PAPER

Effect of sewage sludge type on the partitioning behaviour of pharmaceuticals: a meta-analysis†

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Assessment of the fate of pharmaceutical residues in the environment involves the measurement or prediction of their sewage sludge partition coefficient (K_d). Sewage sludge can be classified into four types: primary, activated, secondary and digested, each one with different physical and chemical properties. Published studies have measured K_d for pharmaceuticals in a variety of sludge types. This paper discusses the variability of reported K_d values of pharmaceuticals in different types of sewage sludge, using a dataset generated from the literature. Using a meta-analysis approach, it was shown that the measured K_d values depend on the type of sludge used in the test. Recommendations are given for the type of sludge to be used when studying the partitioning behaviour of pharmaceuticals in waste water treatment plants. Activated sludge is preferred due to its more homogenous nature and the ease of collection of consistent samples at a plant. Weak statistical relationships were found between K_d values for activated and secondary sludge, and for activated and digested sludge. Pooling of K_d values for these sludge types is not recommended for preliminary fate and risk assessments. In contrast, statistical analyses found stronger similarities between K_d values reported for the same pharmaceutical in primary and activated sludges. This allows the pooling of experimental values for these two sludge types to obtain a larger dataset for modelling purposes.

Water impact

Active pharmaceutical ingredients (API) in waste water treatment plants partition between aqueous and sludge phases. Understanding this behaviour is important for regulatory purposes. A partition coefficient (K_d) describes how chemicals distribute between these phases and can be measured experimentally using specific tests. A number of K_d values have been published for APIs in a range of sludge types. This paper undertakes a meta-analysis of these K_d values to investigate how the partitioning is affected by the different sludge types and if there are correlations between the datasets. This information is useful to make initial predictions of the fate of an API during treatment processes and may reduce the need to undertake time-consuming OECD tests in preliminary environmental risk assessments.

Introduction

Over the past decade the environmental fate of active pharmaceutical ingredients (APIs) and personal care products and their potential effects on organisms have been investigated.[1] Municipal and hospital waste effluents are the most important sources of APIs entering the aquatic environment.[2,3] Although some APIs are removed by waste water treatment plants (WWTPs), many substances are not fully biodegraded during treatment processes.[4] In this case, the partitioning behaviour of the API between sludge and aqueous phases at WWTPs is the key indicator of their subsequent environmental fate. The distribution of APIs between these two phases is described by the partition coefficient K_d. It is defined as the dimensionless ratio of the equilibrium concentrations (expressed as L kg^{-1}) of the substance in the sludge and aqueous phases:

$$K_d = [\text{API}]_{\text{sludge}}/[\text{API}]_{\text{aqueous}} \qquad (1)$$

The K_d values of APIs in different sewage sludges have been reported in many studies.[5–18]

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Values of K_d can be measured experimentally or estimated by mathematical models. Usually, experimental measurements use specific guidelines, *e.g.* Organisation for Economic Co-operation and Development (OECD) 106,[19] OECD 121 (ref. 20) or the US Environmental Protection Agency's Office of Prevention, Pesticides and Toxic Substances (OPPTS) guideline 835.1110.[21] The OPPTS 835.1110 guideline is currently the only one applicable to the measurement of partitioning behaviour in sewage sludge. In this guideline, a series of experiments are performed using different aqueous concentrations of sludge and the linear section of the slope of the resultant isotherm is used to calculate K_d. The guideline recommends the use of activated sewage sludge, even though this matrix may not exhibit all of the different types of partitioning mechanism that can potentially occur in a WWTP.

Within a WWTP different types of sewage sludge are present, each with varying physico-chemical properties (Table 1). Typically, four types of sludge (primary, activated, secondary and anaerobically digested) can be found within a plant (Fig. 1). All of these have been used in reported laboratory-based sorption experiments to measure K_d (Table 2). The matrix used has been shown to have an effect on the experimental values obtained. For example, comparisons have been made between primary and secondary,[6,16] activated and primary[8,13,17] and activated and digested.[11] Activated sludge was found to be comparable to primary sludge.[13,17] Primary sludge behaved differently to secondary sludge. This was attributed to differences in pH[6] and surface properties of the material.[16] The relationship between activated sludge and digested sludge was less clear.[11]

The location of the sampling point for the sludge within the WWTP is important but there is often inconsistency in different studies. For example, primary sludge can be sampled before the first clarifier[6,17] or after it (Fig. 1).[13] In one study primary sludge was sampled from a primary clarifier that had no secondary sludge recirculation.[16] Comparison of sludge samples obtained from two different types of digesters, mesophilic and thermophilic, showed that sorption was not influenced by the operational conditions of the digester as long as the pH remained between 5.4 and 6.9.[10] A study of the effect of sludge retention time on sorption, comparing the sorption behaviour of APIs with secondary sludge

of different ages, found that sorption was lower with short retention times (2–3 days), than with longer retention times (10 days).[16]

Sewage sludge is a complex matrix. The physico-chemical properties of the sludge vary from plant to plant as well as between different locations within a WWTP. This contributes to the variability of the K_d values reported in the literature for APIs and related compounds. These inconsistencies could lead to incorrect environmental risk assessments (ERA) being made for some APIs. For example, K_d values are frequently measured using activated sludge as the solid phase. However, if assessing the potential of leaching of an API to soil when waste material is subsequently applied to land, it may be more appropriate to use digested sludge as the solid matrix in laboratory measurements.

