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Determination of sorption coefficients for seventy five pharmaceuticals in sewage sludge

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ABSTRACT

Sorption of 75 active pharmaceutical ingredients (APIs) to three different types of sludge (primary sludge, secondary sludge with short and long sludge age respectively) was investigated. To obtain the sorption isotherms batch studies with the APIs mixture were performed in four nominal concentrations to water containing 1 g of sludge. The range of APIs concentrations was between ng L^{-1} to µg L^{-1} which is found in the wastewater effluent. Isotherms were obtained for approximately 45 of the APIs, providing distribution coefficients for linear (K_d), Freundlich (K_f) and Langmuir (K_L) isotherms. K_d, K_f and K_L ranging between 71-3.8×10^{4}, 1.1×10^{-5}- 61 and 9.2×10^{-6}- 1.1×10^{-3}L g^{-1}, respectively. The obtained coefficients were applied to estimate the fraction of API in the water phase (see Abstract Graphic). For 37 of the 75 the APIs predicted presence in the liquid phase was estimated to > 80%. 24 APIs were estimated to be present in the liquid phase between 20 - 80 %, and 14 APIs were found to have < 20% presence in the liquid phase, i.e. high affinity towards sludge. Furthermore, the effect of pH at values 6, 7 and 8 was evaluated using one way ANOVA-test. A significant difference in K_ds due to pH changes was found for 6 of the APIs (variation 10-20%).

Keywords:

Distribution coefficients (K_d)

Pharmaceuticals

Sorption isotherms

Sludge

Wastewater treatment plant (WWTP)

NOMENCLATURE See Table S1, supplementary data.

1. Introduction

The presence of human and veterinary pharmaceuticals in the environment has been recognized as a potential environmental threat (Ternes et al., 2002). After their use, pharmaceutical are either excreted unchanged or as metabolites via urine and faeces or are washed off and subsequently reach a wastewater treatment plant (WWTP) via the sewage system. The active pharmaceutical ingredients (APIs) are designed to have pharmacological effects at low concentrations, which have lead to concerns regarding their distribution in aquatic environments and potential non-wanted biological effects in different organisms.

APIs have been found in several environmental compartments such as waste, surface and ground waters (Calisto and Esteves, 2009; Fick et al., 2009; Gabet-Giraud et al., 2010; Lindberg et al., 2010), as well as in sludge and sediments (Ternes et al., 2002; Andersen et al., 2003). Sorption of APIs to sludge, during wastewater treatment processes in which sludge is separated from the wastewater stream may be an important factor for the removal of non-biodegradable pharmaceuticals from WWTPs.

Solid matter is separated from wastewater during treatment. After the separation of incoming particles, the remaining organic material is generally biologically removed in an activated sludge system. After treatment, sludge is separated from the treated water by a second sedimentation step. If extended nitrogen removal is required, biological nitrogen removal is implemented. In colder regions, nitrogen removal is not needed and only biological oxygen demand (BOD) is removed. Thus the sludge age can be shorter. The pH of wastewater during the treatment process is typically close to 7, within the range of 6.0-8.0 which likely results in minor property changes. Surveys in which pK_a (acid- ionization constant) have been determined, reported pK_a values of

5.3 and 9.5 for dissolved organic matter (DOM) in the sludge (Wang et al., 1998) and 6.1 for sludge particles (Wang et al., 2000). For the APIs however, the pH may change the effect of sorption, especially for APIs with pK_a or pK_b (base-ionization constant) within pH range of 6-8. The effect of pH on the sorption of APIs has been discussed by other studies (Ternes et al., 2004; Jones et al., 2006; Carballa et al., 2008) but without firm conclusions. However, studies have shown that for acidic compounds, such as Ibuprofen and Diclofenac the distribution between water and solid phase is affected by pH changes. At pH 4, which is below the pH values found in WWTP, the distribution coefficient (K_d) increased compared to the K_d obtained at the pH 7 (Urase and Kikuta, 2005). K_d may be experimentally determined or calculated from the octanol-water distribution coefficient (K_{ow}). Stuer-Lauridsen et al., (2000) provides thoroughly described estimations of K_d based on K_{ow} where pKa and the fraction of organic carbon are considered. Also Radjenović et al., (2009) calculated K_d values for APIs ranging between 0.4-16 859 L kg^{-1}. Experimental determination of K_d may be conducted in continuous or batch experiments. In order to obtain K_d values during continuous experiments several different parameters need to be known, such as the order of biodegradation, rate of sorption and rate of desorption. In batch experiments, biodegradation is eliminated by adding sodium azide or some other toxic substance, however the ion strength changes which may affects the APIs sorption. A third option is to freeze dry the sludge gently, this will preserve the tertiary structure of the sludge. Thereafter heat the sludge to 103°C in order to sterilize the sludge. This procedure was used by Andersen et al, (2005). In a continuous experiment K_d values were determined for antiepileptic, antiphlogistic, antibiotic, estrogens, contrast medium. (Carballa et al., 2008) However, these studies cover a rather low number of the APIs available on the market and the experimentally obtained K_d values ranges from negligibly to log K_d 4.43 (Carballa et al., 2008).

The objective of this study was to experimentally determine K_d values for 75 selected APIs. The K_d values were obtained from sorption isotherms in three different types of sludge, primary sludge, and secondary sludge with long and short sludge age, respectively. The obtained K_d values were used to estimate the removal of APIs by sorption to sludge in WWPTs. Furthermore, the influence on sorption caused by normal pH variations (pH 6-8) found in WWTPs was investigated. This study was based on a straightforward approach using fixed nominal concentrations of each API in water mixed with a known amount of sterilized sludge in order to determine the sorption distribution coefficients.

2. Materials and methods

2.1. Sludge

Sludge was collected from three WWTPs which were representative of WWTPs in Sweden and other industrialised countries for treatment of municipal wastewater.

Primary sludge was collected from Avedøre WWTP, which treats wastewater corresponding to 275 000 person equivalents (PE) from 10 municipalities in the southern part of Greater Copenhagen, Denmark. It was chosen since it was possible to collect primary sludge without contamination from internal recirculation of secondary sludge. Suspended solids (SS) and volatile suspended solid (VSS) were 43 and 35 g L^{-1}, respectively. Secondary sludge with a long sludge age and nitrification was collected from Klagshamn WWTP. This plant treats municipal wastewater corresponding to about 60 000 PE from the southern part of Malmö City, Sweden and a nearby municipality. The plant uses primary precipitation and nitrification in activated sludge (sludge content 3 g L^{-1}). SS and VSS were 4 and 3 g L^{-1}, respectively. Denitrification took place in a post-denitrifying, moving bed biofilm reactor. Biological sludge with short sludge

age was collected from Sjölunda WWTP. This is typical for plants in the north and in many inland cities in Sweden. The plant treats wastewater corresponding to approximately 315 000 PE from Malmö city, Sweden and surrounding municipalities. The plant was operated with combined primary and simultaneous precipitations. Removal of organic matter took place in a highly loaded activated sludge plant where sludge was collected (sludge content 6 g L^{-1}). SS and VSS were 8 and 6 g L^{-1}, respectively. Nitrification took place in a fixed bed trickling filter and denitrification in a moving bed biofilm reactor.

Each portion of sludge was washed twice with tap water, decanted in order to remove water soluble constituents and frozen at -18ºC after sample collection. The sludge was gently freeze dried in order to preserve the structure and sterilized by heating at 103 ºC for minimum 3 h.

2.2. Experimental design

Nominal concentrations of the 75 APIs (see Table 1) included in the experiments were chosen based on the solubility, limit of quantification (LOQ) and linear range of the analytical method (Grabic et al., unpublished data; Fick et al., 2009). Volatilisation was considered and Henry's Law constant (K_H; Table S2 supplementary data) was calculated EPI Suite software HenryWin v3.10. All APIs had a $K_H < 9\times10^{-7}$ Atm·$m^3$$mol^{-1}$, therefore volatilisation would be insignificant, since only compounds with $K_H > 3\times10^{-3}$ are considered to be volatile (Ternes and Joss, 2008). The aim was to get four API equilibriums with water concentration (C_w; g L^{-1}) in the range of 90 % of the starting concentration (C_0; g L^{-1}) and the LOQ. The water solubility should be larger than the starting concentration; $C_w << C_0$; LOQ< C_w. Sludge concentration in the experiments was 1 g/L, with exception for one sludge where it was increased to 10 and 50 g L^{-1} (Table 1). The 1 g L^{-1} sludge density was about 5- to 10-fold more than the realistic sludge production that can occur in a WWTP which ensures that APIs that adsorb significantly to sludge in a real

WWTP also would be removed significantly from the water phase in the batch experiment which was the basis for determining a K_d-value, while low sorbing APIs K_ds will not be determined

A stock solution including the 75 API of 0.1g×L^{-1} was prepared in MeOH from which the four MeOH stock solutions of 0.4, 2.0, 10.0 and 50.0 ng µL^{-1} were prepared, respectively. These stock solutions suited the design (Table 1) and were theoretically determined to fit the criteria for the present study. Böhm and During (2010) showed that there was no significant difference between determination of the distribution coefficient K_{DOC} for single compounds or mixtures.

Artificial media was used in the study for the water phase (Berg and Nyholm, 1996), modified as described by Andersen et al. (2005). Fundamentally, the artificial sewage was a phosphate-buffered mineral media containing Ca^{2+}, K^+, Mg^{2+}, Na^+, Cl^- and SO_4^{2-}.

Sludge was added to 1 L borosilicate glass bottles. In order to inhibit microbial growth oxygen was removed by purging with $N_{2(g)}$ for 1 min and Na_2SO_3 was added to a final concentration of 50 mg L^{-1} to each bottle. The bottles were left on stirring in the dark at + 4 ºC in order for the sludge to rehydrate. After 12 h, 200 µL of the API stock solutions of 0.4, 2.0, 10.0 or 50.0 ng µL^{-1} were added to the bottles using a Hamilton syringe giving the final concentrations presented in Table 1. The bottles were left on stirring in the dark at + 4 ºC for 12 h. Experiments were performed at three pH values (Table 1). The pH 7.0 was chosen based on a typical pH in WWTPs and pH 6.0 and 8.0 were based on low and high values from WWTPs. Control batches without APIs in the sludge and standard APIs solutions were prepared (Table 1).

Table 1. The experimental set up, including API concentrations, pH sludge concentration and the number of bottles per blank/zero sludge/sludge. From each bottle triplicate solid phase extractions (SPE) were made.

