# PROCESSES OF DISTRIBUTION OF PHARMACEUTICALS IN SURFACE FRESHWATERS: IMPLICATIONS FOR RISK ASSESSMENT

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## Abstract

The global consumption and production of pharmaceuticals is increasing concomitantly with concern regarding their environmental fate and effects. Active pharmaceutical ingredients are mainly released into the aquatic environment through wastewater effluent discharge. Once in the environment, pharmaceuticals can undergo processes of natural attenuation, i.e. dilution, sorption, transformation, depending on physico-chemical properties of the compound, such as water solubility, lipophilicity, vapour pressure, and environmental conditions, such as pH, temperature and ionic strength. A major natural attenuation process is the sorption on dissolved organic matter, colloids, suspended solids and sediments, which in turn control pharmaceuticals distribution, residence time and persistence in aquatic systems. Here we review studies of sorption capacity of natural sorbents to pharmaceuticals. These report on the importance of several environmental and sorbent-specific properties, such as the composition, quality, and amount of the sorbent, and the environmental pH, which determines the speciation of both the sorbent and compound. The importance of accounting for distribution processes on freshwater sorbents for any determination of environmental concentrations of pharmaceuticals is apparent, while the reliability of surrogate standards for measuring dissolved organic matter (DOM) distribution is evaluated in the context of the need for robust environmental risk assessment protocols.

## Keywords

# 1. Introduction

The global pharmaceuticals market is expanding year on year, leading to their presence in sewage effluent (Gardner et al. 2012, 2013), and subsequent concerns regarding the ecosystem impact of these emerging contaminants. Active pharmaceutical ingredients have received attention, since reports of endocrine disruption in fish from $17\alpha$-ethinylestradiol in the ng $L^{-1}$ range (Purdom et al. 1994; Sumpter and Jobling 1995), secondary poisoning of Indian vulture populations caused by the non-steroidal anti-inflammatory drug diclofenac (Swan et al. 2006) and antibiotic resistance (Kookana et al. 2014). Improvements in analytical technologies mean that many new compounds can be detected in environmental matrices at very low concentrations (< 1 ng $L^{-1}$) and the increased number of studies demonstrating the presence of pharmaceuticals in surface and groundwater worldwide have been undertaken alongside evidence of ecotoxicological effects (Nikolaou et al. 2007; Brausch et al. 2012).

Pharmaceuticals comprise a large and diverse class of compounds used for the prevention, cure or treatment of diseases in humans and animals, and include about 1450 molecules differing in physicochemical and biological properties and mode of action (Kinch et al. 2014). Although clinical testing ensures that human biological effects are well known (Ågerstrand et al. 2015), uncertainties exist concerning the environmental risk posed by pharmaceuticals. This is due to limited knowledge concerning their fate and behaviour in wastewaters and the environment, their uptake, metabolism and excretion, pharmacokinetics, in wildlife, and their target affinity and functional effects, pharmacodynamics, in non-target species (Arnold et al. 2014; Verbruggen et al. 2018). Pharmaceuticals which are persistent, bioavailable, toxic and mobile, i.e. high solubility, are of greatest concern. Furthermore, complexation, or conjugation, of pharmaceuticals

and the generation of metabolites during sewage treatment, or in the environment, create further uncertainty regarding environmental exposure and ecotoxicological effects (Boxall et al. 2012).

The principal source of human pharmaceuticals to the environment is via discharge of treated and untreated wastewater (Daughton and Ternes 1999; Kookana et al. 2014; Malik et al. 2015). Despite the high degree of degradability of some pharmaceuticals, continuous inputs can result in pseudo-persistent behaviour (Grenni et al. 2013). Industrial manufacturing plants are also considered important point sources of pharmaceuticals to the environment (Cardoso et al. 2014; Larsson 2014), as well as livestock farming and aquaculture, which are significant sources of veterinary pharmaceuticals (Carmosini and Lee 2009; Shimizu et al. 2013; Song and Guo 2014). Fig 1 depicts the known environmental pathways of pharmaceuticals (Heberer 2002; Benotti et al. 2009).
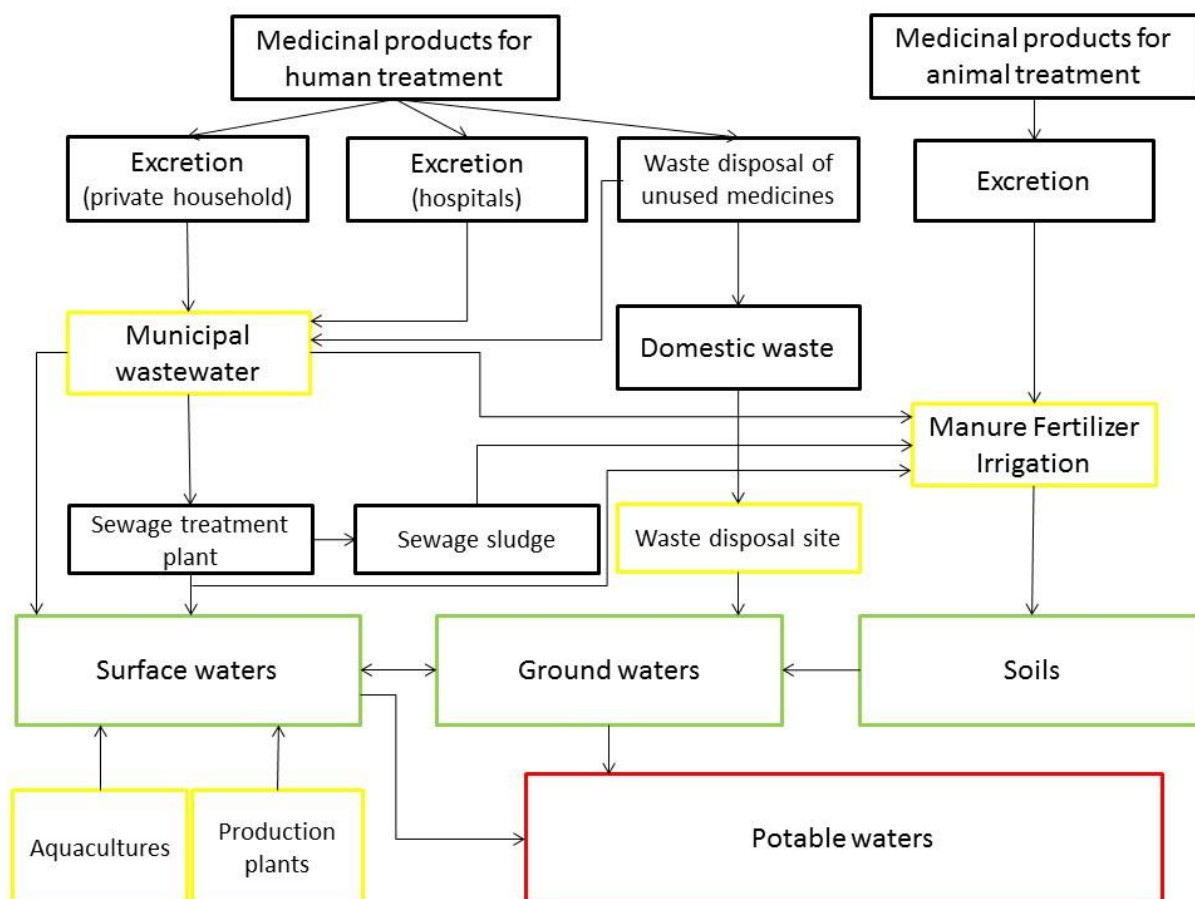
**Fig 1.** Sources and pathways of pharmaceuticals to the environment and the intermediate steps encountered between the point source and the receiving environmental compartment (Heberer 2002). Yellow boxes depict the main point sources to the environment; green boxes represent the receiving environmental compartments; the red box indicates a direct source of human exposure.

Once in the environment, pharmaceutical concentrations may be reduced by physical, biological or chemical processes. These processes, summarised in Fig 2, include dilution, transformation such as photo-degradation, bio-degradation, and hydrolysis, and sorption (Gurr and Reinhard 2006). Natural attenuation may reduce environmental concentrations, and therefore potential toxicity of chemicals (Tappin et al. 2012, 2014; West and Rowland 2012). Its extent determines the fate of contaminants in the environment, namely occurrence, distribution, and bioavailability (Lin et al. 2010).
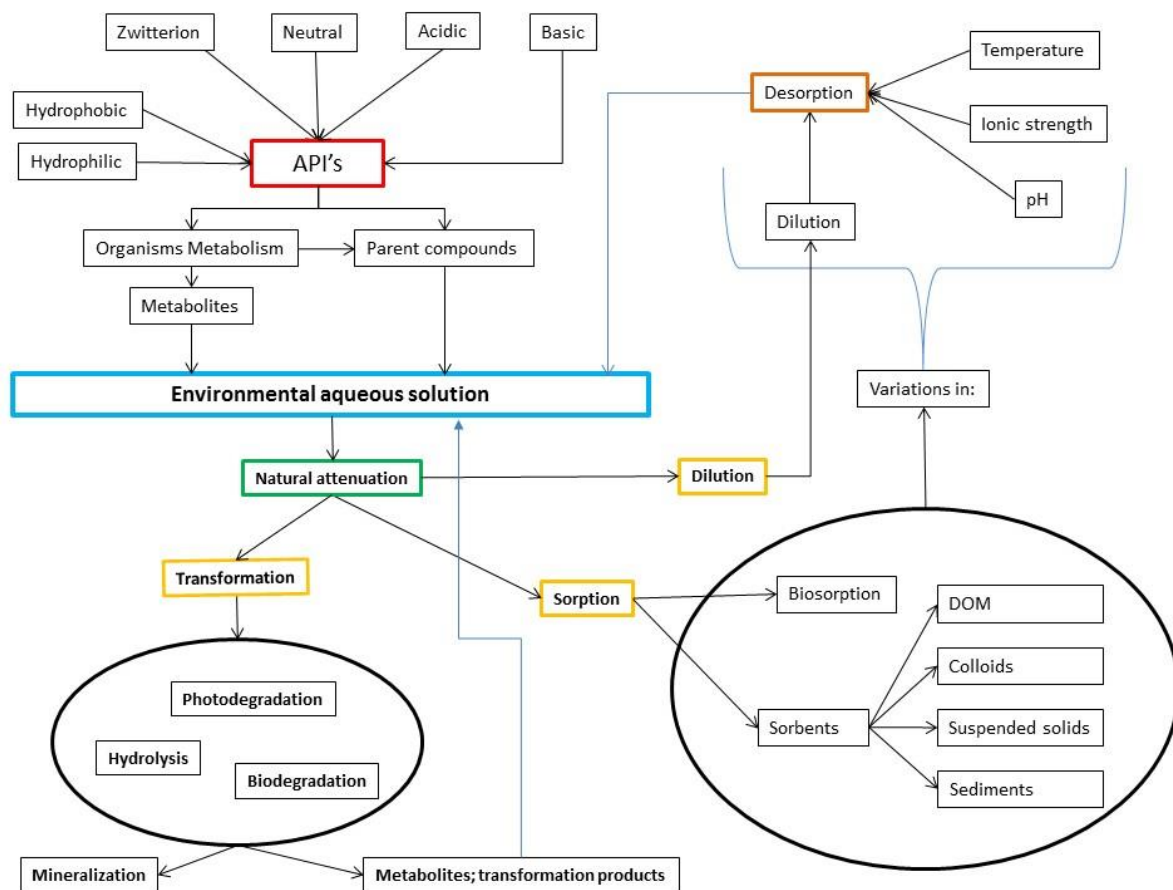
**Fig 2.** Pathways representing the environmental fate of pharmaceuticals. The red box refers to pharmaceutical characteristics; the blue box depicts the environmental receiving compartment; the yellow boxes serve as subdivision of the three main attenuation mechanisms; the orange box indicates the desorption factors; the pale blue coloured arrows are dissolution pathways; DOM is Dissolved Organic Matter.