This paper undertakes a meta-analysis of the K_d values of APIs published in the literature. It aims to identify the possible effects that the type of sewage sludge used in sorption experiments may have on the measured K_d values, and to investigate possible associations between the sorption behaviour of these matrices. This information may be useful in guiding the disposal of sewage sludge, aiding preliminary ERA and generating larger datasets for use in developing predictive mathematical models that describe the partitioning behaviour of APIs.

Materials and methods

Data collection

A literature search was undertaken initially using the major scientific journal databases (Google Scholar, ScienceDirect, Springer, Web of Science, Wiley Online Library) using the combined search terms: partition coefficient, pharmaceutical and sewage sludge. This identified 21 papers satisfying these search criteria. For the purpose of this meta-analysis, it was essential that the type of sludge within the WWTP used for the measurement of K_d for the APIs was specified. Seven papers were rejected on these grounds. Data for this study were collected from the remaining fourteen published papers (Table 2).[5–18] These covered a wide range of APIs (antibiotics, anticancers, anti-inflammatories, cardiovasculars, central

Table 1 Typical physico-chemical properties of sewage sludge types found within a waste water treatment plant

Sludge type	Primary	Activated	Secondary	Digested
pH	5.0–8.0[a]	6.8[b]	6.8[c]	7.7–8.6[a]
TSS[g]	50–125[d] g L^{-1}	10–35[d] g L^{-1}	9[c] g L^{-1}	27–42[a] g L^{-1}
TOC[h]	35%[e]	29[b]–49%	25[c]–34[e]%	25%
VSS[i]	25–70[d] g L^{-1} (50–80%[a])	10–30[d] g L^{-1} (87[f]–100%)	60%[e]	12–20[d] g L^{-1} (44–48%)
COD[j]	45–120[d] g L^{-1}	10–50[d] g L^{-1}	—	15–32[d] g L^{-1}
COD/TSS	90–96%, 146%[e]	100–143%	110%[e]	56–76%
P/TSS[k]	0.8[a]–3.0%[e]	2.8–11.0%[a]	3.0%[e]	1.5–4.0%[a]
Fe(III)/TSS[l]	<1.0%[e]	—	4.0%[e]	3.0–8.0%[a]
N/TSS[m]	1.5–4.0%[a]	2.4–5.0%[a]	5.8%[e]	1.6–3.0%[a]

[a] Tchobanoglous *et al.* 2002 (ref. 22). [b] Wick *et al.* 2011 (ref. 27). [c] Wick *et al.* 2009 (ref. 14). [d] Carballa *et al.* 2007 (ref. 28). [e] Ternes *et al.* 2004 (ref. 6). [f] Radjenović *et al.* 2009 (ref. 13). [g] TSS: total suspended solids. [h] TOC: total organic carbon. [i] VSS: volatile suspended solids. [j] COD: chemical oxygen demand. [k] P/TSS: phosphorus per TSS. [l] Fe(III)/TSS: iron(III) per TSS. [m] N/TSS: nitrogen per TSS.
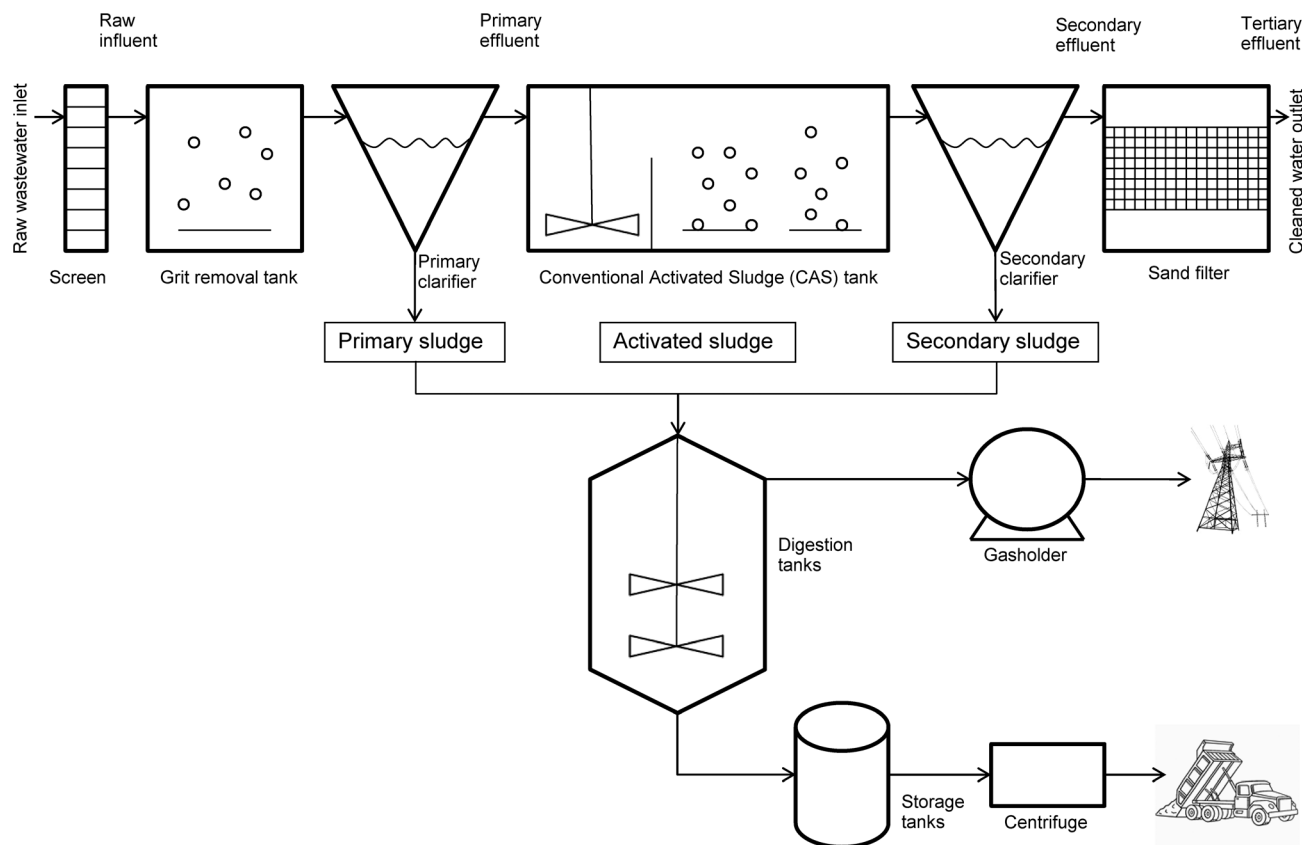
Fig. 1 Typical waste water treatment plant processes.