	API conc. ($\mu g \times L^{-1}$)				pH	Sludge conc. ($g \times L^{-1}$)	No. of bottles
Blank for each sludge	0				7	1	3
No sludge	0.08	0.4	2	10	7	0	4
Primary sludge Avedøre	0.08	0.4	2	10	7	1	4
Secondary sludge short sludge age Sjölunda	0.08	0.4	2	10	7	1	4
	10					10	1
	10					50	1
Secondary sludge long sludge age Klagshamn	10				6	1	1
	0.08	0.4	2	10	7		4
	10				8		1

Table 2. Sorption isotherms obtained during sorption to primary sludge. P is the significance that the linear model has a better fit than another model tested, the model tested was Freundlich and Langmuir**.**

	Linear model		Freundlich model				Langmuir model			
	K_d	R^2	K_f	n	R^2	P	τ_{MAX}	K_L	R^2	P
	L kg^{-1}	%	L g^{-1}		%	%	L g^{-1}		%	%
Afluzosin	1.8×10^{3}	99	2.7	1.1	99	42	5.5×10^{4}	3.7×10^{-5}	99	31
Amitryptiline	4.1×10^{3}	98	3.1	0.96	98	70	no fit			
Atenolol	4.6×10^{2}	88	4.0	1.3	91	17	5.7×10^{3}	1.4×10^{-4}	90	18
Atracurium	3.5×10^{2}	100	0.24	0.96	100	40	no fit			
Azelastine	6.4×10^{3}	82	46	1.4	86	11	2.0×10^{4}	5.8×10^{-4}	89	3.5
Biperiden	8.2×10^{2}	88	1.3	1.1	88	83	2.4×10^{4}	4.6×10^{-5}	89	46
Bupropion	85	98	4.8×10^{-3}	0.76	99	0.99	no fit			
Chloprothixene	3.8×10^{4}	98	8.3	0.77	99	0.98	no fit			
Citalopram	5.4×10^{2}	76	0.97	1.1	76	83	1.0×10^{4}	6.7×10^{-5}	7.7	59
Clomipramine	1.7×10^{4}	99	7.6	0.88	99	8.5	no fit			
Clonazepam	5.7×10^{2}	96	0.10	0.84	96	33	no fit			
Clotrimazol	3.2×10^{4}	91	19.0	0.92	92	59	no fit			
Cyproheptadine	1.1×10^{4}	98	2.2	0.81	91	30	no fit			
Desloratidine	3.7×10^{3}	99	1.9	0.92	100	17	no fit			
Dicycloverin	1.4×10^{3}	92	1.2	0.98	94	90	6.2×10^{4}	2.7×10^{-5}	94	66
Donepezil	3.6×10^{3}	96	10.4	1.2	96	21	1.9×10^{4}	2.6×10^{-4}	97	7.3
Duloxetine	1.3×10^{4}	77	30.8	1.2	78	53	1.6×10^{4}	1.1×10^{-3}	79	37
Etonogestrel	no fit						no fit			
Ezetimibe	2.3×10^{3}	97	4.9×10^{-2}	0.68	99	1.1	no fit			
Fexofenadine	2.7×10^{3}	82	1.1×10^{-5}	0.38	94	0.15	no fit			
Fluoxetine	1.0×10^{4}	99	2.7	0.83	99	3.6	no fit			
Flutamide	1.5×10^{3}	88	0.13	0.77	90	27	no fit			
Glibenclamide	3.6×10^{3}	77	no fit				no fit			
Glimepiride	2.1×10^{3}	92	1.9×10^{-3}	0.53	97	0.8	no fit			
Haloperidol	1.0×10^{4}	76	60.9	1.4	80	21	1.5×10^{4}	1.2×10^{-3}	81	12
Hydroxyzine	1.2×10^{3}	98	3.2	1.1	99	14	1.9×10^{4}	8.3×10^{-5}	99	16
Irbesartan	7.0×10^{2}	92	1.5×10^{-2}	0.70	93	19	no fit			
Ketoconazole	9.7×10^{3}	88	1.6	0.79	90	30	no fit			
Loperamide	1.4×10^{4}	98	0.60	0.69	99	0.04	no fit			
Maprotiline	6.7×10^{3}	99	1.7	0.83	100	0.05	no fit			
Megesterol	no fit						no fit			
Mianserin	3.0×10^{3}	81	12.5	1.2	83	36	1.6×10^{4}	2.9×10^{-4}	85	17

Nefazodone	1.4×10^{4}	98	2.7	0.79	99	4.0	no fit			
Oxazepam	7.9×10^{2}	90	0.80	1.0	90	99	2.1×10^{4}	4.3×10^{-5}	90	71
Paroxetine	1.4×10^{4}	96	5.6	0.87	97	28	no fit			
Pizotifen	4.7×10^{3}	100	no fit				no fit			
Progesterone	7.5×10^{2}	98	0.18	0.86	99	14	no fit			
Repaglinide	1.7×10^{2}	94	1.4	1.3	95	19	7.6×10^{3}	2.8×10^{-5}	94	53
Risperidone	1.9×10^{3}	99	3.1	1.1	99	36	3.2×10^{4}	7.0×10^{-5}	99	17
Sertraline	3.5×10^{4}	97	4.1	0.72	99	0.4	no fit			
Sulfamethoxazol	3.2×10^{2}	77	0.91	1.1	77	79	8.6×10^{3}	5.4×10^{-5}	78	58
Telmisartan	1.3×10^{3}	100	0.86	0.95	100	51	no fit			
Tramadol	1.1×10^{2}	94	4.9×10^{-4}	0.63	96	3.3	no fit			
Trimethoprim	3.9×10^{2}	98	0.43	1.0	98	91	3.7×10^{4}	1.1×10^{-5}	98	73
Verapamil	1.8×10^{3}	99	1.1	0.94	99	26	no fit			

Table 3. Sorption isotherms obtained during sorption to secondary sludge long sludge age P is the significance that the linear model has a better fit than another model tested, the model tested was Freundlich and Langmuir.

	Linear model		Freundlich model				Langmuir model			
	K_d (L kg^{-1})	R^2 (%)	K_f (L g^{-1})	n	R^2 (%)	P (%)	τ_{MAX} (L g^{-1})	K_L	R (%)	P (%)
Afluzosin	1.2×10^{3}	100	2.2	1.1	100	4.0	3.7×10^{4}	4.0×10^{-5}	100	1.3
Alprazolam	7.4×10^{2}	94	1.6×10^{-2}	0.69	96	4.6	no fit			
Amitryptiline	2.8×10^{3}	99	1.9	0.95	100	40	no fit			
Atenolol	1.6×10^{3}	94	22	1.5	99	0.0	7.8×10^{3}	4.9×10^{-4}	99	0.0
Atracurium	4.7×10^{2}	100	0.37	0.97	100	40	no fit			
Azelastine	2.0×10^{3}	99	3.2	1.1	99	31	5.8×10^{4}	3.9×10^{-5}	99	22
Biperiden	7.5×10^{2}	98	0.13	0.84	98	7.7	no fit			
Bisoprolol	1.1×10^{2}	-4.4	46	3.0	68	0.14	9.9×10^{2}	1.3×10^{-3}	86	0.0
Bupropion	1.4×10^{2}	99	0.35	1.1	100	4.2	5.3×10^{3}	3.5×10^{-5}	100	1.4
Chloprothixene	2.0×10^{4}	98	9.4	0.89	99	14	no fit			
Citalopram	2.1×10^{2}	94	0.90	1.2	95	25	3.8×10^{3}	8.1×10^{-5}	95	20
Clomipramine	6.7×10^{3}	100	3.4	0.91	100	1.4	no fit			
Clotrimazol	3.4×10^{4}	96	4.5	0.73	98	2.2	no fit			
Cyproheptadine	3.6×10^{3}	100	3.7	1.0	100	93	no fit			
Desloratidine	2.9×10^{3}	100	2.1	0.96	100	40	no fit			
Dicycloverin	1.7×10^{3}	99	0.50	0.88	99	13	no fit			
Donepezil	9.7×10^{2}	99	4.6	1.2	100	0.0	1.0×10^{4}	1.5×10^{-4}	100	0.0
Duloxetine	2.9×10^{3}	98	2.8	1.0	98	98	no fit			
Eprosartan	71	93	0.43	1.2	94	38	1.8×103	6.6×10^{-5}	94	32
Estradiol	no fit				0.0					
Etonogestrel	no fit				0.0					
Ezetimibe	3.0×10^{3}	96	3.0×10-2	0.63	99	0.0	no fit			
Fexofenadine	3.6×10^{2}	95	0.2	0.93	96	74	no fit			
Fluoxetine	6.0×10^{3}	99	1.3	0.83	100	0.80	no fit			
Flutamide	7.5×10^{2}	90	1.5×10^{-4}	0.50	96	0.13	no fit			
Glibenclamide	1.3×10^{3}	93	0.2	0.82	99	8.2	no fit			
Glimepiride	9.6×10^{2}	99	0.2	0.83	99	11	no fit			
Haloperidol	2.9×10^{3}	98	3.5	1.0	98	78	1.1×10^{5}	2.8×10^{-5}	98	76
Hydroxyzine	7.2×10^{2}	98	0.54	0.97	98	68	no fit			
Irbesartan	9.4×10^{2}	94	5.3×10^{-4}	0.54	97	1.2	no fit			
Ibuprofen	3.6×10^{2}	91	1.6×10^{-2}	0.73	94	38	no fit			
Ketoconazole	8.5×10^{3}	91	0.70	0.73	95	0.8	no fit			

