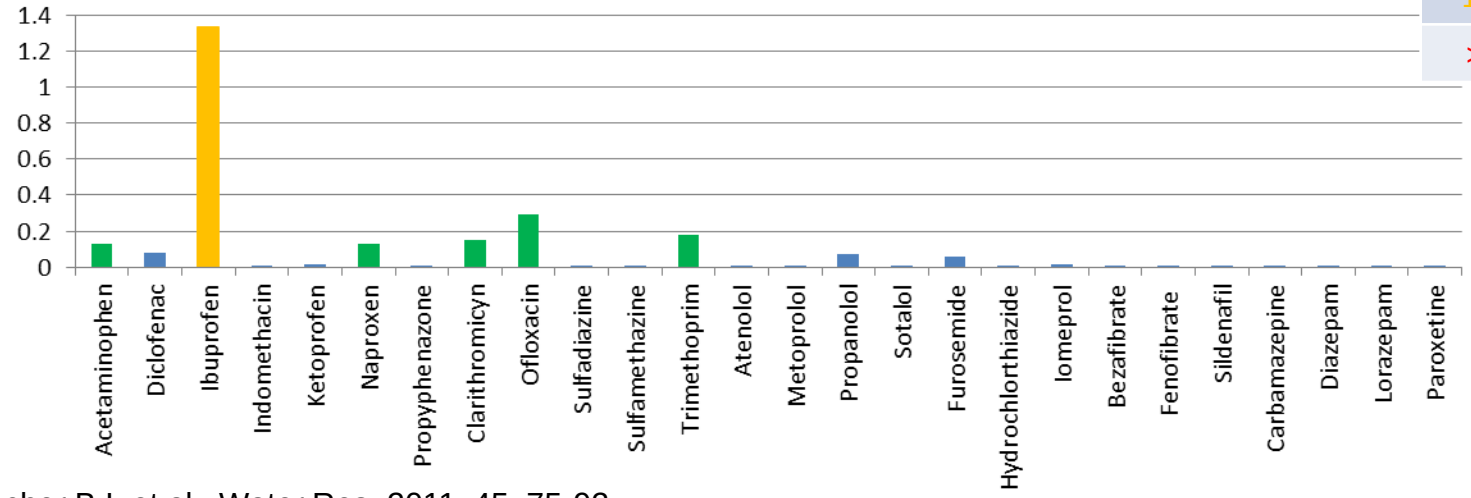
8 comp. HQ>10

5 comp. HQ 1-10

5 comp. HQ 0.1-1

----- dilution and degradation processes -----

HQ	RISK
<0,1	NEGLIGIBLE
0,1-1	LOW
1-10	MODERATE
>10	HIGH



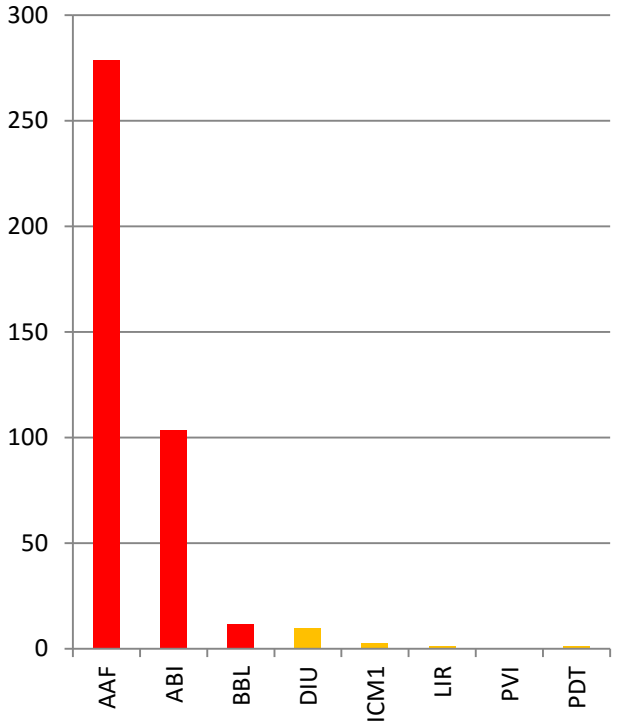
1 comp. HQ 1-10

5 comp. HQ 0.1-1

* Escher B.I. et al. Water Res. 2011, 45, 75-92.