nervous system drugs and hormones). The authors reported K_d values in four types of sewage sludge (primary, activated, secondary or digested) and their classifications were used directly in the meta-analysis. This type of analysis does not take account of any small variations in experimental conditions used in the studies to ascertain the K_d values.

Type of sludge

Primary sludge was collected just after the grit removal stage and before the first clarifier in some papers, or just after the primary clarifier in others (Fig. 1). In some papers the primary clarifier had no secondary sludge recirculation; while in others it did.[6,9,16,17] Activated sludge was always sampled in the activation tank in the nitrification zone.[11,13,17] Secondary sludge was collected in the secondary clarifier. However, there were differences in sludge age and secondary clarifier volume.[6,16] Anaerobically digested sludge was sampled from the digester. Only one paper reported the type of digester (mesophilic or thermophilic) and sludge age.[10]

The key physico-chemical properties (pH, total suspended solids (TSS), total organic carbon (TOC), volatile suspended solids (VSS) and chemical oxygen demand (COD)) of the four sludge types, where available, are detailed in Table 1.

Sorption data

All the experimentally derived K_d values were calculated using a linear isotherm. Due to the relatively small number of

studies the data were grouped by sludge type regardless of any sampling differences. When an API had more than one K_d value for the same type of sludge, the values were averaged and the mean was used. APIs were only included if K_d values were available for more than one type of sludge. This resulted in a set of 79 APIs associated with a set of 196 K_d values (Table 2). Few of these APIs had K_d values available in the literature for all sludge types.

Statistical analysis

To assess any similarities in sorption behaviour between sludge types several statistical tests were performed. Some of these tests require the data to have a normal distribution, and a Box–Cox plot revealed that a log transformation was required to normalise the data and stabilise the variation. The effectiveness of the transformation was confirmed for the transformed data using normal probability plots. First, the correlations between the measured $\ln K_d$ values of the APIs on different pairs of the four sludge types available in the literature were calculated (Table 3). Pearson correlation coefficients were considered significant if their associated p-value was below 0.05. Initially, a multiple comparison between the $\ln K_d$ values for the different sludge types was performed using a Tukey test. However, the results of this test were adversely affected by the sparseness of the data set. For example, there are several large values of $K_d > 10^3$ for primary sludge that have no corresponding measurement for

Table 2 Partition coefficients (K_d) reported in the literature for active pharmaceutical ingredients with different types of sewage sludge. Where multiple values are available the mean value is stated, with the relative standard deviation in parentheses