Levonorgestrel	2.6×10^{2}	61	18	1.9×10^{3}	81	1.4	1.9×10^{3}	6.6×10^{-4}	87	0.23
Loperamide	5.5×10^{3}	97	0.53	0.77	98	0.83	no fit			
Maprotiline	4.5×10^{3}	99	0.65	0.79	100	0.05	no fit			
Medroxyprogesterone	1.7×10^{2}	42	15	2.1	56	11	1.3×10^{3}	6.4×10^{-4}	60	6.1
Megesterol	5.9×10^{2}	82	6.7	1.4	85	16	5.3×10^{3}	2.4×10^{-4}	87	7.1
Mianserin	9.1×10^{2}	99	1.4	1.1	99	45	2.6×10^{4}	4.0×10^{-5}	99	29
Nefazodone	8.3×10^{3}	96	0.96	0.76	98	1.6	no fit			
Orphenadrine	6.4×10^{2}	99	0.12	0.84	98	2.6	no fit			
Oxazepam	1.1×10^{3}	87	11	1.4	91	9.2	6.5×10^{3}	3.6×10^{-4}	92	5.2
Paroxetine	8.3×10^{3}	97	0.63	0.73	98	0.07	no fit			
Pizotifen	3.1×10^{3}	100	1.9	0.94	100	26	no fit			
Progesterone	1.1×10^{3}	87	8.6	1.3	90	17	7.4×10^{3}	2.9×10^{-4}	92	5.4
Repaglinide	2.1×10^{2}	17	10	1.8	98	0.0	2.7×10^{3}	2.8×10^{-4}	99	0.0
Risperidone	6.5×10^{2}	98	2.8	1.2	99	1.1	8.9×10^{3}	1.2×10^{-4}	99	0.15
Sertraline	1.7×10^{4}	92	1.3	0.71	97	1.3	no fit			
Sotalol	3.6×10^{2}	99	0.56	1.1	99	35	1.3×10^{4}	3.3×10^{-5}	99	14
Sulfamethoxazol	3.7×10^{2}	96	5.2×10^{-3}	0.68	98	5.6	no fit			
Telmisartan	no fit									
Tramadol	1.9×10^{2}	99	9.0×10^{-2}	0.92	99	39	no fit			
Trimethoprim	4.2×10^{2}	99	0.18	0.91	99	16	no fit			
Venlafaxine	1.0×10^{2}	85	0.77	1.3	86	32	2.1×10^{3}	7.9×10^{-5}	0.0	25
Verapamil	4.0×10^{2}	84	20	1.8	96	0.0	3.3×10^{3}	4.3×10^{-4}	98	0.0

Table 4. Sorption isotherms obtained during sorption to secondary sludge short sludge age. P is the significance that the linear model has a better fit than another model tested, the model tested was Freundlich and Langmuir.

	Linear model		Freundlich model				Langmuir model			
	K_d (L kg^{-1})	R^2 (%)	K_f (L g^{-1})	n	R^2 (%)	P (%)	τ_{MAX} (L g^{-1})	K_L	R^2 (%)	P (%)
Alprazolam	4.3×10^{2}	80	no fit							
Amitryptiline	2.8×10^{3}	96	4.2×10^{-2}	0.66	98	0.27	no fit			
Atenolol	1.9×10^{3}	100	no fit							
Atracurium	6.1×10^{2}	98	2.9×10^{-2}	0.73	99	0.1				
Azelastine	1.4×10^{3}	96	1.7×10^{-2}	0.65	99	0.0	no fit			
Biperiden	8.4×10^{2}	96	0.13	0.82	96	26	no fit			
Bisoprolol	94	64	7.5	2.0	79.6	2.0	1.1×10^{3}	3.4×10^{-4}	81	1.2
Bupropion	2.0×10^{2}	97	1.9×10^{-2}	0.79	98	6.2	no fit			
Chloprothixene	no fit									
Clomipramine	7.3×10^{3}	88	6.0×10^{-3}	0.49	97	0.0	no fit			
Clotrimazol	no fit									
Cyproheptadine	5.3×10^{3}	97	0.23	0.70	99	0.0	no fit			
Desloratidine	3.2×10^{3}	96	0.10	0.69	99	0.22	no fit			
Dicycloverin	1.7×10^{3}	97	0.11	0.75	98	3.1	no fit			
Diltiazem	4.4×10^{2}	100	0.65	1.0	100	35	5.2×10^{4}	9.2×10^{-6}	100	27
Duloxetine	3.2×10^{3}	80	1.7×10^{-5}	0.37	99	0.0	no fit			
Estradiol	2.3×10^{2}	72	0.16	0.97	72	93	1.6×10^{4}	1.6×10^{-5}	72	85
Etonogestrel	2.4×10^{2}	73	0.11	0.92	73	87	no fit			
Ezetimibe	8.5×10^{3}	87	0.72	0.98	87	91	9.4×10^{4}	1.0×10^{-4}	87	65
Fexofenadine	6.7×10^{2}	94	2.5×10^{-3}	0.60	98	0.54	no fit			
Fluoxetine	5.7×10^{3}	91	1.4×10^{-3}	0.47	99	0.0	no fit			
Flutamide	1.2×10^{3}	93	1.6×10^{-4}	0.49	99	0.0	no fit			

Glibenclamide	2.3×10^{3}	97	0.16	0.75	98	1.2	no fit			
Glimepiride	2.6×10^{3}	94	9.1×10^{-2}	0.70	94	2.0	no fit			
Haloperidol	1.7×10^{3}	98	0.90	1.0	96	75	no fit			
Hydroxyzine	6.0×10^{2}	95	0.27	0.91	95	56	no fit			
Irbesartan	no fit									
Ibuprofen	2.0×10^{2}	80	1.1	1.3	81	62	2.4×10^{3}	1.3×10^{-4}	82	56
Ketoconazole	no fit									
Levonorgestrel	no fit									
Loperamide	1.1×10^{4}	91	0.16	0.62	96	0.88	no fit			
Maprotiline	3.9×10^{3}	91	9.3×10-2	0.66	95	3.1	no fit			
Medroxyprogesterone	2.5×10^{2}	96	0.46	1.1	96	65	9.7×10^{3}	3.0×10^{-5}	96	59
Megesterol	8.3×10^{2}	86	0.30	0.89	86	66	no fit			
Mianserin	5.2×10^{2}	94	6.6×10^{-2}	0.80	95	22	no fit			
Nefazodone	8.9×10^{3}	92	3.0×10^{-2}	0.54	99	0.0	no fit			
Orphenadrine	5.4×10^{2}	98	0.17	0.88	98	25	no fit			
Oxazepam	1.6×10^{3}	97	3.1	1.1	97	40	2.3×10^{4}	8.7×10^{-5}	98	33
Paroxetine	8.6×10^{3}	82	5.6×10^{-5}	0.37	98	0.0	no fit			
Pizotifen	3.1×10^{3}	98	0.20	0.74	1005	0.0	no fit			
Progesterone	1.1×10^{3}	96	0.21	0.83	96	20	no fit			
Repaglinide	5.1×10^{2}	98	1.3	1.1	98	28	2.5×10^{4}	2.4×10^{-5}	98	44
Risperidone	3.3×10^{2}	98	0.15	0.92	98	45	no fit			
Sertraline	no fit									
Sotalol	7.4×10^{2}	99	0.22	0.87	99	6.3	no fit			
Sulfamethoxazol	2.8×10^{2}	95	no fit				no fit			
Telmisartan	no fit									
Trimethoprim	2.8×10^{2}	98	1.3×10^{-2}	0.75	100	0.15	no fit			
Verapamil	6.3×10^{2}	96	0.90	1.0	96	75	3.3×104	2.1×10^{-5}	96	63

2.3. Extraction and chromatography

Triplicate extractions were made from each 1 L borosilicate glass bottle. After 12 h of stirring, the samples were allowed to stand for 30 minutes in order to let the sludge settle. In order to remove particles, the liquid phase was decanted and filtered through a glass microfiber filters (GC/F; VWR Denmark). In the filtered samples (100 g) a surrogate standard mixture was added followed by solid phase extraction using OASIS HLB (6cc, Waters, Sweden). A detailed description of sample preparation and analyses employing the LC-MS/MS methodology reported in Grabic et al., (unpublished data) and Fick et al., (2009) may be found as supplementary data S1.

2.4. Data analysis

The measured concentrations of APIs in the water phase (C_0) where no sludge was added and when sludge was added (C_w) and SS were used to calculate C_s as follows in each experimental replicate:

$$C_s = (C_0 - C_w)/SS \qquad \text{(Eq. 1)}$$

The sorption isotherms define the equilibrium between the concentration of a chemical in aqueous and solid phases (Schwarzenbach et al., 2003). With batch sorption experiments including multiple concentrations, sorption isotherms may be constructed, from which the solid-water distribution coefficients can be determined. Three equations are used here to describe the sorption isotherms; linear (Eq. 2), Freundlich (Eq. 3) and Langmuir (Eq. 4). C_s is the concentration sorbed to the sludge (g kg^{-1}) and K_d is the linear sorption constant. K_f is the Freundlich coefficient and n is the Freundlich exponent. τ represents the total number of surface sites per mass of sorbent and K_L is the Langmuir coefficient.

Linear $C_s = K_d * C_w$ (Eq. 2)

Freundlich $C_s = Kf * C_w^{\frac{1}{n}}$ (Eq. 3)

Langmuir $C_s = \frac{\tau_{\max} * K_L * C_w}{1 + K_L * C_w}$ (Eq. 4)

The linear isotherm is the simplest case where the affinity of the API remains constant over the concentration interval. The Langmuir isotherm may have the best fit in cases where the sorbent becomes saturated at higher concentrations of API. Freundlich, is commonly employed to describe experimentally obtained sorption data (Schwarzenbach et al., 2003).

The software GraphPad Prism 5 for Windows (GraphPad Software, Inc.) was used for data evaluation, using a 95 % confidence interval for the best fit sorption isotherms. The two hypotheses tested were whether the linear isotherm was a better fit than the Freundlich isotherm, and whether the linear was a better fit compared to Langmuir isotherm. Furthermore, in order to qualify as the best fit the R^2-value for the curve should be >0.7, otherwise no fit was made.

2.5. Estimation of the sorbed fraction

The estimation of the sorbed fraction of each API was made by employing the obtained K_d-values (Table 2 to 4). In those cases where both Freundlich and Langmuir isotherms were found to have a better fit than the linear, the one with the best significance was chosen as the best fit. For the APIs where the Freundlich or Langmuir isotherm gave the best fit (see Table 2 to 4), K_d-values were calculated for a water concentration of 1 µg L^{-1}. The fraction of the APIs at equilibrium for a given sludge concentration (SS; kg L^{-1}) was calculated using the K_d-values (L kg^{-1}) according to equation 5.

$$\text{Sorbed fraction } (F_S) = 1\text{-Fw} = \frac{C_S}{C_W + SS \times C_S} = \frac{SS \times K_d}{1 + SS \times K_d} \quad \text{(Eq. 5)}$$

Furthermore, if the mass of the sludge removed from the WWTP per volume of treated sewage (RESS; kg L^{-1}) is known, the fraction of the total APIs load into the activate sludge tank which would not be lost either by degradation or stripping, but that will be removed at equilibrium can be calculated as shown in equation 6.

$$\text{Removed fraction } (F_R) = \frac{RESS \times K_d}{1 + RESS \times K_d} \quad \text{(Eq. 6)}$$

The sludge production from treatment of municipal sewage can be considered reasonably constant irrespective of the methods of treatment. Based on Henze et al. (2002) the typical

amounts of sludge removed from a WWTP can be calculated for primary and secondary sludge. For a WWPT with 2 h of settling time, the removal of primary sludge was estimated to 210 g m^{-3} of treated wastewater. In order to estimate the removal of secondary sludge, the yield coefficient for a low load treatment plant was employed giving a removal of 110 g m^{-3} for the secondary sludge. The corresponding value for a high load treatment plant would be 165 g m^{-3}.