Attenuation of pharmaceuticals through partitioning onto sorbents in surface waters can be significant in controlling distribution, residence time and persistence in aquatic systems (Lützhøft et al. 2000); as a result ecotoxicological effects might be either reduced, as the pharmaceutical is less bioavailable, or increased through bioconcentration (Ra et al. 2008). The extent and reversibility of partitioning depends on both the pharmaceutical and sorbent surface characteristics (Delle Site 2001). The degree of partitioning is expressed by the partition coefficient (K), which is the particulate : solution concentration ratio of the pharmaceutical. The pharmaceutical functionality; basic, acidic, neutral or zwitterion, is critical in controlling its fate. For ionisable compounds, where the degree of ionization is pH-dependent, expressed by the acid dissociation constant,

p$K_a$. Fig 3 demonstrates the ionisation behaviour of molecules representing basic, acidic and zwitterion pharmaceuticals at pH 5 – 9. Basic compounds are fully ionised at the lower pH and the neutral fraction abundance increases above pH 7 (Fig 3A), whilst acidic pharmaceuticals demonstrate converse behaviour (Fig 3B). The zwitterion, ofloxacin, contains at least one charge over the pH range (Fig 3C). These pH-related changes in the abundance of each species affect their distribution in aquatic environments.
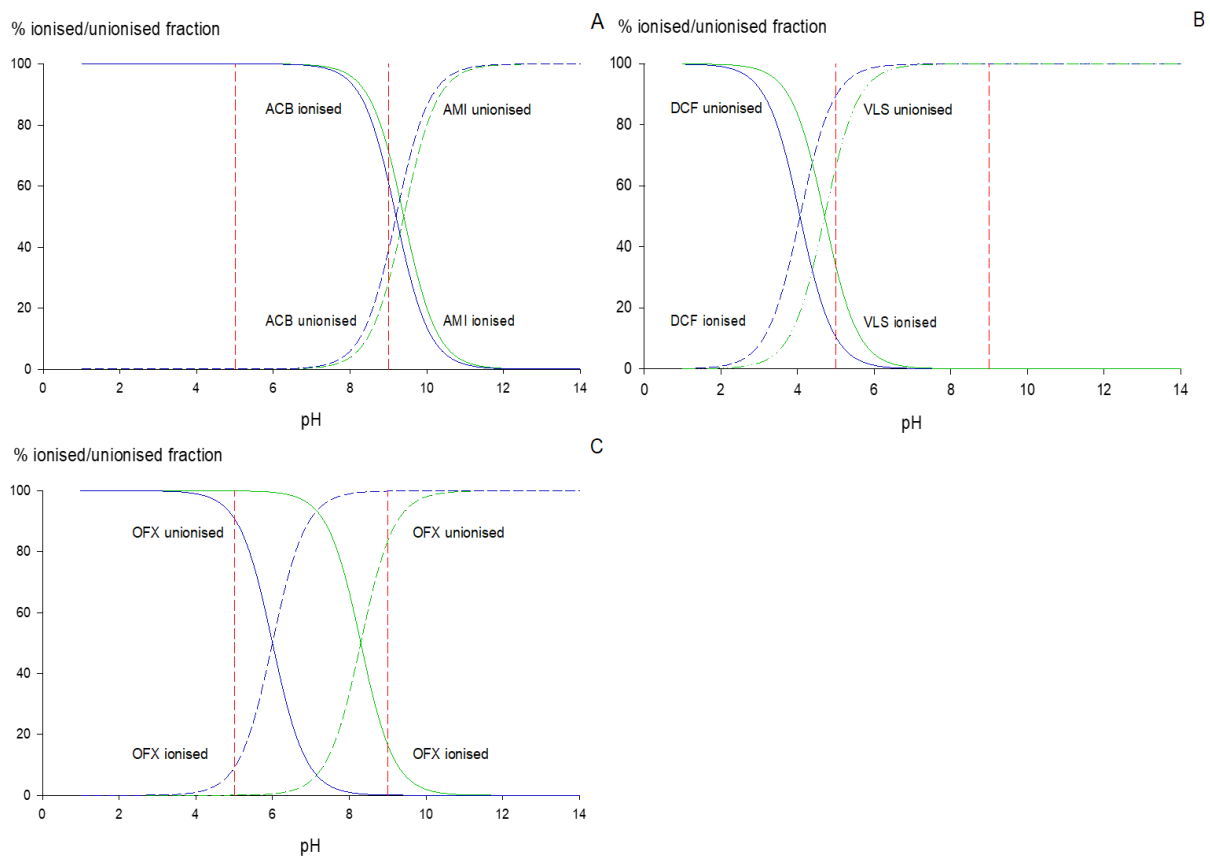


**Fig 3.** pH-dependent ionization for A. two basic compounds, amitriptyline (AMI) (pKa 9.4) and acetobutol (ACB) (pKa 9.2) B. two acidic compounds, diclofenac (DCF)(pKa 4.0) and valsartan (VLS)(pKa 4.7). C. the zwitterion ofloxacin (OFX) (pKa basic 8.3, acidic 6.0). All the functionalities show an unionised fraction environmental pH range (red lines).

The main sorbents in aquatic environments are dissolved organic matter (DOM), colloids, suspended solids and sediments (Fig 2).

## 1.1 Dissolved organic matter

DOM is a biogeochemical product which interacts with organic pollutants in water (Leenheer and Croué 2003). It can be derived from natural or anthropogenic sources and is present in natural waters at concentrations ranging from 0.1 mg $L^{-1}$ in groundwater to above 300 mg $L^{-1}$ in wastewater (Leenheer and Croué 2003; Tchobanoglous et al. 2003). DOM has not been completely characterized but is regarded as a mixture of aliphatic and aromatic compounds with some predominant chemical functionality, including hydroxyl, carboxyl, amido and keto groups (Leenheer and Croué 2003). For experimental purposes, environmental DOM is physically filtrated from water, typically 0.45 or 0.2 μm membranes, and chemically fractionated (e.g. via sorption and elution from resins) in order to obtain operationally-defined DOM fractions, namely hydrophobic or hydrophilic, and the acidic, basic or neutral sub-classes (Filella 2009; Maoz and Chefetz 2010). Further classification is based on fluorescence excitation-emission matrix patterns, which show distinct "protein-like" and "humic-like" peaks (Hudson et al. 2007). DOM in aquatic environments can be derived from *in situ* autochthonous sources by bacterio-plankton activity, or introduced via carbon recycling (Michael-Kordatou et al. 2015).

## 1.2 Colloids

Colloids are often defined as particles in the size range between 1nm and 1 μm; they include clays such as layered silicates, metal oxides such as Fe- and -Al- hydroxides, organic material such as humic acids, proteins, and bio-colloids such as bacteria, viruses, and are ubiquitous in the environment (Zhou et al. 2007). Colloids are formed and transported to surface waters by weathering and biological processes. Their large specific surface area and sorption capacity play a crucial role in the speciation, bioavailability and transport of substances in the aquatic environment (Zhou et al. 2007; Xing et al. 2015).

## 1.3    Suspended solids and sediments

Suspended solids are a source of material that, in the case of contaminant loads, becomes a medium for accumulation in the sediment compartment (Lahti and Oikari 2011). Sediments are defined as settled material derived from weathering, erosion of minerals, and decay of organic matter, and transported by the action of the wind, water or ice, and the force of gravity acting on the suspended solids. Sediments provide an important environmental surface for partitioning processes; and therefore, are of importance in determining the fate of chemicals in the environment.

## 1.4    Importance of sorption in risk assessments

Sorption processes are important in determining predicted environmental concentrations for environmental risk assessments. For example, the OSPAR convention states that compounds with distribution coefficient (log $K_{ow}$) above 4.5 are screened for persistence, bioaccumulation and toxicity, following European Technical Guidance on Risk Assessment (European Comission Joint Research Centre, 2003).  The European Medicines Agency guidelines for the environmental risk assessment of pharmaceutical compounds proposes a Phased approach. Phase 1, a pre-screening worst-case scenario, considers the parent compound only, irrespective of mode of administration, metabolism and excretion (EMA 2006). If the predicted environmental concentration is above 0.01 µg L$^{-1}$, Phase 2 entails analysis of the environmental fate and effects, although a tailored environmental risk assessment could be triggered below this threshold if the pharmaceutical is shown to affect reproduction. A PBT assessment is required at Phase 1 for APIs that have a Log $K_{ow}$ > 4.5.  Phase 2 is a tiered phase, comprising Tiers A and B. Tier A involves the ready biodegradability test (OECD 1992) followed by a water-sediment distribution study if the analyte is shown to be persistent (OECD 2000). Toxicity tests are also performed to allow for a Predicted No Effect Concentration to be estimated.

If the "Predicted Environmental Concentration" : "Predicted No Effect Concentration" ratio indicates a risk, a Tier B assessment should be conducted where the predicted environmental concentration for surface water is refined to include information from wastewater treatment plant modelling using the SimpleTreat model (EMA 2006), where a factor is applied to allow for the partitioning of the chemical.

A terrestrial environmental risk assessment is triggered at Tier B if the $K_{oc}$ of the active pharmaceutical ingredient is >10,000. Fish bioconcentration studies at Tier B are required at Log $K_{ow}$ > 3 and a sediment toxicity assessment is required for pharmaceuticals where 10 % of the applied radioactivity adsorbs to sediment in the water-sediment transformation study conducted at Tier A (EMA , 2006).