Compound	K_d activated	K_d primary	K_d secondary	K_d digested
Acetaminophen	595.0 (134.3)[a,b]	18.0 (89.8)[a,b]	—	—
Alfuzosin	—	1800.0[c]	1200.0[c]	—
Amitriptyline	4555.0[a]	4897.0 (23.0)[a,c]	5020.0 (120.6)[c,d]	1049.0[e]
Androstenedione	156.0[a]	174.0[a]	—	—
Androsterone	579.0[a]	534.0[a]	—	—
Atenolol	44.0 (40.4)[a,b,f]	200.3 (112.9)[a,b,c]	2800.0[c]	11.0[e]
Atorvastatin	198.0[a]	216.0[a]	—	—
Atracurium	—	350.0[c]	1600.0[c]	—
Azelastine	—	6400.0[c]	470.0[c]	—
Biperiden	—	820.0[c]	750.0[c]	—
Bisoprolol	40.0[f]	—	110.0[c]	—
Bupropion	—	85.0[c]	140.0[c]	—
Caffeine	30.0[a]	30.0[a]	—	14.0[e]
Carbamazapine	53.8 (97.0)[a,b,f,g,h]	102.3 (154.9)[a,b,h,i]	120.6 (140.0)[d,i,j]	39.5 (9.7)[e,h,j]
Chlorprothixene	—	38 000.0[c]	20 000.0[c]	—
Citalopram	—	540.0[c]	2105.0 (127.3)[c,d]	282.0[e]
Clofibric Acid	25.5[g]	—	4.8[j]	5.0[e]
Clomipramine	—	17 000.0[c]	6700.0[c]	—
Clotrimazol	—	32 000.0[c]	34 000.0[c]	8128.0[e]
Clozapine	1642.0[a]	1730.0[a]	—	—
Cyclophosphamide	—	55.0[j]	2.4[j]	—
Cyproheptadine	—	11 000.0[c]	3600.0[c]	—
Desloratadine	—	3700.0[c]	2900.0[c]	—
Diazapam	91.8 (109.7)[a,f,h]	125.0 (115.0)[a,h,j]	21.0[i]	—
Diclofenac	55.3 (104.2)[b,g,h]	384.7 (43.3)[b,h,i,j]	16.0[i,j]	77.5 (50.2)[e,h]
Dicycloverine	—	1400.0[c]	1700.0[c]	—
Dilantin	81.0[a]	45.0[a]	—	—
Donepezil	—	3600.0[c]	970.0[c]	—
Duloxetine	—	13 000.0[c]	2900.0[c]	—
Erythromycin	116.0 (51.2)[b,h]	309.0[b]	—	190.0[e]
Estradiol (E2)	787.8 (64.1)[a,g,h,k]	560.0[a]	—	375.5 (69.7)[l,h]
Estriol	63.0[a]	58.0[a]	—	—
Estrone (E1)	424.2 (42.8)[a,g,h,k]	636.0[a]	—	352.1 (62.7)[l,h]
Ethinylestradiol (EE2)	763.0 (69.2)[a,g,h,k]	515.3 (84.3)[a,h,j]	349.0[j]	414.1 (100.4)[l]
Ezetimibe	—	2300.0[c]	3000.0[c]	—
Fexofenadine	—	2700.0[c]	360.0[c]	—
Fluoxetine	—	10 000.0[c]	7400 (26.8)[c,d]	—
Flutamide	—	1500.0[c]	750.0[c]	—
Gemfibrozil	54.8 (75.3)[a,b,g]	34.0 (45.8)[a,b]	—	—
Glibenclamide	239.0[b]	1941.0 (120.9)[b,c]	1300.0[c]	—
Glimepiride	—	2100.0[c]	960.0[c]	—
Haloperidol	—	10 000.0[c]	2900.0[c]	—
Hydrochlorothiazide	20.2[b]	25.8[b]	—	—
Hydroxyzine	819.0[a]	989.0 (30.2)[a,c]	720.0[c]	—
Ibuprofen	32.4 (127.3)[g,h,m]	14.8 (50.3)[b,h,i]	183.6 (136.0)[c,i,j]	31.4 (28.8)[h,j]
Ifosfamide	—	22.0[j]	1.4[j]	—
Indomethacin	39.0[g]	—	—	214.0[e]
Iopromide	10.0[h]	10.0[i]	11.0[j]	10.0 (43.4)[h,j]
Irbesartan	—	700.0[c]	940.0[c]	—
Ketoconazole	—	9700.0[c]	8500.0[c]	—
Ketoprofen	22.5 (40.9)[b,g]	226.0[b]	—	—
Loperamide	—	14 000.0[c]	5500.0[c]	—
Loratidine	3321.0[b]	2336.0[b]	—	—
Maprotiline	—	6700.0[c]	4500.0[c]	—
Mefenamic acid	434.0[b]	294.0[b]	—	—
Meprobamate	30.0[a]	42.0[a]	—	—
Metoprolol	65.0[f]	—	—	18.0[e]
Mianserin	—	3000.0[c]	910.0[c]	—
Naproxen	24.0[g]	217.0[i]	217.0[i]	29.0[e,h]
Nefazodone	—	14 000.0[c]	8300.0[c]	—
Nortriptyline	—	—	6200.0[k]	600.0[e]
Omeprazole	107.0[a]	130.0[a]	—	—
Oxazepam	13.0[f]	790.0[c]	1100.0[c]	—
Paroxetine	—	14 000.0[c]	11 650.0 (40.7)[c,d]	—
Phenylphenol	347.0[a]	652.0[a]	—	—
Pizotifen	—	4700.0[c]	3100.0[c]	—

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Table 2 (continued)

Compound	K_d activated	K_d primary	K_d secondary	K_d digested
Primidone	18.5 (87.9)[a,f]	45.0[a]	—	—
Progesterone	—	750.0[c]	1100.0[c]	—
Propanolol	354.5 (10.2)[b,f]	641.0[b]	—	331.0[e]
Repaglinide	—	170.0[c]	210.0[c]	—
Risperidone	861.0[a]	1432.0[c]	650.0[c]	—
Roxithromycin	282.0[h]	400.0[i]	170.0[i]	49.0 (70.8)[h,l]
Sertraline	—	35 000.0[c]	24 000.0 (41.2)[c,d]	1883.0[e]
Sotalol	18.0[f]	—	360.0[c]	—
Sulfamethoxazole	205.0 (54.4)[b,h,n]	161.6 (129.9)[b,c]	370.0[c]	24.7 (103)[e,h,l]
Testosterone	157.0[a]	178.0[a]	—	—
Tramadol	447.0[f]	110.0[c]	190.0[c]	—
Trimethoprim	195.0 (28.6)[a,b,h,n]	356.0 (26.1)[a,b,c]	420.0[c]	68.0[e]
Verapamil	1501.0[a]	1722.0 (6.4)[a,c]	400.0[c]	—

[a] Stevens-Garmon *et al.* 2011 (ref. 17). [b] Radjenović *et al.* 2009 (ref. 13). [c] Hörsing *et al.* 2011 (ref. 16). [d] Lajeunesse *et al.* 2012 (ref. 18). [e] Barron *et al.* 2009 (ref. 12). [f] Wick *et al.* 2009 (ref. 14). [g] Urase and Kikuta 2005 (ref. 9). [h] Suárez *et al.* 2008 (ref. 11). [i] Joss *et al.* 2005 (ref. 8). [j] Ternes *et al.* 2004 (ref. 6). [k] Andersen *et al.* 2005 (ref. 29). [l] Carballa *et al.* 2008 (ref. 10). [m] Stuer-Lauridsen *et al.* 2000 (ref. 5). [n] Göbel *et al.* 2005 (ref. 7).