3. Results and discussion

3.1 Sludge properties

An ocular inspection of the freeze dried sludge showed that the primary sludge may be described as wadding, whereas the two types of secondary sludge had an appearance as instant coffee. The ocular differences between the different types of sludge may be due to their origin. Primary sludge settable particles of wastewater include faeces, toilet paper particles of food, and secondary sludge consist of bacteria biomass and biopolymers created by bacteria. It is likely that the mainly plant/wood derived primary sludge has different densities of functional groups and aromatic rings compared to the bacteria derived secondary sludge.

3.2 Sorption isotherms

Due to analytical limitations and the experimental conditions it was possible to determine sorption isotherms for 44-52 APIs (Table 2 to 4) out of the 75 APIs (Table S2). The linearly obtained K_d values ranged from 85 to 38 400, 199 to 11 340 and 71 to 34 050 L kg^{-1} for primary sludge, secondary sludge with short sludge age and secondary sludge with long sludge age, respectively.

The sorption isotherm with the best fit was predominantly linear followed by the Freundlich isotherm (Table 2 to 4) within the studied concentration range (0.08-10 µg L^{-1}). Examples of the

obtained isotherms are shown in Figure 1. Table 2 to 4 presents for 1 g L^{-1} sludge the obtained distribution coefficients, Freundlich coefficient, Freundlich exponent, τ_{max} and Langmuir coefficient in the cases where the isotherms fitted these isotherm descriptions. Table 2 to 4 exhibit the order of significance for each hypothesis tested.

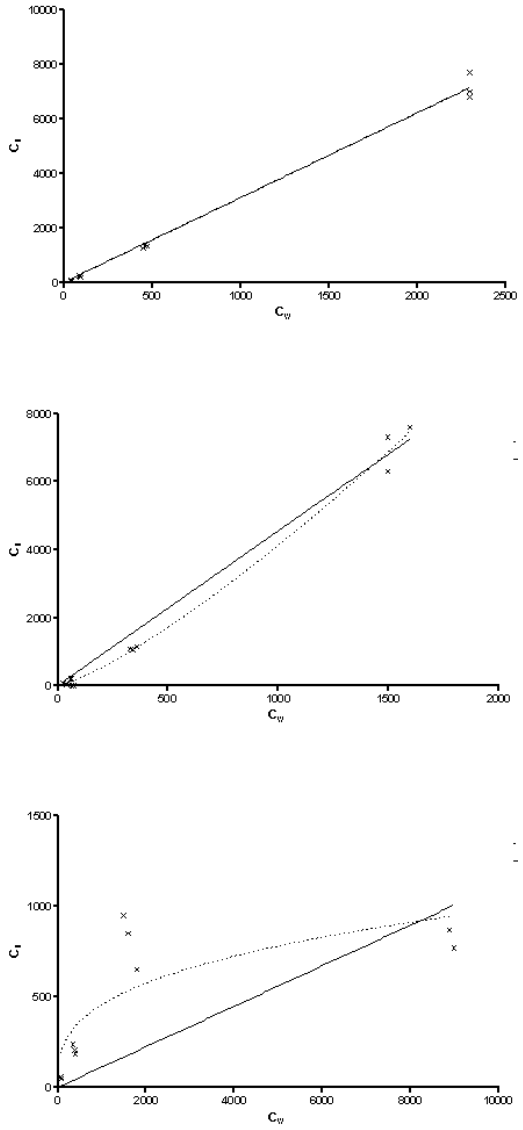

Figure 1. Example of the obtained sorption isotherms. From the top Pizotifen linear isotherm, second Maprotiline Freundlich isotherm and at the bottom Bisoprolol Langmuir isotherm.

The isotherms coefficients did not change significantly even at the higher sludge densities (Table S3). The average difference between the K_d's obtained from 1 g L^{-1} sludge compared to the K_d obtained, when 10 and 50 g L^{-1} sludge was 4%.

3.3 Sorption results and literature comparison

As mentioned before for some of the APIs the sorption isotherms were not obtained under our experimental conditions, possibly because of strong sorption to the glass surface of the bottle and/or the water surface. These APIs were Amiodiarone, Bromocriptine, Chlorpromazine, Clemastine, Dihydroergotamin, Fluphenazine, Levomepromazine, Meclozine, Miconazole, Perphenazine, Prometazine, Roxithromycine and Tamoxifen.

The experimental design of the present study and the LOQ in the present matrixes for the individual APIs measured, provides the limits of K_d. The highest K_d that could be obtained within the concentration range 0.08 – 10 µg L^{-1} and given the median LOQ, 8 ng L^{-1} was 1.2 $\times 10^6$ L kg^{-1}. However, if the LOQ was low (1 ng L^{-1}) or high (170 ng L^{-1}), the highest K_d could be expected within the range from 5×10^4 to 1×10^7 L kg^{-1}. Furthermore, assuming that at least 10% was required to be sorbed in order to determine a K_d value the lowest K_d value obtained within the present study was 100 L kg^{-1}.

Thirteen of the APIs exhibited so low sorption on the sludge that a sorption isotherm was impossible to determine. The low sorbing APIs were Buprenorphine, Cilazapril, Carbamazepine, Codeine, Diclofenac, Estrone, Flecainide, Fluconazole, Metoprolol, Naloxone and Rosuvastatine, Tramadol and Venlafaxine in all three sludge. For the following APIs their sorption vary between each type of sludge. APIs which specifically exhibited low sorption for the primary sludge were Bisoprolol, Diltiazem, Eprosartan, Estradiol, Ibuprofen, Levonorgestrel,

Medroxyprogesterone, Orphenadrine and Sotalol. The obtained K_d values for the APIs above ranged in the two secondary sludge between 71 and 740 L kg^{-1} (Table 3 and 4). APIs which specifically exhibited low sorption for the sludge with short sludge age were Alfuzosin, Citalopram, Clonazepam, Donepezil and Eprosartan. Finally for the secondary sludge with long sludge age the low sorbing APIs were the APIs Clonazepam and Diltiazem, generally the K_d values obtained for these APIs were low in the other sludge types.

Several of the K_d values obtained in other studies would in comparison with the present study be below or around the lowest K_d values that could be obtained. Examples of such APIs are Codeine (Wick et al., 2009) and Estrone, (Andersen et al., 2005; Carballa et al., 2008). Further low K_d values were reported by Ternes et al. (2004) with Carbamazepine in primary and secondary sludge <20 and 1.2 L kg^{-1} and Ibuprofen <20 and 7.1 L kg^{-1}, respectively. Results from Carballa et al. (2008) and Joss et al., (2005) supported these findings. Abegglen et al., (2009) reports K_d values from experiments with secondary sludge from membrane bioreactors for Carbamazepine and Ibuprofen which both were found to have low sorption (<75 L kg^{-1}). Calculated K_d values for primary and secondary sludge were in the same range for Ibuprofen 9.5 and 0 L kg^{-1}, respectively, whereas for Carbamazepine they were 10 to 100 times higher (314 and 135 L kg^{-1}; Radjenović et al., 2009). Urase and Kikuta (2005) evaluated the sorption and degradation of APIs. Two of the APIs included were Ibuprofen and Carbamazepine, which were found to have K_d values of 80 and 66 L kg^{-1}, respectively at pH 6.7 (Urase and Kikuta; 2005). In the present study Ibuprofen had a weak sorption in the two secondary sludge, which resulted in low K_d values, 200 and 360 L kg^{-1}, obtained from the short and long sludge age, respectively, the reason may be due to the differently performed experiments. Contrary to the present study Ternes et al. (2004) report for Diclofenac the K_d value 459 L kg^{-1} for primary sludge which is

within the limits of the present study but no sorption isotherm could be obtained, whereas for secondary sludge the authors report 16 L kg^{-1} which was outside the limits for the present study. Also Joss et al., (2005) report values for Diclofenac in the same range for both sludges. Carballa et al. (2008) reported values ranging between 19-158 L kg^{-1} which would be out of the limits for the present study. Radjenović et al. (2009) calculated the K_d value for Diclofenac for primary and secondary sludge at 194 and 118, respectively. Based on this, Diclofenac appears to have higher affinity for the primary sludge. One explanation could be the difference in pH values (Ternes et al., (2004)). However, in the present study Diclofenac was not among those APIs for which pH was affecting its sorption (see below section 3.4 and Table 5). The K_d values obtained in this study for Sulfamethoxazole (Table 2 to 4) were in the same order as those reported in Göbel et al. (2005) for activated sludge. Abegglen et al., (2009) and Carballa et al., (2009) found the K_d of Sulfamethoxazole to be one order of magnitude lower compared to the present study, and Radjenović et al. (2009) reported two order of magnitude lower K_d values. Another contradictory study of Sulfamethoxazole come from Wu et al. (2009) whom claimed sorption to be too weak, but also reported K_d for other antibiotics in the same level as found here for Sulfamethoxazole. Sulfamethoxazole has been reported to be photosensitive (e.g. Zhou and Moore, 1994; Trovó et al., 2009; Ryan et al., 2010). In the present study precautions were taken against photo-degradation. Depending on how different sorption studies have been carried out and precautions taken against photo-degradation throughout the whole experiment, including the extracts, photo-degradation might be an explanation to the diverging K_d results. The K_d values obtained in this study for Trimetoprim (Table 2 to 4) were in the same order as those reported in Göbel et al. (2005) for activated sludge. Also Radjenović et al. (2009), and Abegglen et al., (2009) found K_d for Trimetoprim to be in the same order of magnitude. The K_d obtained by

Radjenović et al. (2009) for Atenolol and Glibenclamide was one order of magnitude lower compared to those presented in this study (Table 2 to 4). In addition, Maurer et al (2007) obtained even lower K_d values below 40 L kg^{-1} for Atenolol, Sotalol, Metoprolol. Roxythromycin was included in the study conducted by Abegglen et al., (2009) where the authors determined K_d to be 570 L kg^{-1} which is almost 6 times higher than the one reported by Ternes at al., (2004). In the present study Roxythromycin was among those APIs for which no sorption isotherm could be obtained. However, the main differences were found between primary and secondary sludge and not between the two secondary types of sludge. It may therefore be assumed that the explanation can be derived from the origin of the sludge type. Primary sludge originate from particles found in wastewater e.g. much of it is derived from toilet paper and other plant matter found in food waste and secondary sludge mainly contains settled bacteria and biopolymers created by the bacteria. Based on the origin of the sludge it is likely that the sorption of different APIs structures can vary between the sludge types.