ERA results – Toxicity Units

TUs = ∑ HQ

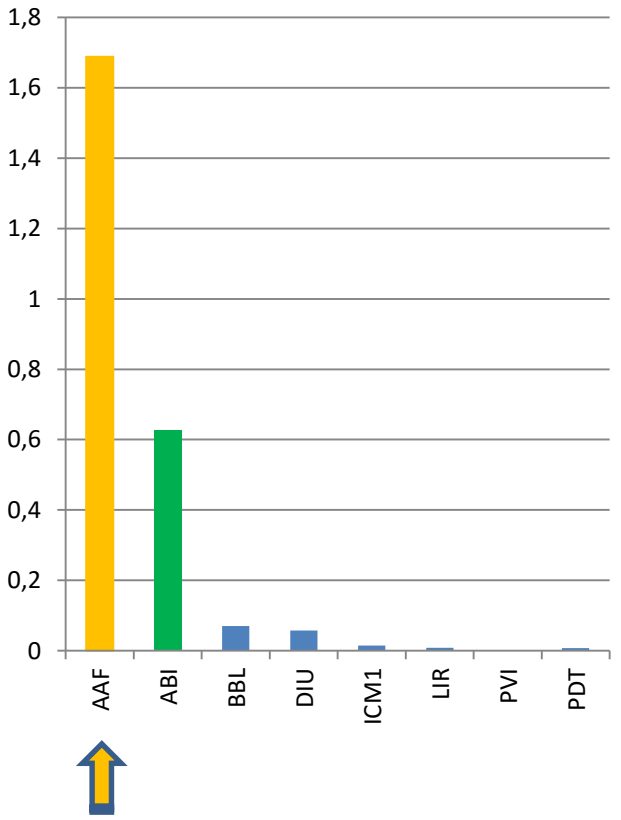


7 families with HQ >1

dilution

removal

degradation



* Escher B.I. et al. Water Res. 2011, 45, 75-92.

solutions

Environmental hazard – PBT index

- 9 for the AAFs diclofenac and ibuprofen and the ABI clarithromycin (great potential to danger the environment)

Therapeutic group	Compound	Log Kow[1]	P[2]	B	T	PBT Index	Env.Risk
ANALGESICS AND ANTI-INFLAMMATORIES (AAF)	Acetaminophen	0.46 (EXP)	3	0	0	3	HIGH
	Diclofenac	4.51 (EXP)	3	3	3	9	HIGH
	Ibuprofen	3.97 (EXP)	3[3]	3	3	9	HIGH
	Indomethacin	4.27 (EXP)	3	3	0	6	INSIGNIFICANT
	Ketoprofen	3.12 (EXP)	3	3	0	6	MODERATE
	Naproxen	3.18 (EXP)	3	3	0	6	HIGH
	Propyphenazone	1.94 (EXP)	3[4]	0	0	3[4]	INSIGNIFICANT
ANTIBIOTICS (ABI)	Clarithromycin	3.16 (EXP)	3	3	3	9	HIGH
	Ofloxacin	-0.39 (EXP)	3	0	3	6	HIGH
	Sulfadiazine	-0.09 (EXP)	3[5]	0	0	3	MODERATE
	Sulfamethazine	0.19 (EXP)	3[6]	0	3	6	LOW
	Trimethoprim	0.91 (EXP)	3	0	3	6	HIGH
β -BLOCKERS (BBL)	Atenolol	0.16 (EXP)	3[4]	0	0	3[4]	LOW
	Metoprolol	1.88 (EXP)	3	0	0	3	INSIGNIFICANT
	Propranolol	3.48 (EXP)	0	3	3	6	HIGH
	Sotalol	0.24 (EXP)	3	0	0	3	INSIGNIFICANT
DIURETICS (DIU)	Furosemide	2.03 (EXP)	3	0	0	3	MODERATE
	Hydrochlorothiazide	-0.07 (EXP)	3	0	0	3	INSIGNIFICANT
IODINATED CONTRAST MEDIA (ICM)	Iomeprol	-2.79 (EXP)	3	0	0	3	MODERATE
LIPID REGULATORS (LIR)	Bezafibrate	4.25 (EST)	3	3	0	6	MODERATE
	Fenofibrate	5.19 (EST)	3	3	0	6	LOW
PDE-V INHIBITORS (PVI)	Sildenafil	2.5 (EST)	0	0	0	0	LOW
PSYCHIATRIC DRUGS TREATMENT (PDT)	Carbamazepine	2.45 (EXP)	3	0	0	3	LOW
	Diazepam	2.82 (EXP)	3[4]	0	0	3[4]	INSIGNIFICANT
	Lorazepam	2.39 (EXP)	3[4]	0	0	3[4]	LOW
	Paroxetine	3.95 (EST)	3	3	0	6	LOW

1 Source: SRC/Physprop (2014). EXP means Experimental Data; EST means Estimated Data. 2 Data from Environmentally Classified Pharmaceuticals. 2014-2015. Stockholm County Council. 3 Girardi et al. (2013). 4 Assessment is uncertain due to lack of data. 5 Hektoen et al.(1995). 6 De Liguoro et al.(2009).