some of the other sludge types. Differences in the mean K_d values thus reflect the coverage of reported values rather than intrinsic differences between the sludge types. Therefore, for each pair of sludge types a paired sample *t*-test was performed to assess their similarity, using only cases where K_d values were available for both sludge types. A 95% confidence level was applied, together with a Bonferroni correction to reduce the risk of a Type I error due to multiple comparisons (Table 4). Finally, linear regression was used to quantify the relationships between the $\ln K_d$ values obtained on the four different sludge types. As regression of the $\ln K_d$ values of one sludge type onto another involves errors in both variables, orthogonal, or total least squares, regression was used, rather than the usual ordinary least squares regression. The results of these three statistical tests were used in combination to assess the feasibility of inferring the $\ln K_d$ value of an API on one sludge type from its measured value on another sludge type.

Table 3 Correlations between reported $\ln K_d$ values for active pharmaceutical ingredients with different types of sewage sludge

		K_d activated	K_d primary	K_d secondary	K_d digested
K_d activated	Correlation coefficient	1			
	p-value				
	n	45			
K_d primary	Correlation coefficient	0.72	1		
	p-value	<0.001			
	n	40	73		
K_d secondary	Correlation coefficient	0.48	0.85	1	
	p-value	0.027	<0.001		
	n	21	51	55	
K_d digested	Correlation coefficient	0.82	0.88	0.80	1
	p-value	<0.001	<0.001	<0.001	
	n	19	19	16	23

Results and discussion

The literature search identified 14 papers satisfying the criteria for the meta-analysis. This relatively small number of publications reflects the fact that the study of the fate of APIs in the environment is relatively new, especially compared with many other classes of regulated pollutants (*e.g.* certain pesticides) that have been extensively investigated for many decades. As further work on the sorption behaviour of APIs within a WWTP is undertaken, the resultant data can be used to augment and strengthen the comparisons presented here.

Activated and primary sludge

The correlation coefficient between the $\ln K_d$ values of activated and primary sludge was 0.72 with a *p*-value <0.001 (Table 3). This indicated that the sorption behaviour of the APIs in the dataset for these sludge types was similar. The paired sample *t*-test for the $\ln K_d$ activated–$\ln K_d$ primary sludge pair gave a *p*-value of 0.08 (Table 4). This was above the Bonferroni-corrected threshold value of $p = 0.05/6 = 0.0083$, indicating that these two sludge types behave similarly. The confidence interval associated with the *t*-test included zero, also showing that there was no significant difference between the sorption behaviour of these two sludges.

The orthogonal regression of $\ln K_d$ activated against $\ln K_d$ primary gave a regression coefficient of 0.96, an intercept of 0.54 and a RMSE (the root mean square of the orthogonal distance from the data points to the regression line) of 0.81 (Fig. 2). These results showed that activated and primary sludge have similar sorption properties for a diverse set of APIs ($n = 40$). These findings are consistent with the observation that primary and activated sludge have similar physicochemical properties; both have a relatively neutral pH, high TOC and comparable COD (Table 1).

Within a WWTP there are several distinct stages where partitioning takes place. The first of these occurs in the primary clarifier.[22] Hence primary sludge is the result of all the partitioning processes occurring prior to and including the

Table 4 Paired sample t-tests for reported $\ln K_d$ values for active pharmaceutical ingredients with different types of sewage sludge

| | | Paired differences | | | | | |
| | | | | 95% confidence interval of the difference | | | |
	n	Mean	Standard deviation	Lower	Upper	t	p
$\ln K_d$ activated–$\ln K_d$ primary	40	−0.33	1.16	−0.70	0.04	−1.79	0.082
$\ln K_d$ activated–$\ln K_d$ secondary	21	−0.57	1.78	−1.38	0.24	−1.47	0.157
$\ln K_d$ activated–$\ln K_d$ digested	19	0.58	0.93	0.13	1.03	2.73	0.014
$\ln K_d$ primary–$\ln K_d$ secondary	51	0.42	1.16	0.09	0.75	2.58	0.013
$\ln K_d$ primary–$\ln K_d$ digested	19	1.18	0.99	0.70	1.65	5.19	<0.001
$\ln K_d$ secondary–$\ln K_d$ digested	16	1.52	1.57	0.69	2.36	3.88	0.001

t = Student's t-statistic. p = p-value associated with the t-test.

primary clarifier (Fig. 1). As shown above, partitioning in activated sludge was similar to that in primary sludge. This means that partitioning in the WWTP would be similar in all compartments of the WWTP up to and including the activation tank.

It should be noted that, although the average reported K_d values for activated and primary sludge were found to be similar, a higher variability in K_d values was observed for some APIs with primary sludge than for activated sludge. For example, in primary sludge, K_d values ranging from 194 to 501 were reported for the anti-inflamatory diclofenac, from 20 to 314 for the anti-convulsant carbamazepine, from 46 to 460 for the cardiovascular drug atenolol, from 32 to 320 for the antibiotic sulfamethoxazole and from 251 to 427 for the antibiotic trimethoprim. This may have been due to differences in the location of the sampling point. In most cases primary sludge was collected after the first clarifier, while in a few instances material was collected by sedimentation/filtration of influent wastewater. By comparison, in activated sludge the variability in K_d values was lower, ranging from 16 to 128 for diclofenac, 17 to 135 for carbamazepine, 30 to 64 for

atenolol, 77 to 282 for sulfamethoxazole and 119 to 253 for trimethoprim (Table 2). This was attributed to the activated sludge being a more homogeneous material due to the aeration process used in the activation tank. These differences aside, analysis of the available data suggests that using either activated or primary sludge would lead to similar measured values of K_d.