Influence of temperature on sorption is not well studied and the temperature may not always be reported in sorption studies. The effect of temperature was studied by Zeng et al., (2009) who found the difference in K_d between 10, 20 and 30 °C was 20-25%. The K_d values obtained in the present study may thus have somewhat higher K_d-values in comparison with other studies conducted at 10 or 20 ˚C.

3.4 Effect of pH on sorption

In the present study, 20 out of 50 APIs were found to have a significant difference in their mean K_d values obtained in the secondary sludge with long sludge age between pH values 6, 7 and 8 (Table 5). By employing one way ANOVA-test, with Tukeys post-test at 95 % confidence level, the significant difference within the pH range of WWTPs was determined and identified.

All structures of the APIs, where the ANOVA-test indicated a significant difference between K_ds included a nitrogen atom and in many case an amine functional group and hence had basic properties. Even though the K_d values were significantly different in the pH range 6 to 8, it will not have any significant effect on the removal via sorption to sludge (in a subsequent appendix Table A1). However, Chlorpramine, Chloprothixene, Duloxetine, Fluoxetine, Levomepromazine, Loperamide, Nefazedone and Sertraline were exceptions. For these APIs the pH variation from 6 to 8 affected the fraction in the liquid phase by 10-20% (in a subsequent appendix Table A1). These APIs can be assumed to be weak bases. Carballa et al., (2008) point out that it has to be considered whether the pH value will affect sorption, as an example for Diclofenac (pK_a 4.15). In the current study the variation of pH did not significantly affected the $K_{d.}$ for Diclofenac even though pH was 2 to 4 pH units higher than the pK_a. Fluoxetine (pKa 9.6) was in the current study shown to be affected by the pH, the difference between pKa and the investigated pH was 2 to 4 pH units. Even though the differences between pKa for Diclofenac and Fluoxetine was in the same range the two APIs showed different influence by changes of the pH. An investigation of the effect of pH on Naproxen and Carbamazepine, found the highest sorption was at pH 4, and no significant difference occur between pH values 6 and 8 (Maoz and Chefetz, 2010). Further investigation of the particulate fraction of the sludge found the overall pKa to be 6.1 (Wang et al., 2000). The present study was conducted at a pH value above the pK_a for sludge. It cannot be excluded that the K_d was affected by changes caused by pH both in the API structure and the structure of the sludge since among the studied compounds were APIs containing N-groups. The APIs which did not show a significant difference in the K_d-values within the pH range 6 to 8 can be expected to be stable in their ionized and neutral form, respectively.

Table 5. Evaluating the effect of pH within the pH rang for a WWTP, pH 6-8. Average one point K_d values with standard deviation (n=3) obtained in sludge from secondary sludge long sludge age at pH 6, 7 and 8for the concentration 10 µg L^{-1}. By employing one way ANOVA with a 95 % confidence interval was the following question asked; are the means significantly different?

	Average K_d				P<0,05?
	pH 6-8	pH 6	pH 7	pH 8	pH 6-8
Alfuzosin	$1.0 \pm 0.2\times10^{3}$	$12 \pm 0.4\times10^{2}$	$7.3 \pm 0.3\times10^{2}$	$11 \pm 0.5\times10^{2}$	no
Amitryptiline	$2.8 \pm 1.0\times10^{3}$	$2.8 \pm 0.2\times10^{3}$	$1.8 \pm 0.3\times10^{3}$	$4.0 \pm 0.7\times10^{3}$	yes
Atenolol	$1.6 \pm 0.2\times10^{3}$	$1.6 \pm 0.2\times10^{3}$	$1.6 \pm 0.2\times10^{3}$	$16 \pm 0.9\times10^{2}$	no
Atracurium	$4.1 \pm 0.6\times10^{2}$	$4.7 \pm 0.2\times10^{2}$	$413 \pm 20\times10^{3}$	$3.4 \pm 0.2\times10^{2}$	yes
Azelastine	$1.7 \pm 0.7\times10^{3}$	$2.0 \pm 0.1\times10^{3}$	$8.7 \pm 0.5\times10^{2}$	$2.3 \pm 0.1\times10^{3}$	yes
Biperiden	$0.8 \pm 0.2\times10^{3}$	$7.6 \pm 0.9\times10^{2}$	$0.6 \pm 0.1\times10^{3}$	$1.0 \pm 0.2\times10^{3}$	no
Bisoprolol	$1.2 \pm 0.9\times10^{2}$	$0.6 \pm 0.6\times10^{2}$	$2.1 \pm 0.9\times10^{2}$	$0.8 \pm 0.4\times10^{2}$	no
Bupropion	$1.4 \pm 0.1\times10^{2}$	$1.4 \pm 0.1\times10^{2}$	$1.4 \pm 0.2\times10^{2}$	$1.5 \pm 0.2\times10^{2}$	no
Chloprothixene	$1.9 \pm 0.8\times10^{4}$	$2.0 \pm 0.1\times10^{4}$	$10 \pm 0.7\times10^{3}$	$2.8 \pm 4.6\times10^{4}$	yes
Clomipramine	$6.6 \pm 2.4\times10^{3}$	$6.7 \pm 0.2\times10^{3}$	$3.9 \pm 0.2\times10^{3}$	$9.3 \pm 1.1\times10^{3}$	yes
Clotrimazol	$3.6 \pm 0.5\times10^{4}$	$3.6 \pm 0.5\times10^{4}$	$3.3 \pm 0.4\times10^{4}$	$4.0 \pm 0.4\times10^{4}$	no
Cyproheptadine	$3.4 \pm 1.0\times10^{3}$	$3.6 \pm 0.2\times10^{3}$	$2.1 \pm 0.1\times10^{3}$	$4.4 \pm 0.3\times10^{3}$	yes
Desloratidine	$2.9 \pm 0.5\times10^{3}$	$2.9 \pm 0.2\times10^{3}$	$2.3 \pm 0.2\times10^{3}$	$3.4 \pm 0.3\times10^{3}$	no
Diclofenac	$0.8 \pm 0.4\times10^{3}$	$8.0 \pm 0.6\times10^{2}$	$4.8 \pm 81\times10^{2}$	$1.2 \pm 0.6\times10^{3}$	no
Dicycloverin	$1.8 \pm 0.6\times10^{3}$	$1.7 \pm 0.2\times10^{3}$	$1.2 \pm 0.3\times10^{3}$	$2.4 \pm 0.5\times10^{3}$	no
Donepezil	$0.8 \pm 0.3\times10^{3}$	$9.6 \pm 0.1\times10^{2}$	$4.8 \pm 0.3\times10^{2}$	$10 \pm 0.4\times10^{2}$	no
Duloxetine	$3.0 \pm 1.2\times10^{3}$	$2.9 \pm 0.1\times10^{3}$	$1.8 \pm 0.3\times10^{3}$	$4.4 \pm 0.7\times10^{3}$	yes
Eprosartan	$0.6 \pm 0.7\times10^{2}$	$0.5 \pm 0.4\times10^{2}$	$0.6 \pm 0.9\times10^{2}$	$0.8 \pm 1.0\times10^{2}$	no
Estradiol	$0.3 \pm 0.2\times10^{3}$	$0.4 \pm 0.3\times10^{23}$	$0.2 \pm 0.9\times10^{2}$	$4.2 \pm 0.7\times10^{2}$	no
Ezetimibe	$3.3 \pm 0.6\times10^{3}$	$3.2 \pm 0.3\times10^{3}$	$3.0 \pm 0.6\times10^{3}$	$3.9 \pm 0.7\times10^{3}$	no
Fexofenadine	$2.7 \pm 1.4\times10^{2}$	$3.6 \pm 0.8\times10^{2}$	$3.5 \pm 0.5\times10^{2}$	$1.0 \pm 0.9\times10^{2}$	yes
Fluoxetine	$6.2 \pm 2.3\times10^{3}$	$6.1 \pm 0.4\times10^{3}$	$3.7 \pm 0.7\times10^{3}$	$8.7 \pm 1.6\times10^{3}$	yes
Flutamide	$0.8 \pm 0.1\times10^{3}$	$0.8 \pm 0.1\times10^{3}$	$0.8 \pm 0.1\times10^{3}$	$0.6 \pm 0.1\times10^{3}$	no
Glibenclamide	$1.2 \pm 0.2\times10^{3}$	$1.4 \pm 0.1\times10^{3}$	$1.1 \pm 0.1\times10^{3}$	$1.1 \pm 0.1\times10^{3}$	yes
Glimepiride	$9.4 \pm 0.8\times10^{2}$	$9.6 \pm 0.8\times10^{2}$	$0.9 \pm 0.1\times10^{3}$	964 ± 12	no
Haloperidol	$2.3 \pm 0.8\times10^{3}$	$2.9 \pm 0.2\times10^{3}$	$1.2 \pm 0.1\times10^{3}$	$28 \pm 0.3\times10^{2}$	no
Hydroxyzine	$0.5 \pm 0.2\times10^{3}$	$7.1 \pm 0.9\times10^{2}$	$5.3 \pm 1.0\times10^{2}$	$0.3 \pm 0.1\times10^{3}$	yes
Irbesartan	$0.3 \pm 0.5\times10^{3}$	$0.9 \pm 0.2\times10^{3}$	1 ± 0	14 ± 2	yes
Levomepromazine	$2.5 \pm 1.5\times10^{3}$	$2.4 \pm 70.\times10^{3}$	$1.0 \pm 0.3\times10^{3}$	$4.2 \pm 0.1\times10^{3}$	yes
Levonorgestrel	$0.1 \pm 0.2\times10^{3}$	$2.5 \pm 0.6\times10^{2}$	7 ± 193	$0.2 \pm 0.1\times10^{3}$	no
Loperamide	$5.4 \pm 2.0\times10^{3}$	$5.7 \pm 0.6\times10^{3}$	$3.0 \pm 0.3\times10^{3}$	$7.3 \pm 1.2\times10^{3}$	no
Maprotiline	$4.5 \pm 1.7\times10^{3}$	$4.6 \pm 0.4\times10^{3}$	$2.7 \pm 0.4\times10^{3}$	$6.2 \pm 1.2\times10^{3}$	no
Medroxyprogesterone	$0.1 \pm 0.1\times10^{3}$	$0.2 \pm 0.1\times10^{3}$	$-0.2 \pm 0.8\times10^{2}$	$0.2 \pm 0.1\times10^{3}$	no
Megestrol	$0.5 \pm 0.3\times10^{3}$	$0.6 \pm 0.2\times10^{3}$	$0.3 \pm 0.2\times10^{3}$	$0.7 \pm 0.2\times10^{3}$	no
Mianserin	$0.6 \pm 0.2\times10^{3}$	$9.1 \pm 0.9\times10^{2}$	$404 \pm 0.3\times10^{2}$	$6.2 \pm 0.3\times10^{2}$	yes
Nefazodone	$6.4 \pm 2.2\times10^{3}$	$8.8 \pm 1.1\times10^{3}$	$6.3 \pm 0.9\times10^{3}$	$4.2 \pm 0.9\times10^{3}$	yes
Orphenadrine	$0.7 \pm 0.2\times10^{3}$	$6.5 \pm 0.5\times10^{2}$	$5.0 \pm 0.5\times10^{2}$	$8.2 \pm 0.9\times10^{2}$	yes
Oxazepam	$1.5 \pm 0.4\times10^{3}$	$1.1 \pm 0.2\times10^{3}$	$1.9 \pm 0.2\times10^{3}$	$1.6 \pm 0.3\times10^{3}$	no
Paroxetine	$8.2 \pm 3.0\times10^{3}$	$8.5 \pm 1.2\times10^{3}$	$4.9 \pm 0.8\times10^{3}$	$11 \pm 2.0\times10^{3}$	no
Pizotifen	$3.1 \pm 1.0\times10^{3}$	$3.1 \pm 0.2\times10^{3}$	$2.0 \pm 0.2\times10^{3}$	$4.3 \pm 0.6\times10^{3}$	yes
Progesterone	$1.0 \pm 0.4\times10^{3}$	$1.1 \pm 0.3\times10^{3}$	$0.6 \pm 0.1\times10^{3}$	$1.3 \pm 0.2\times10^{3}$	no
Repaglinide	$0.1 \pm 0.1\times10^{3}$	$0.1 \pm 0.1\times10^{3}$	$0.2 \pm 0.1\times10^{3}$	$0.7 \pm 1.2\times10^{2}$	no
Risperidone	$0.6 \pm 0.1\times10^{3}$	$6.5 \pm 0.6\times10^{2}$	$4.2 \pm 0.4\times10^{2}$	$6.2 \pm 0.3\times10^{2}$	no
Sertraline	$1.8 \pm 0.7\times10^{4}$	$1.8 \pm 0.2\times10^{4}$	$9.8 \pm 0.7\times10^{3}$	$2.6 \pm 0.4\times10^{4}$	yes
Sotalol	$3.0 \pm 0.6\times10^{2}$	$4.0 \pm 0.3\times10^{2}$	$2.4 \pm 0.5\times10^{2}$	$3.0 \pm 0.2\times10^{2}$	no
Sulfamethoxazol	$0.3 \pm 0.1\times10^{3}$	$0.3 \pm 0.2\times10^{3}$	$0.3 \pm 0.1\times10^{3}$	$2.7 \pm 0.8\times10^{2}$	no