The distribution of a pharmaceutical between the particulate and dissolved phases is therefore critical in determining its environmental fate, including mobility, persistence, bioavailability and subsequent toxicity. It is also critical for defining whether a terrestrial- or sediment-based environmental risk assessment is required as part of the marketing application in Europe. There is currently no study that compiles the available partitioning data for pharmaceuticals, nor identifies the significant data gaps and relates it to pharmaceutical environmental fate. This review evaluates, for the first time, published information regarding the partitioning of pharmaceuticals to DOM, colloids, suspended solids and sediments in natural surface aquatic environments and relates this to risk assessment processes.

## 2. Meta-analysis

### 2.1. Data collection

Published studies on the distribution of pharmaceuticals in freshwater environments were screened for the collection of data, documenting the source and concentration of the sorbents used in the experiments, pH, and pharmaceutical partition coefficients along with physicochemical parameters such as p$K_a$ and log $K_{ow}$. Data sources included the open chemistry database PubChem (https://pubchem.ncbi.nlm.nih.gov/), available scientific literature and environmental fate estimation program software (EPI Suite™, Table 1, Table 2, Table 3, Table 4).

Fig 4 shows a graphical comparison of the number of articles, pharmaceuticals, metabolites and transformation products, and compounds per functionality investigated for each sorbent. Nine articles about sorption processes of pharmaceuticals to DOM, mostly reference materials but also some wastewater-derived DOM (Table 1), were identified (Lützhøft et al. 2000; Yamamoto et al. 2003; Bai et al. 2008; Carmosini and Lee 2009; Kim et al. 2010; Maoz and Chefetz 2010; Ding et al. 2013; Martínez-Hernández et al. 2014; Peng et al. 2014).

The total number of pharmaceuticals studied was 20, comprising 1 neutral species, 3 acidic, 3 basic, 13 zwitterions, and 3 metabolites. The experimental pH ranged from 3 to 8, which is a critical parameter regarding the charge present on the pharmaceutical molecule and its subsequent fate.

Four articles related to the partitioning of pharmaceuticals to colloids; extracted from samples of river water, groundwater, seawater and wastewater (Table 2) (Holbrook et al. 2004; Maskaoui et al. 2007; J. L. Zhou et al. 2007; Maskaoui and Zhou 2010). Here, 10

compounds were studied comprising 2 neutral, 3 acidic, and 5 basic species, with experimental pH ranging from 6.4 to 8.5.

Fourteen articles referring to suspended solids and sediment partitioning were identified, with 70 compounds studied (Löffler et al. 2005; Stein et al. 2008; Ra et al. 2008; Yamamoto et al. 2009; Lin et al. 2010; Maskaoui and Zhou 2010; Githinji et al. 2011; Lahti and Oikari 2011; Zhou and Broodbank 2014; Martínez-Hernández et al. 2014; Paul et al. 2014; Svahn and Bjorklund 2015; Li et al. 2015; Al-Khazrajy and Boxall 2016). Of the compounds studied, 4 were metabolites and 8 were transformation products; 20 were acidic, 38 basic, 7 neutral, and 3 were zwitterions across a pH range of 3.5 to 10 (Table 3, Table 4).

Suspended solids and sediments dominated the studies on pharmaceuticals (70), where a number of metabolites and transformation products were also investigated. Basic compounds were most studied in suspended solids and sediments (38), followed by the acidic (20), neutral compounds (7), and zwitterions (3). The distribution to colloids was investigated for 5 basic, 3 acidic and 2 neutral compounds. The DOM distribution studies included the largest amount of zwitterion compounds (13), followed by acidic (3), basic (3) and neutral (2).
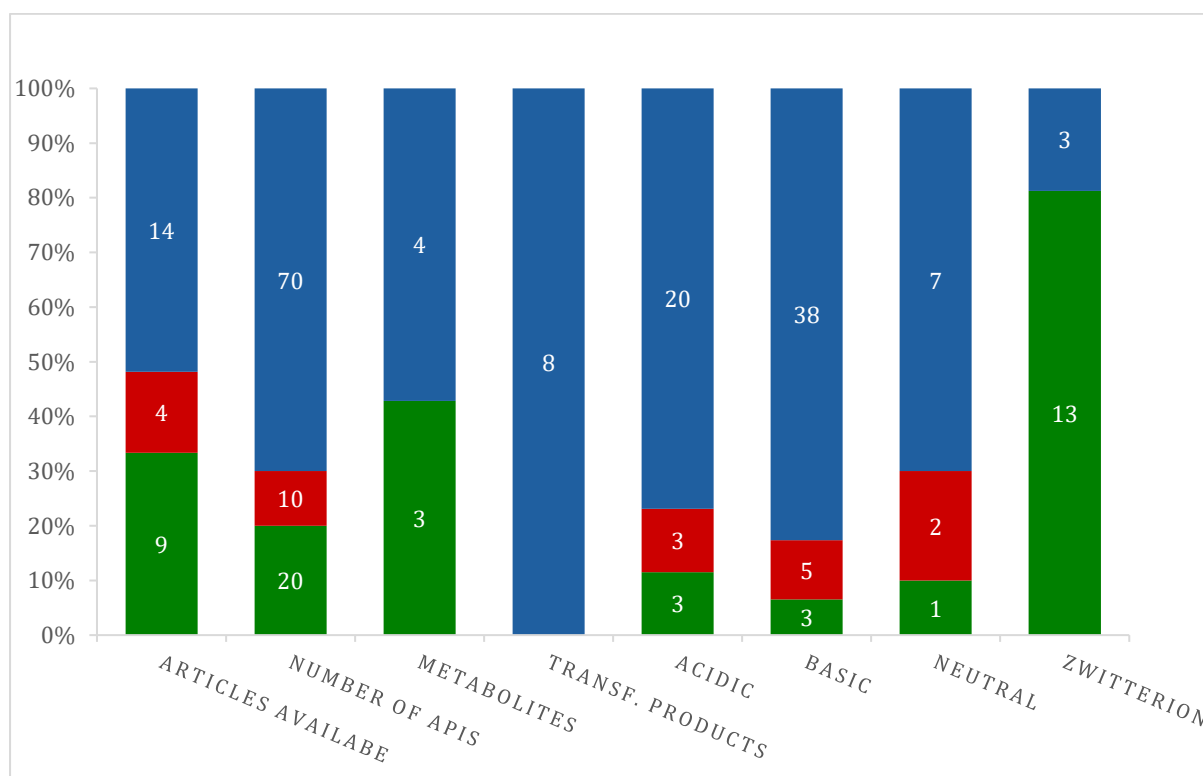
**Fig 4.** A comparison of published articles on pharmaceuticals partitioning to DOM (green), colloids (red), suspended solids and sediments (blue). The columns, from left to right, refer to the number of articles, the number of studied active pharmaceutical ingredients (APIs), metabolites identified, transformation products identified, classification according to pharmaceuticals' functionality: acidic, basic, neutral and zwitterion.

The measured organic carbon-water distribution values ($K_{oc}$) of each compound were plotted against the corresponding octanol-water distribution coefficient values ($K_{ow}$) for the three sorbents; i.e. DOM, colloids, and suspended solids and sediments. No relationship was apparent which deviates from correlations for non-polar organics. However, selecting only the neutral pharmaceuticals and plotting organic carbon normalised log $K_{oc}$ against corresponding log $K_{ow}$ for each sorbent did show a linear relationship for DOM ($R^2$=0.846), albeit for a limited number of data (n=5). No significant relationship was observed for other sorbents (Fig 5).
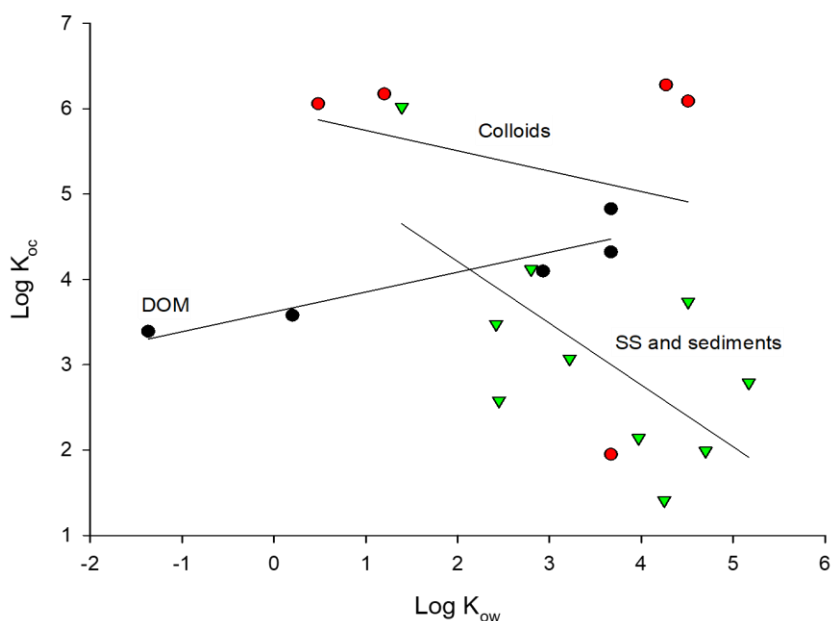
**Fig 5.** Organic carbon-water ($K_{oc}$) distribution values of the neutral compounds plotted against the correspondent octanol-water ($K_{ow}$) distribution coefficient value for each sorbent, namely dissolved organic matter (DOM) (black dots) $R^2$=0.846, colloids (red dots) $R^2$=0.055, suspended solids and sediments (green triangles) $R^2$=0.450; Showing a significant relationship only for DOM, though for a very limited number of data (5).

## 2.2. Partitioning to dissolved organic matter

Yang et al. (2011) reported a weak positive linear relationship ($R^2$= 0.509) between the freshwater total concentration of five groups of antibiotics and DOM. Furthermore, Lützhøft et al. (2000) demonstrated an inverse relationship between the concentration of "free" pharmaceuticals in solution and DOM concentration, limiting bioavailability and possibly toxicity (Urrestarazu Ramos et al. 1998; Rowett et al. 2016), but increasing environmental persistence. These two studies highlight both the lack of available data as well as a potentially significant role for DOM in determining environmental exposure to pharmaceuticals.

### 2.2.1   Dissolved organic matter composition

The composition of DOM is source-dependent. For example, anthropogenic wastewater is mainly composed of proteinaceous matter, whilst freshwater DOM is dominated by

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humic substances (Hudson et al. 2007; Hernandez-Ruiz et al. 2012). The partitioning of the β-blocker propranolol on DOM derived from river and lake surface water generated log $K_{dom}$ values ranging from 3.9 - 5.2 L kg$^{-1}$ (Table 1), with protein-like DOM associated with lower values and humic-like substances exhibiting highest log $K_{dom}$ (Peng et al., 2014). Similar results were obtained for the anti-epileptic drug, carbamazepine, which showed most extensive partitioning to humic substances, including fulvic acids from landfill leachate, river water and Amherst humic acid, with log $K_{dom}$ between 3.41 and 5.04 L kg$^{-1}$ (Table 1)(Hernandez-Ruiz et al. 2012). However, complexation of carbamazepine with tryptophan-like DOM was also significant, suggesting an important role for anthropogenic organic matter in the transport and transformation of such pharmaceuticals (Wang et al. 2016). Since carbamazepine is a neutral compound, hydrophobic sorption mechanisms to humic acid were proposed (Bai et al. 2008).