Activated and secondary sludge

The correlation coefficient between the $\ln K_d$ values of activated and secondary sludge was 0.48 with a p-value = 0.027 (Table 3). This was lower than the correlation coefficient between activated and primary sludge. The paired sample t-test indicated that there was no significant difference between the $\ln K_d$ values for activated and secondary sludge.

The regression analysis of these two sludge types for the available dataset (n = 21) gave a RMSE of 1.22 (Fig. 3).

In a WWTP, secondary sludge is formed mainly from activated sludge which has been allowed to settle, and their physico-chemical properties, with the exception of TSS, are
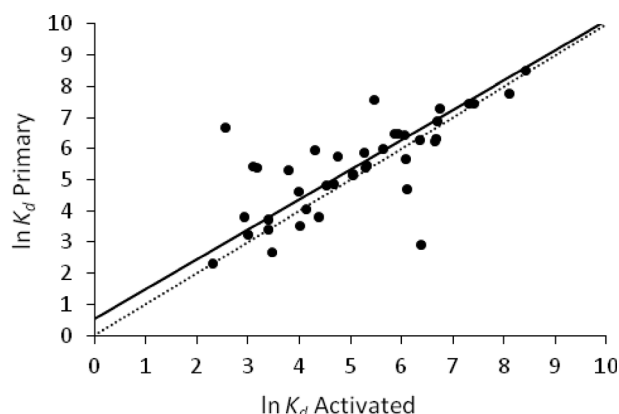

Fig. 2 Plot of $\ln K_d$ values reported for active pharmaceutical ingredients in primary sludge ($\ln K_d$ primary) against activated sludge ($\ln K_d$ activated). The orthogonal regression equation was $\ln K_d$ primary = $0.96 \ln K_d$ activated + 0.54 (solid line), RMSE = 0.81, n = 40 compounds. The dotted line indicates the diagonal ($y = x$).
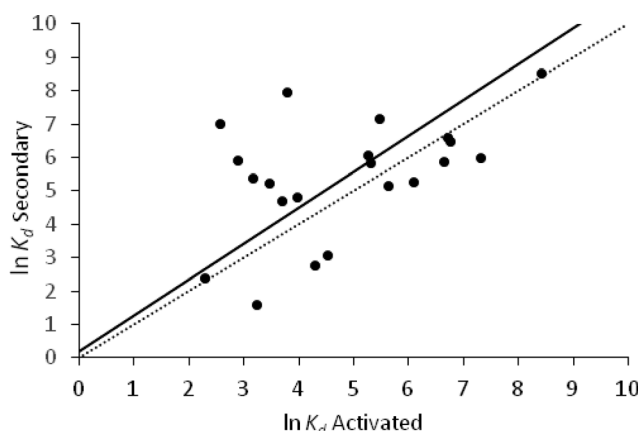

Fig. 3 Plot of $\ln K_d$ values reported for active pharmaceutical ingredients in secondary sludge ($\ln K_d$ secondary) against activated sludge ($\ln K_d$ activated). The orthogonal regression line was $\ln K_d$ secondary = $1.08 \ln K_d$ activated + 0.20 (solid line), RMSE = 1.22, n = 21. The dotted line indicates the diagonal ($y = x$).

broadly similar (Table 1). This would suggest that the sorption properties of these two sludges would be similar, but this was not supported by our analysis of the data reported in the literature. It is difficult to explain these statistical results. Sorption of pharmaceuticals to sewage sludge is a complex process. Unlike some other environmental media, such as soils, the partitioning mechanisms involved are not well understood. The bulk properties commonly used to characterise sewage sludge may not be adequate to describe fully these interactions and the inclusion of other properties of the matrix such as cation-exchange capacity may be required.

Activated and digested sludge

A higher correlation coefficient (0.82, $p < 0.001$) was found between the $\ln K_d$ values of activated and digested sludge (Table 3). The paired sample t-test gave $p = 0.014$, showing no difference between activated and digested sludge; however, the confidence interval did not contain 0 (Table 4). The orthogonal regression of these $\ln K_d$ values ($n = 19$) gave a RMSE of 0.84 with a regression coefficient of 0.99 and intercept 0.20 (Fig. 4).

These observed differences between the sorptive properties of activated and digested sludge may be influenced by their physico-chemical properties and the availability of oxygen. Generally, digested sludge is more basic than activated sludge (Table 1). The pH of the sludge affects the sorption of ionic compounds and will be more influential for APIs with pK_a values in the range 6–9. There were differences in other physico-chemical properties, such as TOC, TSS and VSS, between these sludge types but their effect on sorption is more difficult to predict. Sorption may also have been affected by local variations of the bacterial population in the digester.
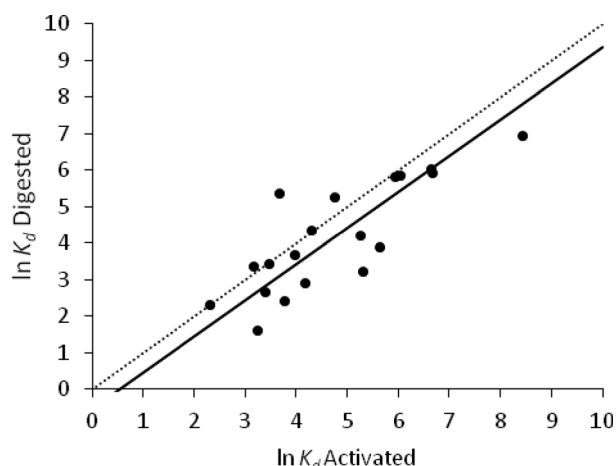
Primary and secondary sludge