Telmisartan	$0.8 \pm 0.4\times10^3$	$1.0 \pm 0.1\times10^3$	$0.9 \pm 0.4\times10^3$	$0.4 \pm 0.2\times10^3$	no
Trimetoprim	$3.5 \pm 0.7\times10^2$	$4.3 \pm 0.3\times10^2$	348 ± 9	$2.8 \pm 0.\ 2\times10^2$	yes
Venlafaxine	$0.5 \pm 0.6\times10^2$	$1.0 \pm 0.4\times10^2$	-6 ± 21	$0.6 \pm 0.4\times10^2$	no
Verapamil	$4.0 \pm 0.8\times10^2$	$3.8 \pm 0.7\times10^2$	$3.6 \pm 0.8\times10^2$	$0.4 \pm 0.1\times10^3$	yes

3.5 Correlation of sorption with K_{ow}

An illustration of the absence of correlation between log D_{ow} (calculated) and log K_d-values is shown in Figure 2. The calculation of log D_{ow} was based on calculated values of log K_{ow} using KOWIN and calculated pK_a values presented by Manallack (2009). Log D_{ow} was for acidic compounds calculated according to $D_{ow}=K_{ow}+1/(1+10^{(pH-pKa)})$ and for basic compounds $D_{ow}=K_{ow}+(1/(1+10^{(pKa-pH)})$. To estimate the sorption behavior based only on log D_{ow} gives an incorrect sequence when compared and put in relation to other compounds. A few examples to illustrate the difficulties include Atenolol log K_d 3.6 and log D_{ow} -2.6 and Bisoprolol log K_d 3.1 and log D_{ow} -0.7, with the calculated pKa 9.6 and 9.5, respectively. However, using log D_{ow} to predict the tendency of sorption for Glimpiride and Ibuprofen with the log D_{ow} 2.7 and 2.0, respectively, using pKa 5.0 and 4.3, respectively would give the impression that Glimperide could be expected to have higher affinity to sludge than Ibuprofen. The experimentally determined log K_d (3.0 and 2.6, respectively) values obtained in the present study confirm such a hypothesis. However, applying the same hypothesis for Estradiol and Ezetimibe with the same log K_{ow} 3.94 but with respect to pK_a (9.72 and 10.3) the log D_{ow} would be 0.67 and 1.22, respectively, the tendency would be that Ezetimibe would have higher affinity to sludge. But the results from the present study imply the opposite, log K_d 2.47 and log K_d-1.98, respectively. Even though efforts have been made to calculate the K_d based on K_{ow} with respect to pK_a values, the inherent properties of the APIs and the sludge will need multiple descriptors to get close to experimentally derived K_d-values.

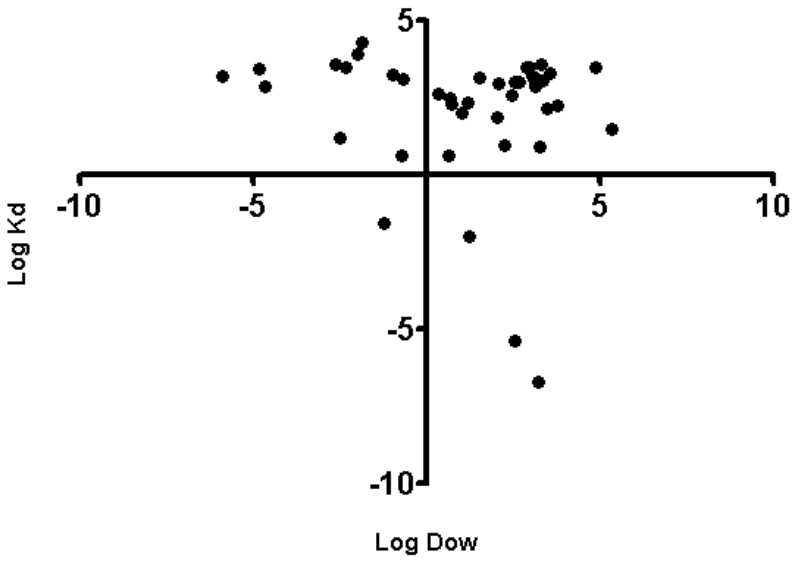

Figure 2. The plot illustrates that for majoring of the APIs in this study it was not possible estimate their sorption behavior based on log D_{ow}.

3.7 Consequence of sorption for the fate of APIs

In order to estimate the removal (see Materials and methods 2.5) of APIs that were not lost from degradation or stripping but due to sorption in the WWTP process, the obtained K_d values were employed to estimate the fraction of API in the water phase (see Fig. 3; Table S4). The K_d values obtained from the primary sludge and secondary sludge with long sludge age were used for the estimation. However, the difference from the other secondary sludge was not larger than 6 percentage points with the median at 4 percentage points. Therefore, the results can be considered to be similar. Figure 3 presents the predicted distribution between the water and sludge of APIs based on the determined K_ds and selected typical primary and secondary sludge outputs from the WWTP. All APIs detected, and hence the APIs for which no sorption isotherms were determined are included (both those with too low sorption and those with too strong

sorption for the experimental design used). Figure 3 includes 37 APIs which mainly are present in the water phase at >80%. For 15 of the APIs, the sorption was so strong that the fraction in the water phase was 20% or less. For 13 of those, sorption was too strong that isotherms were not obtained. The estimated water fraction for the APIs showed that they could be distributed from 100 % in the water phase to 13% in the water phase (see Fig. 3).

Earlier investigations of APIs removal in activated sludge (Göbel et al., 2005) distinguished between different treatments steps in the WWTP. For Sulfamethoxazole and Trimetoprim the API removed by sorption can be compared with the present study. Göbel et al. (2005) found 1.5% and 4% as total removal of these compounds to primary and secondary sludge, respectively. The removal of those compounds was in this study approximately 10% (see Fig. 3) for both APIs. Ra et al. (2008) presents the removal for Estradiol, Diclofenac and Ibuprofen which were in the same range as in the present study, see Figure 3.