### 2.2.2   *Organic matter reference standards as a proxy for partitioning of pharmaceuticals*

The use of reference standards of humic DOM as a proxy for measuring partitioning of pharmaceuticals to DOM may result in an overestimation of the binding capacity. Carmosini and Lee (2009) and Peng et al. (2014) investigated the partitioning of the zwitterion, ciprofloxacin, to contrasting DOM types at different pH and ionic strengths. The DOM included Leonardite standard humic acid, Pahokee Peat humic acid, Pahokee Peat II standard fulvic acid and Elliott Soil II standard fulvic acid. Other DOM types were obtained from digested and undigested municipal biosolids, municipal wastewater effluent, and beef industry lagoon wastewater. The wastewater-derived DOM showed much less affinity for ciprofloxacin than the reference humic standards. Furthermore, the former did not show a pH-sorption correlation as in the latter DOM type, which suggests that a mechanism other than ion exchange was controlling the sorption process. These interactions are likely driven by the more aliphatic protein composition of the

wastewater-derived DOM than the aromatic humic DOM of the reference standards, exhibiting a different sorption characteristic and cation exchange capacity. Such variation in partitioning has also been observed for pharmaceuticals, carbadox, tetracycline, and lincomycin, tested using reference standards such as Leonardite humic acid and Aldrich humic acid, where the former showed greatest sorption capacity, probably as a result of more interaction sites being available (Table 1) (Ding et al., 2013).

**Table 1** Dissolved organic matter (DOM) partition coefficient (Log K$_{DOM}$) for pharmaceuticals, sources and type of organic matter, experimental concentration and pH. Legend: * metabolites; N.A. not available.

| Compound | Type | pKa | LogK$_{ow}$ | Source of DOM | DOM type | Concentration [mg/L] | pH | Log K$_{DOM}$ [L/kg] | Reference | Year |
|---|---|---|---|---|---|---|---|---|---|---|
| 17α – ethynylestradiol | acidic | 10.21 | 3.67 | Reference standards; river; | Aldrich humic acid | 2, 10 | 7 | 4.78 | Yamamoto et al. | 2003 |
| | | | | | Suwannee river humic acid | 2, 10 | 7 | 4.80 | Yamamoto et al. | 2003 |
| | | | | | Suwannee river fulvic acid | 2, 10 | 7 | 4.55 | Yamamoto et al. | 2003 |
| | | | | | Nordic fulvic acid | 2, 10 | 7 | 4.63 | Yamamoto et al. | 2003 |
| | | | | | Alginic acid | 2, 10 | 7 | 3.23 | Yamamoto et al. | 2003 |
| | | | | | Dextran | 2, 10 | 7 | 3.04 | Yamamoto et al. | 2003 |
| | | | | | Tannic acid | 2, 10 | 7 | 5.22 | Yamamoto et al. | 2003 |
| Albendazole | zwitterion | 3.37, 9.93 | 3.07 | Reference standards; synthesis; | Aldrich humic acid | 5000-15000 | 7 | 3.52 | Kim et al. | 2010 |
| | | | | | hydroxypropyl-b-cyclodextrin | 20000 | 7 | 2.96 | Kim et al. | 2010 |
| | | | | | POPC liposome | 480-1700 | 7 | 3.77 | Kim et al. | 2010 |
| | | | | | sodium dodecyl sulfate | 10000-25000 | 7 | 3.02 | Kim et al. | 2010 |
| Amino-fenbendazole | Zwitterion | 6.94, 10.65 | 3.17 | Reference standards; synthesis | Aldrich humic acid; hydroxypropyl-b-cyclodextrin; sodium dodecyl sulfate; 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; lyposome; | 5000-15000 | 7 | n. a. | Kim et al. | 2010 |
| Carbadox | Basic | 1.98 | n. a. | Reference standards; | Leonardite | 46.4 | 8 | 3.52 | Ding et al. | 2013 |
| | | | | | Humic acids | 79.4 | 8 | 3.26 | Ding et al. | 2013 |
| Carbamazepine | Neutral | 13.9 | 2.93 | Landfill leachate | FA | 25 | 7 | 3.41 to 5.04 | Bai et al. | 2008 |
| | | | | Amherst humic acid | HA | 25 | 7 | 4.58 - 4.82 | Bai et al. | 2008 |
| | | | | Wastewater and Suwannee river. | n. a. | 8 | n. a. | n. a. | Hernandez-Ruiz et al. | 2012 |
| | | | | Sewage sludge | Bulk DOM | 1000 | 8 | 2.64 | Maoz and Chefetz | 2010 |
| Ciprofloxacin | Zwitterion | 5.9; 8.9 | 0.4 | Digested and undigested biosolids; treated wastewater; | ≤1000 Da; ≥1000 Da fraction; | 25 | n. a. | n. a. | Carmosini and Lee | 2009 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | beef lagoon wastewater; humic acids reference standards; | | | | | | |
| **Fenbendazole** | Zwitterion | 5.12, 12.72 | 3.85 | Reference standards; synthesis; | Aldrich humic acid | 5000-15000 | 7 | 3.06 | Kim et al. | 2010 |
| | | | | | hydroxypropyl-b-cyclodextrin | 20000 | 7 | 3.25 | Kim et al. | 2010 |
| | | | | | POPC liposome | 480-1701 | 7 | 3.23 | Kim et al. | 2010 |
| | | | | | sodium dodecyl sulfate | 10000-25000 | 7 | 2.92 | Kim et al. | 2010 |
| **Fenbendazole sulfone\*** | Zwitterion | 3.41, 11.12 | 2.17 | Reference standards; synthesis; | Aldrich humic acid; hydroxypropyl-b-cyclodextrin; sodium dodecyl sulfate; 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine; lyposome; | 5000-15000 | 7 | n. a. | Kim et al. | 2010 |
| **Flubendazole** | Zwitterion | 3.6, 9.6 | 2.91 | Reference standards; synthesis; | Aldrich humic acid | 5000-15000 | 7 | 2.60 | Kim et al. | 2010 |
| | | | | | hydroxypropyl-b-cyclodextrin | 20000 | 7 | 2.08 | Kim et al. | 2010 |
| | | | | | POPC liposome | 480-1702 | 7 | n.a. | Kim et al. | 2010 |
| | | | | | sodium dodecyl sulfate | 10000-25000 | 7 | 2.04 | Kim et al. | 2010 |
| **Flumequine** | Zwitterion | 6.4 | 1.72 | Reference standard; | Aldrich Humic acid | 1, 5, 12.5, 25, 50 | 3 | 3.44 | Lutzhoft et al. | 2000 |
| | | | | | | 1, 5, 12.5, 25, 50 | 4 | 3.65 | Lutzhoft et al. | 2000 |
| | | | | | | 1, 5, 12.5, 25, 50 | 5 | 4.23 | Lutzhoft et al. | 2000 |
| | | | | | | 1, 5, 12.5, 25, 50 | 6 | 4.39 | Lutzhoft et al. | 2000 |
| | | | | | | 1, 5, 12.5, 25, 60 | 7 | 4.23 | Lützhøft et al. | 2000 |
| | | | | | | 1, 5, 12.5, 25, 50 | 8 | 4.36 | Lützhøft et al. | 2000 |
| **Ibuprofen** | Acidic | 4.41 | 3.5 | Wastewater and Suwannee river. | n. a. | 8 | n. a. | n. a. | Hernandez-Ruiz et al. | 2012 |
| **Lincomycin** | Basic | 7.6 | 0.2 | Reference standard | Leonardite humic acid | 46.4 | 8 | 3.96 | Ding et al. | 2013 |
| | | | | | Aldrich humic acid | 79.4 | 8 | 3.20 | Ding et al. | 2013 |
| **Naproxen** | Acidic | 4.2 | 3.18 | Sewage sludge | Hydrophobic acid, basic, and neutral fractions; hydrophilic acid, basic, and neutral fractions. | 1000 | 8 | negligible | Maoz and Chefetz | 2010 |
| **Oxfendazole\*** | Zwitterion | 4.13, 11.79 | 1.63 | Reference standards; synthesis; | n. a. | 5000-15000 | 7 | n. a. | Kim et al. | 2010 |
| **Oxolinic acid** | Zwitterion | 6.9 | 0.68 | Aldrich humic acids; | Humic acids; | 1, 5, 12.5, 25, 50 | 3 | 3.87 | Lützhøft et al. | 2000 |
| | | | | | | 1, 5, 12.5, 25, 50 | 4 | 4.00 | Lützhøft et al. | 2000 |
| | | | | | | 1, 5, 12.5, 25, 50 | 5 | 4.37 | Lützhøft et al. | 2000 |
| | | | | | | 1, 5, 12.5, 25, 50 | 6 | 4.50 | Lützhøft et al. | 2000 |
| | | | | | | 1, 5, 12.5, 25, 50 | 7 | 4.48 | Lützhøft et al. | 2000 |

| Name | Type | pKa | log | Source | Binding phase | Concentration | pH | log value | Reference | Year |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 1, 5, 12.5, 25, 50 | 8 | 4.37 | Lützhøft et al. | 2000 |
| **p-hydroxyfenbendazole*** | Zwitterion | 5.49, 9.48, 11.38 | 3.37 | Reference standards; synthesis; | n. a. | 5000-15000 | 7 | n. a. | Kim et al., | 2010 |
| **Propranolol** | Basic | 9.7 | n. a. | River and lake surface–water filtered DOM; sediment-extracted DOM; | Humic acids; Fulvic acids; pony lake fulvic acid; | 10 | 7 | 3.90/5.20 | Peng et al. | 2014 |
| | | | | | Suwannee river fulvic acid; | 10 | 7 | 4.70 | Peng et al. | 2014 |
| **Sarafloxacin** | Zwitterion | n. a. | n. a. | Aldrich humic acids; | Humic acids; | 1, 5, 12.5, 25, 50 | 3 | 4.77 | Lützhøft et al.. | 2000 |
| | | | | | Humic acids; | 1, 5, 12.5, 25, 50 | 4 | 4.86 | Lützhøft et al. | 2000 |
| | | | | | Humic acids; | 1, 5, 12.5, 25, 50 | 5 | 5.19 | Lützhøft et al. | 2000 |
| | | | | | Humic acids; | 1, 5, 12.5, 25, 50 | 6 | 4.98 | Lützhøft et al. | 2000 |
| | | | | | Humic acids; | 1, 5, 12.5, 25, 50 | 7 | 4,74 | Lützhøft et al. | 2000 |
| | | | | | Humic acids; | 1, 5, 12.5, 25, 50 | 8 | 4.52 | Lützhøft et al. | 2000 |
| **Tetracycline** | Zwitterion | 3.3; 7.7; 7.9 | n. a. | Reference standards | Leonardite humic acid | 46.4 | 8 | 4.60 | Ding et al. | 2013 |
| | | | | | Aldrich humic acid | 79.4 | 8 | 3.27 | Ding et al. | 2013 |
| **Thiabendazole** | Zwitterion | 4.7, 12 | 2.47 | Reference standards; synthesis; | Aldrich humic acid | 5000-15000 | 7 | 2.58 | Kim et al. | 2010 |
| | | | | | hydroxypropyl-b-cyclodextrin | 20000 | 7 | 2.39 | Kim et al. | 2010 |
| | | | | | POPC liposome | 480-1703 | 7 | n. a. | Kim et al. | 2010 |
| | | | | | sodium dodecyl sulfate | 10000-25003 | 7 | 2.01 | Kim et al. | 2010 |