In a WWTP a portion of primary and secondary sludge is mixed to form the sludge which is fed in to the anaerobic digester (Fig. 1). Secondary sludge is formed after the activation treatment in which microorganisms biodegrade some compounds and generate new biomass material. Therefore, the primary and secondary sludge may be expected to have different sorption characteristics for APIs. The correlation coefficient between the $\ln K_d$ values of primary and secondary sludge was 0.85 with a p-value <0.001 (Table 3). The paired sample t-test gave a p-value of 0.013, above the critical value, but the confidence interval was slightly to the right of 0, providing some evidence that primary and secondary sludge were similar in terms of their partitioning properties.

The orthogonal regression of the $\ln K_d$ values for primary and secondary sludge ($n = 51$) gave a RMSE of 0.81, a regression coefficient of 1.06 and intercept −0.81 (Fig. 5). This indicated that the sorption properties of APIs between primary and secondary sludge were correlated, with APIs sorbed more strongly to primary sludge than to secondary sludge (Fig. 5).

Some differences in the physico-chemical properties of primary and secondary sludge are apparent (Table 1). Most notably, TSS is markedly lower for secondary sludge compared with primary sludge. A smaller difference between TOC values suggests that the higher TSS value in primary sludge is mainly due to inorganic material.

Primary/secondary and digested sludge

Anaerobic digestion of sludge leads to changes in the physico-chemical properties of the sludge (Table 1). Therefore the partitioning behaviour for both primary and secondary sludge was expected to differ from the behaviour for anaerobically digested sludge. However, both primary and secondary
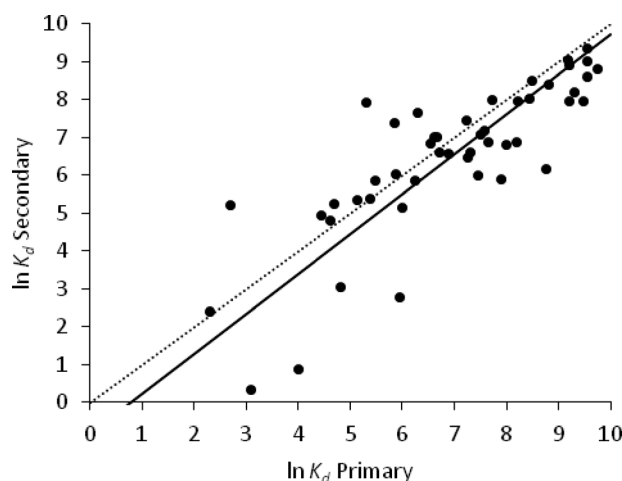
Fig. 4 Plot of $\ln K_d$ values reported for active pharmaceutical ingredients in digested sludge ($\ln K_d$ digested) against activated sludge ($\ln K_d$ activated). The orthogonal regression line was $\ln K_d$ digested = $0.99 \ln K_d$ activated −0.54 (solid line), RMSE = 0.64, $n = 19$. The dotted line indicates the diagonal ($y = x$).

Fig. 5 Plot of $\ln K_d$ values reported for active pharmaceutical ingredients in secondary sludge ($\ln K_d$ secondary) against primary sludge ($\ln K_d$ primary). The orthogonal regression line was $\ln K_d$ secondary = $1.06 \ln K_d$ primary −0.81 (solid line), RMSE = 0.81, $n = 51$. The dotted line indicates the diagonal ($y = x$).

sludges are used as feedstocks to form the digested sludge within a WWTP (Fig. 1), so their relationships with digested sludge were investigated.

The correlation coefficients of the $\ln K_d$ values for primary and secondary sludge with digested sludge were 0.88 and 0.80, respectively (both with p-values <0.001) (Table 3). The paired sample t-tests show that these sludge pairs behave differently, with p-values below the threshold and confidence intervals not containing the origin (Table 4). The orthogonal regressions of the $\ln K_d$ values between primary and digested sludge ($n = 19$), and between secondary and digested sludge ($n = 16$) gave RMSE values of 0.65 and 1.00, respectively. Their corresponding regression coefficients were 0.86 and 0.76.

The statistical analysis of the different sludge pairs is summarized in Table 5. This includes suggested criteria for the pooling of K_d values based on the three statistical tests.

Factors affecting sorption of APIs to sludge

The sludges formed in a WWTP are complex matrices, with variable properties depending in part on design, operating temperature and hydraulic retention times within the plant. It is possible to identify the broad physico-chemical characteristics of the different sludge types. However, there is often a wide variation in properties (Table 1), making it hard to identify the specific interactions contributing to the sorption of APIs throughout the treatment process. As many APIs, in contrast to other types of pollutant (e.g. PAHs, PCBs, several pesticides), are ionisable, their partitioning behaviour, for example, may be particularly sensitive to small changes in pH. This will affect the charge on the dominant species and could vary across different compartments of a WWTP. Attempts have been made to incorporate this behaviour in predictive models.[23] Due to the complexity of the media within the different compartments of a WWTP, the direct influence of differences in pH are hard to predict from physico-chemical properties with confidence and further investigation is warranted. The retention time of the sludge within the different compartments of the plant may also influence sorption, as shown by Hörsing et al.[16] for secondary sludge. Highly aged materials may eventually show a reduction in their overall sorption capacity for APIs and other chemicals due to the reduction in available sites for binding.