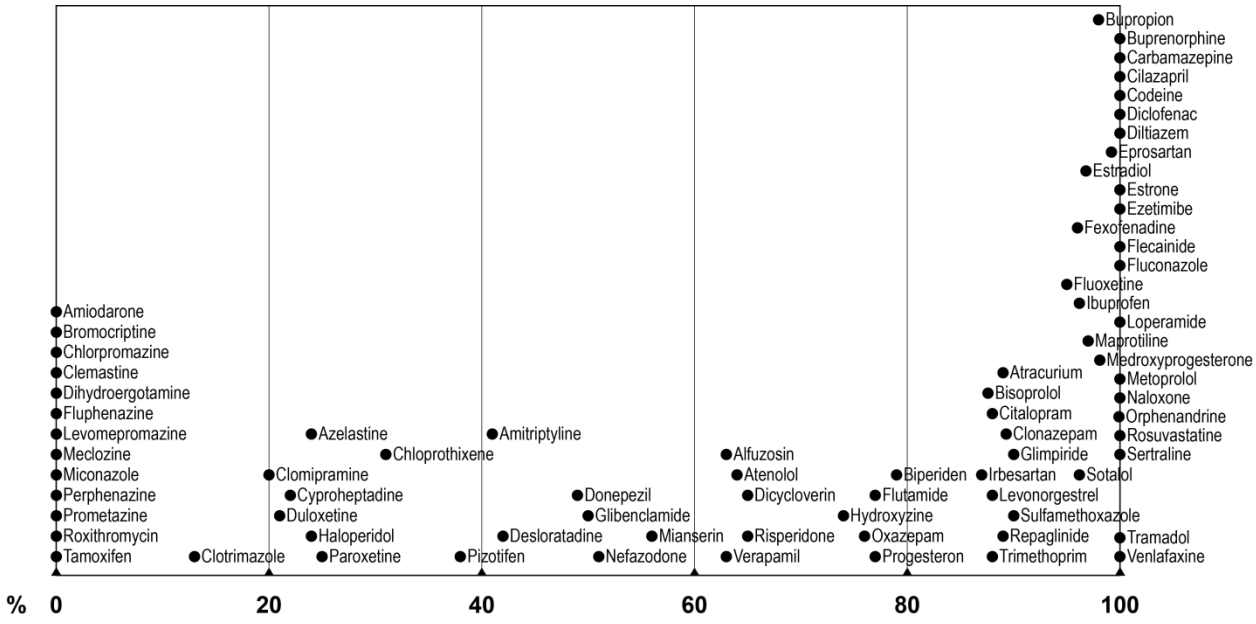

Figure 3. Estimated fraction, i.e. the fraction of the total APIs load into the activated sludge tank which isn't lost either by degradation or stripping, of the API in the water phase based on

experimentally determined sorption isotherms obtained by using primary and secondary sludge. For further information see supplementary data Figure S1.

4. Conclusion

In this study experimentally derived sorption isotherms are presented along with the corresponding obtained K_d values. The obtained K_d values were used in order to estimate the removal of the APIs in the WWTPs due to sorption to sludge.

The major findings from this study are:

- Experimentally derived K_d values and sorption isotherms for 52 APIs.
- For 13 APIs sorption to sludge was stronger than 1.2×10^6 L kg^{-1}
- For 10 APIs sorption to sludge was less than 100 L kg^{-1}.
- The estimation of removal due to sorption (in the absence of degradation and stripping) demonstrated that for 31 APIs were fractioned >80% of the initial concentration would be recovered in the liquid phase.
- 15 APIs have high affinity towards the sludge, i.e. <20% of the initial concentration would be found in the liquid phase. These APIs will therefore mainly be removed from the wastewater with the sludge, unless they are biodegraded significantly during treatment.

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Supplementary information

S1. Supplementary information regarding sample extraction and analyses using LC-MS/MS.

The filters used in order to remove particles from the water phase were rinsed once in MeOH followed by deionized water before use. The filtered samples were adjusted to pH 3 with a strong phosphate buffer. As surrogate standards, a mixture of 13 ^{13}C and ^{2}D labelled APIs was employed, containing Amytriptyline, Carbamazepine, Ciprofloxacin, 17β-Ethinylestradiol (EE2), Fluoxetinee, Ibuprofen, Oxazepam, Promethazinee, Risperidone, Sulfamethoxazole, Tamoxifen, Tramadol and Trimetoprim. The samples were extracted employing solid phase extraction (SPE), Oasis HLB 6cc/200 mg, 30µm (Waters, Sweden). Before loading the samples, the cartridges were solvated and conditioned as follows; 5 mL EtAc followed by 5 mL MeOH and 5 mL acified water pH 3. The cartridges were freeze dried over night and thereafter stored in a freezer at -20ºC until analysis was performed. The cartridges were eluted with 5 mL MeOH followed by 2 mL EtAc, extracts were evaporated to dryness and the solvent was changed to 30 % MeOH with 0.1 % formic acid before analysis by LC-MS/MS. The same methodology as that reported in Grabic et al. (unpublished data), Fick et al., (2009) was used for this analysis. Hence, detailed information on chromatographic settings, mass transitions, collision energies, scan times, mass spectrometric settings, etc. can be found there. In short, a triple stage quadrupole MS/MS TSQ Quantum Ultra EMR (Thermo Fisher Scientific, San Jose, CA, USA) coupled with an Accela LC pump (Thermo Fisher Scientific, San Jose, CA, USA) and a PAL HTC autosampler (CTC Analytics AG, Zwingen, Switzerland) were used as analytical system. 20 µL of the sample was loaded onto a Hypersil GOLD aQ TM column (50 mm x 2.1 mm ID x 5 µm particles, Thermo Fisher Scientific, San Jose, CA, USA) preceded by a guard column. A gradient of flow and

MeOH and ACN in water (all solvents buffered by 0.1% formic acid) was used for elution of analytes. Both heated electrospray (HESI) and atmospheric pressure photoionization (**APPI**) in positive and negative ion modes were used for ionisation of target compounds. Both first and third quadrupoles were operated at resolution 0.7 FMWH, and two or three selected reaction monitoring (SRM) transitions were monitored for each analyte. SRM is an analogue to the more common monitoring method, single ion monitoring (SIM) in standard mass spectrometry. With SRM, the ion monitored in the first step is required to form a given fragment through a selected reaction in order to be positively identified. Samples were quantified using the SRM method. Several calibration standards covering all concentration ranges were measured before, in the middle and at the end of sample sequences. The maximum difference between results at quantification and qualification mass transition was set to 30% as criterion for positive identification.

Table S1 NOMENCLATURE

API	active pharmaceutical ingredient
APPI	atmospheric pressure photoionization
C_0	measured concentrations of API in the water phase without sludge
C_s	calculate concentration of APIs sorbed to the sludge
C_w	measured concentrations of API in the water phase
DOM	dissolved organic matter
GC/F	glass microfiber filter
HESI	heated electro spray ionisation
K_d	distribution coefficient
K_{DOC}	distribution coefficient dissolved organic carbon
LC-MS/MS	liquid chromatography coupled with tandem mass selective detector
LOQ	limit of quantification
n	Freundlich exponent
PE	person equivalents
SIM	single ion monitoring
SPE	solid phase extraction
SRM	selected reaction monitoring
SS	suspended solids
RESS	mass of the sludge removed
τ_{max}	the total number of surface sites per mass of sorbent
VSS	volatile suspended solid

Table S2. Presenting the APIs included in the present study and the calculated Henry's Law constant (K_H; Atm m^3 mol^{-1})

Alfuzosin	9.5×10^{-20}	Dihydroergotamine	1.1×10^{-26}	Medroxyprogesterone	1.3×10^{-8}
Amiodarone	1.8×10^{-12}	Diltiazem	8.6×10^{-17}	Metoprolol	1.4×10^{-13}
Amitriptyline	6.8×10^{-8}	Donepezil	1.2×10^{-12}	Mianserin	8.1×10^{-10}
Atenolol	1.4×10^{-18}	Duloxetine	5.4×10^{-10}	Miconazole	2.4×10^{-9}
Atracurium	2.0×10^{-35}	Eprosartan	5.6×10^{-17}	Naloxone	5.4×10^{-19}
Azelastine	2.6×10^{-13}	Estradiol	3.6×10^{-11}	Nefazodone	1.5×10^{-17}
Biperiden	2.5×10^{-10}	Estrone	3.8×10^{-10}	Orphenadrine	4.1×10^{-9}
Bisoprolol	2.9×10^{-15}	Ezetimibe	4.4×10^{-18}	Oxazepam	5.5×10^{-10}
Bromocriptine	1.1×10^{-25}	Fexofenadine	1.2×10^{-18}	Paroxetine	1.1×10^{-11}
Buprenorphine	7.8×10^{-18}	Fecainide	5.8×10^{-13}	Perphenazine	5.2×10^{-18}
Bupropion	1.0×10^{-7}	Fluconazole	1.0×10^{-13}	Pizotifen	2.6×10^{-8}
Carbamazepine	1.1×10^{-10}	Fluoxetine	8.9×10^{-8}	Progesterone	6.5×10^{-8}
Chlorpromazine	3.7×10^{-10}	Fluphenazine	6.1×10^{-17}	Promethazine	5.0×10^{-10}
Chlorprothixene	2.5×10^{-9}	Flutamide	3.7×10^{-10}	Repaglinide	1.3×10^{-17}
Cilazapril	1.8×10^{-18}	Glibenclamide	7.6×10^{-19}	Risperidone	2.2×10^{-16}
Citalopram	2.7×10^{-11}	Glimepiride	1.4×10^{-21}	Rosuvastatin	1.5×10^{-16}
Clemastine	3.8×10^{-9}	Haloperidol	2.3×10^{-14}	Roxithromycin	5.0×10^{-31}
Clomipramine	7.5×10^{-9}	Hydroxyzine	3.9×10^{-17}	Sertraline	5.1×10^{-8}
Clonazepam	7.0×10^{-13}	Ibuprofen	1.5×10^{-7}	Sotalol	2.5×10^{-14}
Clotrimazole	3.1×10^{-8}	Irbesartan	7.0×10^{-15}	Sulfamethoxazole	9.6×10^{-13}
Codeine	7.6×10^{-14}	Levomepromazine	3.9×10^{-11}	Tamoxifen	4.5×10^{-10}
Cyproheptadine	9.2×10^{-9}	Levonorgestrel	7.7×10^{-10}	Tramadol	1.5×10^{-11}
Desloratadine	2.1×10^{-11}	Loperamide	6.9×10^{-19}	Trimethoprim	2.4×10^{-14}
Diclofenac	4.7×10^{-12}	Maprotiline	8.0×10^{-8}	Venlafaxine	2.0×10^{-11}
Dicycloverine	8.9×10^{-7}	Meclozine	4.6×10^{-12}	Verapamil	8.8×10^{-15}

Table S3. Sorption isotherms obtained during sorption to secondary sludge short sludge age, including 1, 10 and 50 g sludge. P is the significance that the linear model has a better fit than another model tested, the model tested was Freundlich and Langmuir.