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### 2.2.3 Hydrophobicity of dissolved organic matter and its impact on partitioning

The role of the different DOM fractions, namely hydrophobic or hydrophilic, and the sub-classes acidic, basic or neutral, on partitioning of pharmaceuticals depends on their chemical functionalities and degree of ionisation (Lützhøft et al. 2000; Michael-Kordatou et al. 2015). For example, hydrophobic DOM fractions dominate the distribution of the acidic naproxen and the neutral carbamazepine at low pH (4), whilst at more environmentally relevant pH (6.5 - 8), the hydrophilic DOM fractions were more influential (Maoz and Chefetz 2010). In fact, despite the predominance of the acidic fraction of the hydrophilic DOM, which is expected to show little affinity for the negatively-charged naproxen, there is evidence that the neutral and basic moieties play an important role in the binding of the neutral carbamazepine and the acidic ibuprofen (Hernandez-Ruiz et al. 2013). Notwithstanding, the contribution to binding of each fraction is determined by its relative abundance in DOM mixtures (Maoz and Chefetz 2010). The calculated values regarding sorption of pharmaceuticals to bulk DOM are based on experimentally discrete fractional sorption values, and differ from bulk experimental measurements (Maoz and Chefetz 2010). On this basis, it is hypothesised that DOM fractions interact with each other at the molecular level and do not behave as independent entities in the binding processes. Thus, studying DOM fractions as discrete entities may lead to incorrect estimates of pharmaceuticals partitioning to the bulk DOM (Maoz and Chefetz 2010).

### 2.3. Partitioning to colloids

The partitioning of pharmaceuticals to colloids is poorly understood, with little supporting research available. The available data show that pharmaceuticals partition to colloids to a greater degree than other sorbents (Fig 6) (Table 2). The sorption capacity

29 of colloids is determined by the type, influenced by its source and environmental

30 compartment, such as freshwater, wastewater, or seawater. Such a variation can lead to

31 large differences in partition coefficient values for the same pharmaceutical (Zhou et al.,

32 2007). Examples include data for colloids from river water, treated effluent, and seawater

33 showing a distribution coefficient variation of a factor of 6 - 12 for the synthetic oestrogen

34 17-α ethynylestradiol. In addition, despite a higher amount of colloidal fraction in the

35 wastewater effluent, no major partitioning variation was observed between wastewater

36 effluents and freshwater colloids, whilst higher $K_{coc}$ values were observed for the lower

37 concentrations of seawater colloids. This data confirms that the physical-chemical

38 properties of the colloids have much more influence than their actual concentration on

39 the distribution of pharmaceuticals (Zhou et al., 2007).
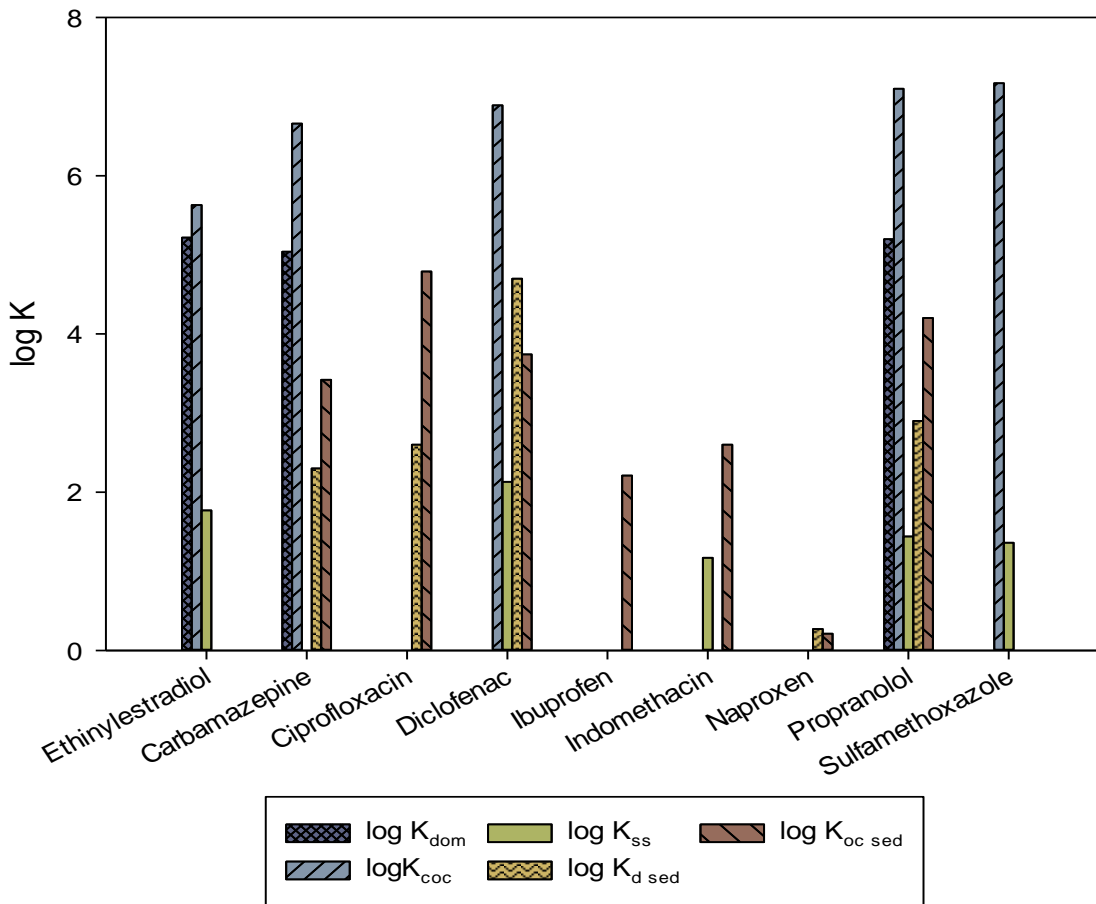
**Fig 6.** Comparison of pharmaceuticals partition coefficients for different sorbents, namely dissolved organic matter (log $K_{dom}$), colloids (log $K_{coc}$), suspended solids (log $K_{ss}$), and sediments -bulk (log $K_{d\ sed}$) and -normalized per organic matter fraction (log $K_{oc\ sed}$).

**Table 2** Colloids partition coefficients (Log K$_{coc}$) for pharmaceuticals, source and size fraction, experimental concentration and pH.
Legend: * metabolites; N.A. not available.

| Compound | Type | pKa | LogK$_{ow}$ | Source | Size fraction | Concentration (mg/L) | pH | Log K$_{coc}$ [L/kg] | Reference | Year |
|---|---|---|---|---|---|---|---|---|---|---|
| 17α-Ethynilestradiol | neutral | 10.2 | 3.67 | Biological wastewater treatment system | <30kD | 6.0 | 7.1 | 5.2 | Holbrook et al. | 2004 |
| | | | | Biological wastewater treatment system | <30kD | 5.3 | 7.1 | 3.0 | Holbrook et al. | 2004 |
| | | | | Biological wastewater treatment system | <30kD | 4.9 | 7.1 | 5.2 | Holbrook et al. | 2004 |
| | | | | Biological wastewater treatment system | <30kD | 5.1 | 7.1 | 4.5 | Holbrook et al. | 2004 |
| | | | | Biological wastewater treatment system | <100kD | 5.9 | 7.1 | 4.7 | Holbrook et al. | 2004 |
| | | | | Biological wastewater treatment system | <100kD | 5.4 | 7.1 | 4.5 | Holbrook et al. | 2004 |
| | | | | Biological wastewater treatment system | <0.22 µm | 7.7 | 7.1 | 5.4 | Holbrook et al. | 2004 |
| | | | | Biological wastewater treatment system | <0.22 µm | 7.5 | 7.1 | 4.9 | Holbrook et al. | 2004 |
| | | | | Biological wastewater treatment system | <0.22 µm | 5.5 | 7.1 | 5.0 | Holbrook et al. | 2004 |
| | | | | Biological wastewater treatment system | <0.22 µm | 7.1 | 7.1 | 5.3 | Holbrook et al. | 2004 |
| | | | | Biological wastewater treatment system | <1.5µm | 8.9 | 7.1 | 4.8 | Holbrook et al. | 2004 |
| | | | | Biological wastewater treatment system | <1.5µm | 7.7 | 7.1 | 5.0 | Holbrook et al. | 2004 |
| | | | | Biological wastewater treatment system | <1.5µm | 6.2 | 7.1 | 4.9 | Holbrook et al. | 2004 |
| | | | | Biological wastewater treatment system | <1.5µm | 7.8 | 7.1 | 5.2 | Holbrook et al. | 2004 |
| | | | | River water | between >1 kDa and <0.7 µm; | 2.3 | 6.4 | 4.57 | Zhou et al. | 2007 |
| | | | | River water | between >1 kDa and <0.7 µm; | 3 | 7.3 | 3.8 | Zhou et al. | 2007 |
| | | | | STWs effluents | between >1 kDa and <0.7 µm; | 9.2 | 7.1 | 3.73 | Zhou et al. | 2007 |
| | | | | River water | between >1 kDa and <0.7 µm; | 2.9 | 8.5 | 3.84 | Zhou et al. | 2007 |
| | | | | Sea water | between >1 kDa and <0.7 µm; | 0.4 | 8 | 4.47 | Zhou et al. | 2007 |
| | | | | STWs effluents | between >1 kDa and <0.7 µm; | 7.5 | 6.8 | 4.63 | Zhou et al. | 2007 |
| Carbamazepine | neutral | 13.94 | 2.93 | River water; STWs effluents; groundwate; | | | n. a. | 6.66 | Maskaoui and Zhou | 2010 |
| | | | | River water | between >1 kDa and <0.7 µm; | 0-30 | n. a. | 4.74 | Maskaoui, Hibberd, & Zhou | 2007 |
| Diclofenac | acidic | 4 | 4.51 | River water; STWs effluents; groundwater; | | | n. a. | 6.89 | Maskaoui and Zhou | 2010 |
| | | | | River water | between >1 kDa and <0.7 µm; | 0-30 | n. a. | 5.29 | Maskaoui, Hibberd, & Zhou | 2007 |
| Indomethacin | acidic | 3.96 | 4.27 | River water; STWs effluents; groundwater; | | | n. a. | 7.06 | Maskaoui and Zhou | 2010 |
| | | | | River water | between >1 kDa and <0.7 µm; | 0-30 | n. a. | 5.5 | Maskaoui, Hibberd, & Zhou | 2007 |
| Mebeverine | basic | 8.2 | 5.12 | River water; STWs effluents; groundwater; | | | n. a. | n. a. | Maskaoui and Zhou | 2010 |
| | | | | River water | between >1 kDa and <0.7 µm; | 0-30 | n. a. | 5.88 | Maskaoui, Hibberd, & Zhou | 2007 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Meclofenamic acid** | acidic | 3.73 | 5 | River water; STWs effluents; groundwater; | | | n. a. | n. a. | Maskaoui and Zhou | 2010 |
| | | | | River water | between >1 kDa and <0.7 μm; | 0-30 | n. a. | 5.29 | Maskaoui, Hibberd, & Zhou | 2007 |
| **Propranolol** | basic | 9.7 | 1.2 | River water; STWs effluents; groundwater; | | | n. a. | 7.1 | Maskaoui and Zhou | 2010 |
| | | | | River water | between >1 kDa and <0.7 μm; | 0-30 | n. a. | 5.25 | Maskaoui, Hibberd, & Zhou | 2007 |
| **Sulfamethoxazole** | basic | 6.2 | 0.48 | River water; STWs effluents; groundwater; | | | n. a. | 7.17 | Maskaoui and Zhou | 2010 |
| | | | | River water | between >1 kDa and <0.7 μm; | 0-30 | n. a. | 4.95 | Maskaoui, Hibberd, & Zhou | 2007 |
| **Tamoxifen** | basic | 8.87 | 6.3 | River water; STWs effluents; groundwater; | n. a. | n. a. | n. a. | n. a. | Maskaoui and Zhou | 2010 |
| **Thioridazine** | basic | 9.5 | 5.9 | River water; STWs effluents; groundwater; | | | n. a. | n. a. | Maskaoui and Zhou | 2010 |