CONCLUSIONS

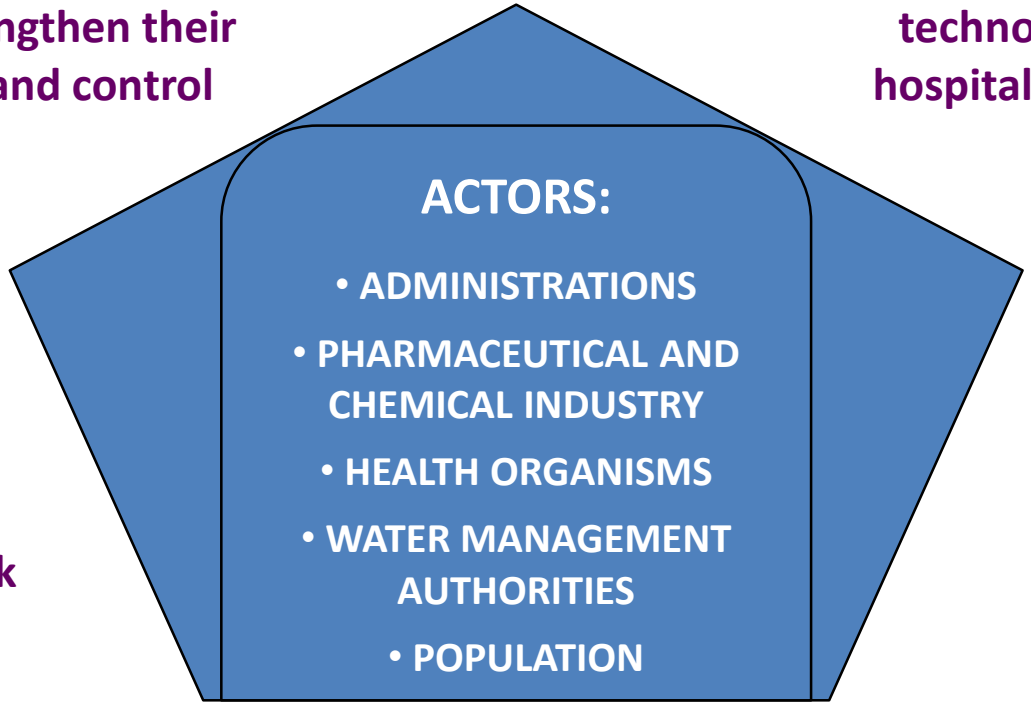
- Some pharmaceuticals found to be present in HWWs show **potential to cause negative effects** on aquatic organisms in the receiving water bodies and should be subject to control and eventual attenuation measures.
- The most dangerous pharmaceuticals are the **AAAs ibuprofen, diclofenac* and naproxen, the ABs clarithromycin*, ofloxacin and trimethoprim, and the BBL propanolol**.
- The **approach** presented can be used to categorize and prioritize pharmaceuticals on the basis of their occurrence in hospital effluents, their derived environmental risks, and their associated environmental hazard.
- This classification may be **useful for hospitals** in the process of developing environmentally sustainable policies and as an argument to justify the adoption of advanced, specific treatments for hospital effluents before being discharged into the public sewage system.

*Watch List

POSSIBLE FUTURE ACTIONS

Establishment of EQS for the prioritized pharmaceuticals to improve/strengthen their monitoring and control

Implementation/improvement of wastewater treatment technologies at hospitals/WWTPs



Promotion of research in ecotoxicology, risk characterization, water treatment

Planning of training and information activities for the population

Use of alternative drugs less harmful to the environment

solutions

Acknowledgements

The authors thank the **financial support** provided by

- the Spanish Ministry for Economy and Competitiveness through the Carlos III Health Institute with the program "Projects on Health Research 2014-2016 FIS (PI14/00516)",
- the European Commission through the project SOLUTIONS (contract 603437),
- the Generalitat de Catalunya (Consolidated Research Groups "2014SGR418-Water and Soil Quality Unit" and 2014SGR291-ICRA65).

General Management of Hospital is acknowledged for **sample collection** permission.

Merck is acknowledged for the gift of **LC columns**.

The SOLUTIONS project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 603437