	Linear		Freundlich				Langmuir			
	K_d	R^2 (%)	K_f	n	R^2 (%)	P (%)	τ_{MAX}	K_L	R^2 (%)	P (%)
Alfuzosin	3.5×10^{2}	73	1.2×10^{-5}	0.4	98	0.23	no fit			
Alprazolam	3.1×10^{2}	55	1.6×10^{-8}	0.3	77	0.25	no fit			
Amitryptiline	2.7×10^{3}	91	3.3×10^{-2}	0.6	98	0.01	no fit			
Atracurium	5.5×10^{2}	89	1.5×10^{-3}	0.6	98	0.01	no fit			
Azelastine	1.4×10^{3}	96	9.4×10^{-2}	0.8	97	0.72	no fit			
Biperiden	8.0×10^{2}	91	2.9×10^{-2}	0.7	95	0.52	no fit			
Bromocriptine	7.7×10^{3}	75	5.4×10^{-6}	0.3	92	0.01	no fit			
Buprenorphine	9.6E+01	71	no fit				no fit			
Bupropion	1.9×10^{2}	96	2.6×10^{-2}	0.8	97	0.60	no fit			
Chlorpromazine	8.8×10^{3}	72	3.9×10^{-8}	0.2	94	0.01	no fit			
Clemastine	7.6×10^{3}	91	3.2×10^{-2}	0.6	97	0.02	no fit			
Clomipramine	7.1×10^{3}	86	1.4×10^{-2}	0.5	97	0.01	no fit			
Clonazepam	2.9×10^{2}	66	no fit				no fit			
Cyproheptadine	5.3×10^{3}	97	0.4	0.7	99	0.01	no fit			
Desloratidine	3.0×10^{3}	90	2.9×10^{-2}	0.6	97	0.01	no fit			
Dicycloverin	1.7×10^{3}	95	9.0×10^{-2}	0.7	98	0.05	no fit			
Diltiazem	4.2×10^{2}	96	3.4×10^{-2}	0.8	98	0.15	no fit			
Duloxetine	3.2×10^{3}	84	2.6×10^{-5}	0.4	97	0.01	no fit			
Estradiol	2.3×10^{2}	70	0.3	1.0	70	87	1.4×10^{4}	1.8×10^{-5}	71	75
Etonogestrel	2.4×10^{2}	72	0.4	1.1	72	80	1.2×10^{4}	2.3×10^{-5}	72	78
Ezetimibe	8.5×103	87	7.2	1.0	87	89	no fit			
Fexofenadine	6.6×10^{2}	93	2.7×10^{-3}	0.6	98	0.03	no fit			
Finasteride	8.1×10^{2}	77	no fit				no fit			
Fluoxetine	5.3×10^{3}	86	3.8×10^{-3}	0.5	99	0.01	no fit			
Flutamide	1.2×10^{3}	94	1.7×10^{-2}	0.7	97	0.21	no fit			
Glibenclamide	2.2×10^{3}	93	3.2×10^{-2}	0.7	97	0.03	no fit			
Haloperidol	1.7×10^{3}	98	no fit				no fit			
Hydroxyzine	5.9×10^{2}	93	0.1	0.8	94	6.9	no fit			
Levomepromazine	3.8×10^{3}	96	0.3	0.7	99	0.02	no fit			
Loperamid	1.1×10^{4}	91	0.3	0.7	95	0.58	no fit			
Maprotiline	3.7×10^{3}	89	7.9×10^{-2}	0.7	95	0.06	no fit			
Medroxyprogesterone	2.5×10^{2}	92	0.6	1.1	92	41	1.3×10^{4}	2.1×10^{-5}	92	64
Megestrol	8.2×10^{2}	86	0.2	0.9	86	39	no fit			
Mianserin	5.3×10^{2}	91	0.6	1.0	91	88	no fit			
Nefazodone	8.8×10^{3}	92	7.4×10^{-2}	0.6	98	0.01	no fit			
Orphenadrine	4.8×10^{2}	87	2.1×10^{-3}	0.6	93	0.09	no fit			
Oxazepam	1.6×10^{3}	95	no fit				no fit			
Paroxetine	8.1×10^{3}	79	1.9×10^{-4}	0.4	97	0.01	no fit			
Pizotifen	3.0×10^{3}	97	0.2	0.7	99	0.01	no fit			
Progesterone	1.0×10^{3}	95	0.2	0.8	96	3.3	no fit			
Promethazine	2.8×10^{3}	89	3.2×10^{-2}	0.6	96	0.03	no fit			
Sotalol	7.1×10^{2}	95	6.3×10^{-2}	0.8	98	0.09	no fit			
Telmisartan	5.8×10^{2}	70	no fit				no fit			
Trihexyphenidyl	6.8×10^{2}	83	5.8×10^{-4}	0.6	92	0.04	no fit			
Trimetoprim	2.6×10^{2}	91	3.4×10^{-3}	0.7	97	0.01	no fit			
Zolpidem	1.4×10^{2}	91	no fit				no fit			

Table S4. Based on the best fitted sorption isotherms for each API and the removal of sludge in a Swedish average WWTP the fraction of the APIs passing through the WWTP was calculated. In the case were the linear isotherm were not the best fitted a K_d value was calculated assuming an water concentration of 1µg L^{-1}. F_{wP} = Primary sludge water fraction, F_{wS}= Secondary sludge water fraction and F_{wT}=total fraction in water.

	Primary sludge	Secondary sludge long sludge age	F_{wP} (%)	F_{wS} (%)	F_{wT} (%)
Afluzosin	Linear	Langmuir	73	86	63
Amitryptiline	Linear	Linear	54	77	41
Atenolol	Linear	Langmuir	91	70	64
Atracurium	Linear	Linear	93	95	89
Azelastine	Langmuir	Linear	29	82	24
Biperiden	Linear	Linear	85	92	79
Bupropion	Freundlich	Linear	100	98	98
Chloprothixene	Linear	Linear	97	32	31
Citalopram	Linear	Linear	90	98	88
Clomipramine	Linear	Freundlich	22	91	20
Clotrimazol	Linear	Freundlich	13	100	13
Cyproheptadine	Linear	Linear	31	72	22
Desloratidine	Linear	Linear	56	76	42
Dicycloverin	Linear	Linear	77	84	65
Donepezil	Linear	La	57	86	49
Duloxetine	Linear	Linear	28	76	21
Ezetimibe	Freundlich	Freundlich	100	100	100
Fexofenadine	Linear	Linear	100	96	96
Fluoxetine	Freundlich	Freundlich	96	99	95
Flutamide	Linear	Freundlich	77	100	77
Glibenclamide	Linear	Linear	57	87	50
Glimepiride	Freundlich	Linear	100	90	90
Haloperidol	Linear	Linear	31	76	24
Hydroxyzine	Linear	Linear	80	93	74
Irbesartan	Linear	Freundlich	87	100	87
Loperamide	Freundlich	Freundlich	100	100	100
Maprotiline	Freundlich	Freundlich	98	100	97
Mianserin	Linear	Linear	61	91	56
Nefazodone	Freundlich	Linear	98	52	51
Oxazepam	Linear	Linear	86	89	76
Paroxetine	Linear	Freundlich	25	100	25
Pizotifen	Linear	Linear	51	75	38
Progesterone	Linear	Linear	86	89	77
Repaglinide	Linear	Langmuir	97	92	89
Risperidone	Linear	Langmuir	72	90	65
Sertraline	Freundlich	Freundlich	100	100	100
Sulfamethoxazol	Linear	Linear	94	96	90
Trimethoprim	Linear	Linear	92	96	88
Verapamil	Linear	Langmuir	72	86	63

Figure S1.

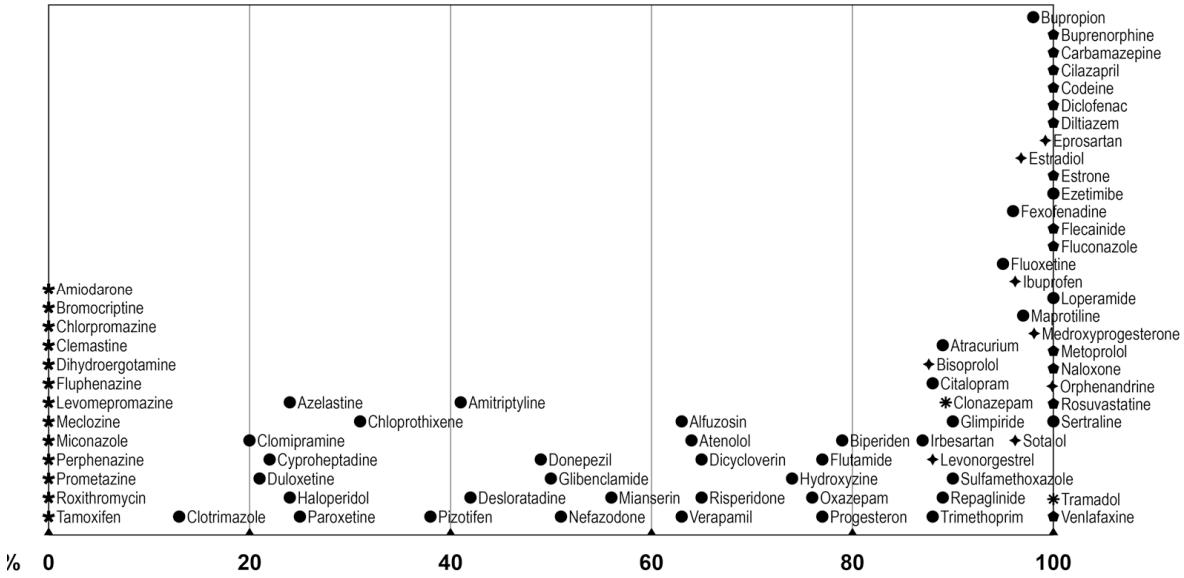

Figure S1. Estimated fraction, i.e. the fraction of the total APIs load into the activated sludge tank which isn't lost either by degradation or stripping, of the API in the water phase based on experimentally determined sorption isotherms. ●) experimentally determined K_ds for primary and secondary sludge; ✱) experimentally determined K_ds for the primary sludge and assuming no sorption to the secondary sludge as sorption were too low to be obtained in the present experiment; ✦) experimentally determined K_ds for the secondary sludge and assuming no sorption to the primary sludge as sorption were too low to be obtained in the present experiment; ⬟) assuming no sorption to neither one of the sludges as the sorption were too low to be obtained in the present experiment; ✱) assuming high sorption due to too high sorption in the present study.