48

49    Published data show no relationship between $K_{oc}$ and $K_{ow}$ for a series of pharmaceuticals

50    (Yamamoto et al. 2003; Holbrook et al. 2004; Liu et al. 2005; Maskaoui et al. 2007), which

51    has been related to mechanisms of sorption dictated chiefly by the charge on the

52    pharmaceuticals rather than hydrophobicity(Yamamoto et al. 2003; Holbrook et al.

53    2004). Nevertheless, it should be noted that Maskaoui et al. (2007) showed a positive

54    relationship between $K_{coc}$ and $K_{ow}$, and postulated a role for hydrophobicity in controlling

55    the partitioning processes of pharmaceuticals on colloids. However, the study did not

56    present the experimental pH and the variability of the charge of the compounds studied.

57    The p$K_a$s suggest that most of the acidic and basic compounds would have been

58    dissociated at environmental pH, which would strongly influence the relationship

59    between $K_{ow}$ and $K_{coc}$.

60        2.4. Partitioning to suspended solids & sediments

61    Preferential partitioning of some pharmaceuticals to suspended solids, and their absence

62    in surface water solution in river catchments, highlights the significance of such sorbents

63    (Ferreira Da Silva et al. 2011). Both the characteristics of the pharmaceutical and the

64    suspended solids are important in determining observed behaviour; in this case, sorption

65    was driven by the positively-charged functionality of the pharmaceutical (Ferreira Da

66    Silva et al. 2011) (Table 3).

Table 3 Suspended solids partition coefficients (Log $K_d$) and normalized to organic matter content (log Koc) for pharmaceuticals, source, sorbent, experimental concentration and pH. Legend: * metabolites; N.A. not available.

| Compound | Type | pKa | LogK$_{ow}$ | Source | Sorbent | Concentration (mg/L) | pH | Log K$_d$ [L/Kg] | Log K$_{oc}$ [L/Kg] | Reference | Year |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 17α-Ethynilestradiol | neutral | 10.2 | 3.67 | Synthetic | Artificial alumina suspended particles coated with humic acid; | 1 | 7.8 | 1.77 | 3.93 | Ra et al. | 2008 |
| Amoxicillin | Zwitterion | 2.8; 7.2 | 0.87 | Synthetic wastewater | Suspended solids | 160 | 3.5 | 0.41 | n. a. | Githinji et al. | 2011 |
| | | | | | | | 5.5 | 0.55 | n. a. | Githinji et al. | 2011 |
| | | | | | | | 6.6 | 0.64 | n. a. | Githinji et al. | 2011 |
| | | | | | | | 7.5 | 0.80 | n. a. | Githinji et al. | 2011 |
| | | | | | | | 8.5 | 1.08 | n. a. | Githinji et al. | 2011 |
| Ciprofloxacin | Zwitterion | 5.9; 8.9 | 0.28 | Synthetic wastewater | Suspended solids | 160 | 3.5 | -0.17 | n. a. | Githinji et al. | 2011 |
| | | | | | | | 5.5 | -0.05 | n. a. | Githinji et al. | 2011 |
| | | | | | | | 6.6 | -0.07 | n. a. | Githinji et al. | 2011 |
| | | | | | | | 7.5 | -0.21 | n. a. | Githinji et al. | 2011 |
| | | | | | | | 8.5 | -0.36 | n. a. | Githinji et al. | 2011 |
| Diclofenac | acidic | 4 | 4.51 | River water; STWs effluents; | Suspended solids | n. a. | n. a. | 0.95 | n. a. | Maskaoui and Zhou | 2010 |
| | | | | Synthetic | Artificial alumina suspended particles coated with humic acid; | 1 | 7.8 | 2.13 | 4.29 | Ra et al. | 2008 |
| Gemfibrozil | acidic | 4.5 | 4.7 | Synthetic | Artificial alumina suspended particles coated with humic acid; | 1 | 7.8 | 2.39 | 4.55 | Ra et al. | 2008 |
| Ibuprofen | acidic | 4.41 | 3.5 | Synthetic wastewater | Suspended solids | n. a. | 3.5 | -2.77 | n. a. | Paul et al. | 2013 |
| | | | | Synthetic wastewater | Suspended solids | n. a. | 6.5 | -2.96 | n. a. | Paul et al. | 2013 |
| | | | | Synthetic | Alumina suspended particles coated with humic acid | 1 | 7.8 | 1.59 | 3.76 | Ra et al. | 2008 |
| Indomethacine | acidic | 3.96 | 15 | River water; STWs effluents; | Suspended solids | n. a. | n. a. | 1.17 | n. a. | Maskaoui and Zhou | 2010 |
| Mebeverine | neutral | 8.2 | 5.12 | River water; STWs effluents; | Suspended solids | n. a. | n. a. | n. a. | n. a. | Maskaoui and Zhou | 2010 |
| Meclofenamic acid | acidic | 3.73 | 5 | River water; STWs effluents; | Suspended solids | n. a. | n. a. | n. a. | n. a. | Maskaoui and Zhou | 2010 |
| Naproxen | acidic | 4.2 | 3.18 | Synthetic wastewater | Suspended solids | n. a. | 3.5 | -4.52 | n. a. | Paul et al. | 2013 |
| | | | | | | n. a. | 6.5 | -3.14 | n. a. | Paul et al. | 2013 |
| Propranolol | basic | 9.7 | 1.2 | River water; STWs effluents; | Suspended solids | n. a. | n. a. | 1.44 | n. a. | Maskaoui and Zhou | 2010 |
| Sulfamethoxazole | basic | 9.14; 13.84 | 0.48 | River water; STWs effluents; | Suspended solids | n. a. | n. a. | 1.36 | n. a. | Maskaoui and Zhou | 2010 |
| Tamoxifen | basic | 8.87 | 6.3 | River water; STWs effluents; | Suspended solids | n. a. | n. a. | n. a. | n. a. | Maskaoui and Zhou | 2010 |
| Thioridazine | basic | 9.5 | 5.9 | River water; STWs effluents; | Suspended solids | n. a. | n. a. | n. a. | n. a. | Maskaoui and Zhou | 2010 |

| Tolfenamic acid | acidic | 4.3 | 5.17 | Synthetic | Artificial alumina suspended particles coated with humic acid; | 1 | 7.8 | 2.79 | 4.95 | Ra et al. | 2008 |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |

69

70    There are limited data on pharmaceutical sediment sorption, accumulation, and

71    formation of transformation products (Bu et al. 2013; Savci 2013) (Table 4). One study

72    reported concentrations 10 – 32 times higher in sediments than in water (Agunbiade and

73    Moodley 2015) with other studies confirming the importance of sediments as sorbents

74    (Stein et al. 2008; Yamamoto et al. 2009; Varga et al. 2010; Martínez-Hernández et al.

75    2014; Svahn and Bjorklund 2015; Li et al. 2015). For acidic pharmaceuticals, however,

76    the charge repulsion limits pharmaceutical - sediment interactions (Koumaki et al. 2016).