In addition, some characteristics of sewage sludge may change with improvements to treatment processes mandated by stricter environmental regulations.

APIs can also undergo biodegradation within a WWTP. Different plant designs will influence the extent of these aerobic and anaerobic processes. The treatment of urban effluents can be further complicated by the presence of both APIs and their metabolites. Often, metabolites can be biodegraded (e.g. conjugation products) during various treatments to yield the parent compound, which may then undergo sorption to a sludge in later compartments of the plant.

This is in contrast to soils, where the matrices are more clearly defined, for example as clays, loams, sands and silts, which are available commercially as standard materials for testing the sorption behaviour of compounds. Activated sewage sludge is recommended for use in regulatory sorption tests (EPA, 1998). The data (K_d) from such tests may be used to model the distribution of a chemical in a WWTP and these results can be used to assesses the potential for release of APIs from the WWTP in aqueous effluent. However, it is important to understand the partitioning of chemicals with other sludge types. For example, if digested sludge is disposed of to land, there is a subsequent potential for desorption of the API from the sludge and the leaching of APIs into ground and surface waters.

APIs form a diverse set of chemicals, but tend to occupy specific regions in physico-chemical property space, for example satisfying the Lipinski rules.[24] Unlike many pollutants, the majority of APIs exhibit ionic behaviour which must be considered when their environmental fate is assessed. The sorption behaviour of APIs reported in the literature covers a large range of K_d values (up to ~40 000), but these are not distributed uniformly, with large regions containing few values. To strengthen the statistical analysis of the reported K_d values with all the different sewage types, further measurements are needed to obtain a more comprehensive dataset with more even coverage of the range of the observed partitioning behaviour of these compounds. In particular, there is a paucity of data for digested sludge.

An extensive body of work has been undertaken on the fate of regulated (priority) pollutants in sewage sludge and soils. This has been necessary as frequently sludge has been applied to land as a means of disposal.[25] Emerging pollutants of recent concern such as APIs have received much less

Table 5 Summary of the statistical tests performed on each pair of different sludge types

	Correlation matrix		Paired t-test		Orthogonal regression			
	Pearson coefficient	p-value	p-value	Confidence interval	Regression coefficient	Intercept	RMSE	
Pooling criteria	Close to 1	<0.05	>0.0083	To include 0	Close to 1	Close to 0	Close to 0	Pooled
Sludge pairs								
$\ln K_d$ activated–$\ln K_d$ primary	0.72	<0.001	0.082	Yes	0.96	0.54	0.81	Yes
$\ln K_d$ activated–$\ln K_d$ secondary	0.48	0.027	0.157	Yes	1.08	0.20	1.22	No
$\ln K_d$ activated–$\ln K_d$ digested	0.82	<0.001	0.014	No	0.99	−0.54	0.64	No
$\ln K_d$ primary–$\ln K_d$ secondary	0.85	<0.001	0.013	No	1.06	−0.81	0.81	No
$\ln K_d$ primary–$\ln K_d$ digested	0.88	<0.001	<0.001	No	0.86	−0.33	0.65	No
$\ln K_d$ secondary–$\ln K_d$ digested	0.80	<0.001	0.001	No	0.76	−0.02	1.00	No

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attention, although this situation is changing rapidly.[26] As awareness of the presence of these chemicals in the environment increases, there is an urgent need to understand fully their fate. The analysis carried out in this study brings together the available sorption data for APIs and may be beneficial to those responsible for performing environmental risk assessment for these types of substances.

Conclusions

Despite the lack of available K_d values for some sludge types and the variability of K_d measurements between different studies, there is sufficient published data to undertake an initial meta-analysis. The statistical analysis showed that the sorption behaviour of the APIs in the dataset with activated and primary sludge was similar. More data points were available for the comparison of these sludge types ($n = 40$) and this dataset included compounds with a range of K_d values. Either matrix could be used in laboratory tests to assess sorption of APIs in a WWTP. However, it may be advantageous to use activated sludge to avoid the higher variability observed in K_d measurements with primary sludge. For mathematical modelling, where it is beneficial to have large datasets for the development of predictive models, K_d values for these sludge types may be pooled.

Comparisons of the sorption behaviour of other sludge pairs did not show such strong similarities. Therefore, it is not recommended that the experimental K_d values for these matrices are combined directly. The orthogonal regressions between the different sludge pairs did not provide evidence for different sorption behaviour, with the 95% confidence intervals for the slope and intercept containing 1 and 0, respectively, in each case. However, the RMSE values for the activated–secondary and secondary–digested pairs were above one ln unit. The paired t-tests showed that the primary–digested and secondary–digested pairs could not be pooled and the correlation coefficient for the activated–secondary pair was very low, showing these sludge types behaved differently in terms of their sorption properties.

This analysis shows that there are statistical grounds for pooling the K_d values for APIs in activated and primary sludge. The evidence for pooling the other sludge types is weaker and is therefore not recommended for the purposes of preliminary ERA. In order to obtain a full understanding of the sorption behaviour of APIs within a WWTP additional experimental measurements are needed to ascertain K_d values for secondary and digested sludge.

Acknowledgements

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