77 **Table 4** Sediments partition coefficients (Log $K_d$) and normalized to organic matter content (log $K_{oc}$) for pharmaceuticals, source, and pH.
78 Legend: * metabolites; N.A. not available.

| Compound | Type | pKa | logK$_{ow}$ | Source | pH | Log K$_d$ (L/Kg) | Log K$_{oc}$ (L/Kg) | Author | Year |
|---|---|---|---|---|---|---|---|---|---|
| 10,11-dihydro-10,11-dihydroxycarbamazepine* | n. a. | n. a. | n. a. | River | 7.7 | -0.52 | 1.46 | Loffler et al. | 2005 |
| | | | | River | n. a. | -0.8-0.25 | 1.3-1.6 | Stein et al. | 2008 |
| 10,11-dihydrocarbamazepine* | n. a. | n. a. | n. a. | Settleable particulate matter from wastewater treatment works effluents | n. a. | n. a. | n. a. | Lahti and Oikari | 2011 |
| | | | | River | n. a. | 0.08-0.94 | 2.2-2.3 | Stein et al. | 2008 |
| 1-Naphthol+ | neutral | 9.6 | 2.7 | Lake | 6.8-8 | n. a. | n. a. | Li et al. | 2015 |
| 2-Hydroxyibuprofen+ | acidic | 4.6 | 2.4 | Lake | 6.8-9 | n. a. | n. a. | Li et al. | 2015 |
| | | | | River | 7.7 | n. a. | n. a. | Loffler et al. | 2005 |
| 4-Amino-6-chloro-1,3-benzenedisulfonamide+ | basic | 9.2 | -1 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| 4-chlorobenzoic acid+ | acidic | 4.1 | 2.2 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| 4'-Hydroxydiclofenac+ | acidic | 3.8 | 4 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| Acebutolol | basic | 9.2 | 1.71 | Settleable particulate matter from wastewater treatment works effluents | n. a. | 0.5-1.0 | 2.35-2.47 | Lahti and Oikari | 2011 |
| | | | | River | | 3.28 | 5.05 | Lin et al. | 2010 |
| Acetaminophen | neutral | 9.5 | 0.91 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| | | | | River | n. a. | -0.3 | 0.75 | Martínez-Hernández et al. | 2014 |
| | | | | River | n. a. | 0.41-1-0.44 | 4.11-2.43-5.4 | Yamamoto et al. | 2009 |
| | | | | River | | 0.7 | 2.47 | Lin et al. | 2010 |
| Alprenolol | basic | n. a. | n. a. | Settleable particulate matter from wastewater treatment works effluents | n. a. | n. a. | n. a. | Lahti and Oikari | 2011 |
| Amitryptyline | basic | 9.4 | 4.92 | River | 7 | 0.94-2.39 | 2.95-4.10 | Al-Khazrajy and Boxall | 2016 |
| Atenolol | basic | 9.6 | 0.16 | Settleable particulate matter from wastewater treatment works effluents | n. a. | 0.05-0.5 | 1.85-2.05 | Lahti and Oikari | 2011 |
| | | | | River | n. a. | 0.9 | -0.25 | Martínez-Hernández et al. | 2014 |
| | | | | River, lake | n. a. | n. a. | n. a. | Svahn and Bjorklund | 2015 |
| | | | | River | | 0.11-0.9-0.72 | 3.23-2.92-2.5 | Yamamoto et al. | 2009 |
| | | | | River | 7 | 0.34-1.31 | 1.93-2.7 | Al-Khazrajy and Boxall | 2016 |
| Bendroflumethiazide | basic | n. a. | n. a. | River, lake | | n. a. | n. a. | Svahn and Bjorklund | 2015 |
| Bezafibrate | acidic | 3.6 | 4.25 | Settleable particulate matter from wastewater treatment works effluents | n. a. | -0.5 | 1.41 | Lahti and Oikari | 2011 |
| | | | | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| Bicalutamide | basic | 12 | 2.7 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| Bisoprolol hemifumarate | basic | 9.5 | 1.87 | Settleable particulate matter from wastewater treatment works effluents | n. a. | 0.3-0.8 | 2.17-2.3 | Lahti and Oikari | 2011 |
| Caffeine | basic | 6.1 | <0 | River | | 1.25 | -0.8 | Martínez-Hernández et al. | 2014 |
| | | | | River | | 2.4 | 4.16 | Lin et al. | 2010 |
| Carbamazepine | neutral | 13.9 | 2.45 | Settleable particulate matter from wastewater treatment works effluents | n. a. | 0.2-2.3 | 2.00-3.42 | Lahti and Oikari | 2011 |
| | | | | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| | | | | River | 7.7 | 0.11 | 1.92 | Loffler et al. | 2005 |
| | | | | River | | -0.39 | 1.8 | Martínez-Hernández et al. | 2014 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | River | | 0.23-1.09 | 2.4-2.5 | Stein et al. | 2008 |
| | | | | River, lake | | n. a. | n. a. | Svahn and Bjorklund | 2015 |
| | | | | River | | -1.07-0.14-0.25 | 1.04-2.14-2 | Yamamoto et al. | 2009 |
| | | | | River | | n. a. | 2.6-3.7 | Zhou and Broodbank | 2014 |
| **Carbamazepine-10,11-epoxide+** | neutral | 16 | 2 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| **Carboxyibuprofen** | acidic | 4 | 2.8 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| **Chlorothiazide** | basic | 9.1 | -0.44 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| **Chlortalidone** | basic | 8.6 | 1.6 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| **Cimetidine** | basic | 6.8 | 0.40 | River | 7 | 0.35-1.20 | 2.00-2.63 | Al-Khazrajy and Boxall | 2016 |
| **Ciprofloxacin** | zwitterion | 5.9-8.9 | 0.4 | Settleable particulate matter from wastewater treatment works effluents | n. a. | 2.6 | 4.79 | Lahti and Oikari | 2011 |
| **Citalopram** | basic | 9.6 | 1.39 | Settleable particulate matter from wastewater treatment works effluents | n. a. | 3.9-4.6 | 5.32-6.02 | Lahti and Oikari | 2011 |
| **Clofibric acid** | acidic | 3.4 | 2.9 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| | | | | River | 7.7 | -0.52 | 1.41 | Loffler et al. | 2005 |
| **Codeine** | basic | 8.2 | 1.2 | River | | 0.32-1.15 | 2.4-2.5 | Stein et al. | 2008 |
| **D3-ibuprofen** | acidic | n. a. | n. a. | Settleable particulate matter from wastewater treatment works effluents | n. a. | n. a. | n. a. | Lahti and Oikari | 2011 |
| **D5-fluoxetine** | basic | n. a. | n. a. | Settleable particulate matter from wastewater treatment works effluents | n. a. | n. a. | n. a. | Lahti and Oikari | 2011 |
| **Demeclocycline** | basic | n. a. | n. a. | Setteable particulate matter from wastewater treatment works effluents | n. a. | n. a. | n. a. | Lahti and Oikari | 2011 |
| **Diazepam** | basic | 3.4 | 2.85 | River | 7.7 | 0.48 | 2.28 | Loffler et al. | 2005 |
| | | | | River | n. a. | 0.28-1.4 | 2.4-2.8 | Stein et al. | 2008 |
| **Diclofenac** | acidic | 4.2 | 4.51 | Settleable particulate matter from wastewater treatment works effluents | n. a. | 4.7 | 2.45-3.74 | Lahti and Oikari | 2011 |
| | | | | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| | | | | River, lake | | n. a. | n. a. | Svahn and Bjorklund | 2015 |
| | | | | River | n. a. | 1.58 to 2.71 | n. a. | Zhou and Broodbank | 2014 |
| **Dihydrocodeine*** | basic | 8.8 | -1.5 | River | | 0.15-0.81 | 2.3-2.2 | Stein et al. | 2008 |
| **Diltiazem** | basic | 8.06 | 2.8 | River | 7 | 1.34-3.00 | 2.90-4.12 | Al-Khazrajy and Boxall | 2016 |
| **Enrofloxacin** | acidic | n. a. | n. a. | Settleable particulate matter from wastewater treatment works effluents | n. a. | n. a. | n. a. | Lahti and Oikari | 2011 |
| **Fluconazole** | basic | 13 | 0.56 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| **Fluoxetine** | basic | 10.1 | 1.22 | Settleable particulate matter from wastewater treatment works effluents | n. a. | 2.9-4.1 | 4.09-5.49 | Lahti and Oikari | 2011 |
| | | | | River | | 1.25-2.7-3.63 | 4.38-4.7-5.4 | Yamamoto et al. | 2009 |
| **Furosemide** | acidic | 4.2 | 1.8 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| | | | | River, lake | | n. a. | n. a. | Svahn and Bjorklund | 2015 |
| **Glimepiride** | basic | 4.3 | 3.1 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| **Hydrochlorothiazide** | basic | 9.1 | -0.58 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| **Ibuprofen** | acidic | 4.9 | 3.97 | Settleable particulate matter from wastewater treatment works effluents | n. a. | 1.7 | 2.14-2.21 | Lahti and Oikari | 2011 |
| | | | | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| | | | | River | | 7.7 | n. a. | Loffler et al. | 2005 |
| | | | | River | | -1.03- -0.04- -0.52 | 2.07- 1.97 -1.25 | Yamamoto et al. | 2009 |
| **Ifenprodil** | basic | 9.34, 9.99 | n. a. | River | | 1.5 - 2.66 - 3.14 | 4.61 - 4.67 - 4.91 | Yamamoto et al. | 2009 |
| **Indomethacin** | acidic | 3.96 | n. a. | River | | -0.92 - 0.17 - 0.83 | 2.20 - 2.20 - 2.60 | Yamamoto et al. | 2009 |
| **Iopromide** | basic | n. a. | -2.33 | River | | 7.7 | n. a. | Loffler et al. | 2005 |
| **Ivermectin** | neutral | n. a. | 3.22 | River | | 7.7 | 3.07 | Loffler et al. | 2005 |
| **Ketoprofen** | acidic | 4.5 | 3.12 | Settleable particulate matter from wastewater treatment works effluents | n. a. | n. a. | n. a. | Lahti and Oikari | 2011 |
| | | | | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Mefenamic acid** | acidic | 3.73 | 2.42 | River | | 1.30-0.74-1.08 | 4.43- -0.38-2.85 | Yamamoto et al. | 2009 |
| | | | | River | 7 | 0.26-1.27 | 1.88-2.52 | Al-Khazrajy and Boxall | 2016 |
| **Metoprolol** | basic | 9.7 | 1.69 | Settleable particulate matter from wastewater treatment works effluents | n. a. | 0.2-0.9 | 2.22-2.24 | Lahti and Oikari | 2011 |
| | | | | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| **Metoprolol acid+** | acidic | 3.5 | -1.2 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| **Morphine** | basic | 8 | -0.1 | River | | 0.5-1.33 | 12.6-2.7 | Stein et al. | 2008 |
| **N4-acetyl-sulfamethoxazole*** | basic | n. a. | n. a. | River | | -1.88- -0.15 | 0.24-1.2 | Stein et al. | 2008 |
| **Naproxen** | acidic | 4.2 | 3.18 | Settleable particulate matter from wastewater treatment works effluents | n. a. | n. a. | n. a. | Lahti and Oikari | 2011 |
| | | | | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| | | | | River | | 0.27 | 0.21 | Martínez-Hernández et al. | 2014 |
| **Ofloxacin** | zwitterion | 6.0, 8.3 | 0.35 | Suspended particulate matter from wastewater treatment works effluents | n. a. | 2.5 | 4.64 | Lahti and Oikari | 2011 |
| **Oxazepam** | basic | 1.7 | 2.4 | Suspended particulate matter from wastewater treatment works effluents | 7.7 | 0.34 | 2.18 | Loffler et al. | 2005 |
| | | | | River | | 0.30-1.37 | 2.4-2.7 | Stein et al. | 2008 |
| | | | | River, lake | | n. a. | n. a. | Svahn and Bjorklund | 2015 |
| **Oxytetracycline** | basic | 3.3, 7.3, 9.1 | -1.22 | Suspended particulate matter from wastewater treatment works effluents | n. a. | 2.5 | 4.64 | Lahti and Oikari | 2011 |
| **Paracetamol** | basic | 9.4 | 0.46 | Suspended particulate matter from wastewater treatment works effluents | n. a. | n. a. | n. a. | Lahti and Oikari | 2011 |
| | | | | Suspended particulate matter from wastewater treatment works effluents | 7.7 | n. a. | n. a. | Loffler et al. | 2005 |
| **Propranolol** | basic | 9.7 | 2.6 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| | | | | River sediment | | 0.34-2-2.20 | 3.46-4-3.97 | Yamamoto et al. | 2009 |
| | | | | River | | 2.43 | 4.2 | Yu-Chen Lin et al. | 2010 |
| | | | | River | | 1.89 to 2.9 | 3.11-3.95 | Zhou and Broodbank | 2014 |
| **Saluamine** | acidic | 4.4 | 0.66 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| **Sotalol** | basic | 9.6 | 0.24 | Suspended particulate matter from wastewater treatment works effluents | n. a. | 0.1-0.6 | 1.94-2.15 | Lahti and Oikari | 2011 |
| | | | | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| **Sulfamethoxazole** | acidic | 6.2 | 0.9 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| | | | | Aquifer | | 0.63 | -0.17 | Martínez-Hernández et al. | 2014 |
| | | | | River | | -0.7- -0.05 | 1.4-1.3 | Stein et al. | 2008 |
| | | | | River | | 1.41 to 2.67 | n. a. | Zhou and Broodbank | 2014 |
| | | | | River | | 0.75-1.44 | 2.19-2.8 | Stein et al. | 2008 |
| **Tramadol** | basic | 2.4 | 9.2 | Lake | 6.8-10 | n. a. | n. a. | Li et al. | 2015 |
| | | | | River | | 0.38-0.89 | 3.01-2.5 | Stein et al. | 2008 |
| **α-Hydroxymetoprolol+** | basic | 0.84 | 9.7 | Lake | | n. a. | n. a. | Li et al. | 2015 |

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### 2.4.1. Influence of compound speciation

The degree of pharmaceuticals ionisation influences partitioning on suspended solids (Table 3), with strong pH dependence for zwitterions, such as ciprofloxacin and amoxicillin, controlling partitioning to suspended solids in wastewater (Githinij et al. 2011). Acidic ibuprofen and naproxen were adsorbed in larger amounts at pH lower than their p$K_a$ (4.4 and 4.2, respectively), where they were mainly in unionized form (Paul et al., 2014). In contrast, for zwitterions, an increase in $K_d$ was observed at lower pH due to protonation of the amine group. As might be expected, higher $K_d$ values were observed for amine-containing pharmaceuticals than for neutral or carboxylic compounds (Stein et al. 2008; Yamamoto et al. 2009; Martínez-Hernández et al. 2014; Svahn and Bjorklund 2015) (Table 4). For example, ibuprofen showed a significant increase in $K_d$ as pH decreased from 7 to 4, the latter pH value being below the p$K_a$ of the acidic compound (4.5), meaning that the neutral species dominated (Oh et al. 2016). Stein et al. (2008) showed that compounds with structures similar to carbamazepine and its metabolites, and some opiates and tranquilizers, had a similar distribution trend. Furthermore, the dominance of ionization over hydrophobicity as a sorption mechanism to suspended solids and sediments was confirmed by poor correlation of $K_d$ and $K_{ow}$ (Stein et al. 2008; Yamamoto et al. 2009).

### 2.4.2. Sediment composition

The importance of the sediment composition to sorption was demonstrated by a large variation in partition coefficients (log $K_d$) using field data from varying sampling locations (Zhou & Broodbank 2014). The organic carbon content of the sediment correlated with the degree of pharmaceutical sorption (Stein et al. 2008; Varga et al. 2010; Martínez-Hernández et al. 2014; Svahn and Bjorklund 2015), which is consistent with the large $K_{oc}$ values reported (Table 4). Despite the important role played by the organic carbon

fraction, variability in cation exchange capacity and sediment texture can also influence sorption of pharmaceuticals (Al-Khazrajy and Boxall 2016; Le Guet et al. 2018). Furthermore, the molecular weight of pharmaceuticals was found to be positively correlated with $K_{oc}$, showing that the partitioning processes tended to favour relatively large molecules, similar to hydrophobic contaminants (Zhou and Broodbank 2014). Resuspension of sediment leads to a decrease in $K_d$ (Zhou and Broodbank 2014). This is likely due the larger specific surface area of suspended solids compared with sediments, leading to a shift in equilibrium towards the more readily available exchange sites of the suspended solids.

### 2.4.3. Accumulation in sediments

The sorption of pharmaceuticals onto sediments and resuspendable suspended solids may lead to accumulation. pharmaceuticals contamination of the benthic environment in areas close to urban wastewater treatment works, with concentrations up to 200 ng $g^{-1}$ dry weight, was reported (Lahti and Oikari 2011). Once in the sediment, pharmaceuticals may undergo transformation processes and release lower molecular weight, more soluble transformation products into the dissolved phase which, in turn, partition according to the physico-chemical properties of the newly-formed moieties. Thus, sediments have been considered a potential secondary source of pharmaceutical contamination, likely to occur over a wide area downstream of discharges and therefore should be recognized as part of the environmental risk caused by pharmaceuticals in the environment (Li et al. 2015).

### 2.4.5 Metabolite sorption

In addition to the parent compounds, sorption of metabolites is little understood, with only three studies having included metabolic products (Löffler et al. 2005; Stein et al.

2008; Lahti and Oikari 2011). Löffler et al. (2005) compared the sorption to sediments of 10 pharmaceuticals and metabolites, including diazepam and its metabolite oxazepam; ibuprofen and its metabolite 2-hydroxyibuprofen; carbamazepine and its metabolite 10, 11-dihydro-10,11-dihydroxycarbamazepine, metabolite and the active form of clofibrate of clofibric acid, iopromide, paracetamol, and ivermectin. Binding to sediments was ascribed by the authors as the main reason for rapid elimination of paracetamol from solution. Carbamazepine showed a moderate affinity for sediments, whilst the accumulation of 10,11-dihydro-10,11-dihydroxycarbamazepine was insignificant, most likely because of its high solubility and hydrophilicity (log $K_{ow}$ = 0.13) (Miao et al. 2005). The lipid regulator, clofibric acid, showed a very low affinity for sediments at pH close to its p$K_a$ of 7.7, suggesting low sorption under most environmental conditions. Due to its moderate hydrophobicity, oxazepam was rapidly and extensively partitioned to sediments (Löffler et al. 2005). The high hydrophobicity of ivermectin was reported as the main cause of rapid and extensive sorption to sediments. Ibuprofen partitioned to sediments only moderately, as did its metabolite 2-hydroxyibuprofen. In summary, sorption to sediments was elevated for ivermectin, diazepam, oxazepam, and carbamazepine with $K_{oc}$ ranging from 1172 L kg$^{-1}$ for ivermectin to 83 L kg$^{-1}$ for carbamazepine (Löffler et al. 2005), consistent with their respective physico-chemical properties (Table 4).

2.5. Implication for environmental risk assessments

In the environmental risk assessment for `down-the-drain chemicals', such as pharmaceuticals, water is the main environmental compartment of concern (EMA 2006). As such, the distribution to DOM, colloids, suspended solids and sediments in surface fresh water are of importance in determining the environmental exposure of these contaminants. The sorption to freshwater sorbents is accounted for in the predicted

environmental concentration refinement of Tier B of the environmental risk assessment for pharmaceuticals by the calculation of a factor, as shown in Equation 1 (European Comission Joint Research Centre 2003; EMA 2006):

$$FACTOR = \left(1 + Kp_{susp} * SUSP_{water} * 10^{-6}\right) \qquad (1)$$

Where $Kp_{susp}$ is the distribution coefficient to suspended solids; and $SUSP_{water}$ the concentration of suspended solids.

However, this calculation considers sorption on suspended solids but not specifically on DOM and/or colloidal fractions. As DOM and colloidal matter are responsible for most sorption (Fig 6), their omission could lead to overestimation of exposure. Additionally, as evidenced from this study, the source and quality of the sorbent is a key factor in determining the partitioning extent of pharmaceuticals. This is particularly apparent when reference standards are used to assess the degree of sorption to DOM, and results in a high degree of uncertainty of the distribution capacity. These aspects should be addressed in site-specific risk assessment as they could profoundly affect the exposure estimate. The importance of the pH dissociation of the pharmaceuticals is also clearly demonstrable, which impacts significantly on the extent of sorption to freshwater sorbents.

## 3. Conclusions

As a general conclusion, there is a paucity of information on processes by which pharmaceuticals sorb to surfaces in aquatic environments. Nevertheless, reports show that the sorption of pharmaceuticals in the aquatic environment strongly depends on their chemical functionality and the sorbent properties, with basic compounds more readily adsorbed than neutral or acidic ones. Therefore, sorption increases at pH below $pK_a$ for all functionalities. The comparison of the partition coefficients of the different

sorbents (Fig 6) shows a net predominance of sorption onto colloids, and the following general trend of sorption: colloids > DOM > sediments > suspended solids. The $K_{ow}$ does not demonstrate a relationship with the distribution coefficients (K) of the polar and ionizable pharmaceuticals and the analyzed sorbents, which is most likely due to additional polar interactions between ionized pharmaceutical functional groups and the sorbent. Also, the adjustment of K to pH has not established a relationship between the adjusted partition coefficient (D) and $K_{ow}$.

With regard to DOM composition, humic substances generally show more affinity for pharmaceuticals than protein-like DOM, while a poor correlation was found between sorption of pharmaceuticals reference and to environmental DOM. Furthermore, it is important to note that the investigation of the role of different fractions of DOM in isolation does not represent an environmentally-realistic estimate of pharmaceutical sorption. Partitioning to colloids is significantly under-researched, with the limited available information suggesting they are a major physico-chemical variable controlling pharmaceutical partitioning in water. Concerning other identified sorbents, suspended solids interactions with pharmaceuticals show dependence on the degree of pharmaceutical ionization. Again, no relationship between $K_{ow}$ and $K_{dss}$ was demonstrated. Sediments can be considered both as a sink for pharmaceuticals and as a secondary source of pharmaceutical contamination in the form of transformation products. Differences in sediment $K_d$ from separate studies are most likely influenced by differences in sediment composition, e.g. organic carbon content, grain size, clay fraction, cation exchange capacity, experimental conditions, and the concentration of pharmaceutical used, which can vary from mg $L^{-1}$ in experimental conditions to ng $L^{-1}$.

## 4. Acknowledgments:

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