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Evaluation and development of models for estimating the sorption behaviour of pharmaceuticals in soils

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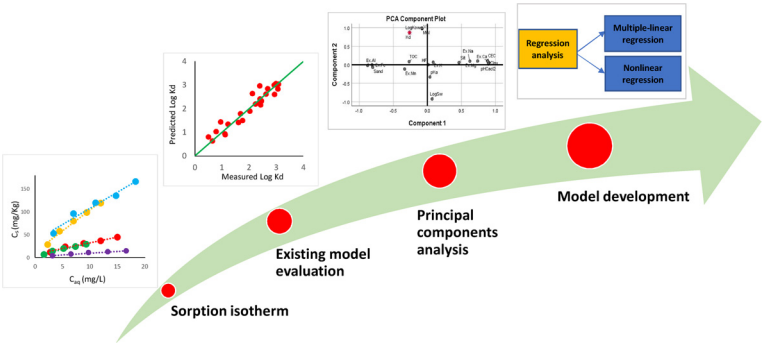
GRAPHICAL ABSTRACT



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ABSTRACT

Sorption is one of the key process that affects the fate and mobility of pharmaceuticals in the soil environment. Several models have been developed for estimating the sorption of organic chemicals, including ionisable compounds, in soil. However, the applicability of these models to pharmaceuticals has not been extensively tested. In this study, we generated a high-quality dataset on the sorption of twenty-one pharmaceuticals in different soil types and used these data to evaluate existing models and to develop new improved models. Sorption coefficients (Kd) of the pharmaceuticals ranged from 0.2 to 1249.2 L/kg. Existing models were unable to adequately estimate the measured sorption data. Using the data, new models were developed, incorporating molecular and soil descriptors, that outperformed the published models when evaluated against external data sets. While there is a need for further evaluation of these new models against broader sorption datasets obtained at environmentally relevant concentrations, in the future they could be highly useful in supporting environmental risk assessment and prioritization efforts for pharmaceutical ingredients.

1. Introduction

Pharmaceuticals are administered to prevent, diagnose and treat diseases and hence protect the health of human beings and other animals (Boxall et al., 2003; Li, 2014). Following use, a large fraction of these compounds is excreted in urine and feces, which are then mostly discharged into domestic wastewater and can subsequently reach agricultural soils through irrigation using reclaimed wastewater effluent or via the application of processed or unprocessed sewage sludge to land (Shenker et al., 2011; Carter et al., 2015). A range of pharmaceuticals has been detected in agricultural soil with concentrations of antiepileptics, anti-inflammatory drugs, antimicrobial agents and

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anticoagulants being reported up to μg/kg levels (Ho et al., 2014; Qin et al., 2015).

Several studies have revealed that, following application to soil, pharmaceuticals can be taken up by soil-dwelling organisms (Carter et al., 2014; Kinney et al., 2012; Pan et al., 2014). The presence of pharmaceuticals in soil has been shown to reduce plant biomass and significantly affect the survival and reproduction of invertebrates (Carter et al., 2015; Kinney et al., 2012). Pharmaceutical accumulation in plants could result in exposure of humans to these compounds when they consume fruit and vegetables (Shenker et al., 2011). Furthermore, highly mobile and persistent pharmaceuticals may be transported to surface water through field runoff or leach to groundwater and subsequently affect aquatic organisms or enter human drinking water supplies (Qin et al., 2015; Kodešová et al., 2015; Tolls, 2001). Long-term exposure to pharmaceutical residues could pose a risk to ecological systems and exert adverse effects on top predators via food chain transfer (Shenker et al., 2011; Wu et al., 2015).

Sorption is a key factor in determining the ultimate fate of pharmaceuticals applied to the soil environment as it influences many important processes such as the rate of leaching or the fraction of chemical that is bioavailable to organisms (Drillia et al., 2005; Wang and Wang, 2015; Carter et al., 2016). It is estimated that around 1912 pharmaceuticals are on the British market and the number is steadily increasing (Burns et al., 2018). However, around 40 studies have been published exploring the sorption behaviour of pharmaceuticals in soil with data only being available for around 6% of the total number of pharmaceuticals and for 100 soil types. Results show that sorption coefficients for pharmaceuticals in soil can vary by many orders of magnitude e.g. 0.09 sulfameter < Kd < 1277873 ciprofloxacin L/kg (Leal et al., 2013; Zhang et al., 2014) and sorption coefficients for a single pharmaceutical can vary by up to three orders of magnitude across different soil types (e.g. Kd values for ciprofloxacin range from 726.8 to 1277873 L/kg) (Leal et al., 2013). It is therefore clear that both chemical properties and soil characteristics are important in controlling the sorption behaviour of these compounds in soil (Kodešová et al., 2015; Williams et al., 2009; Kim et al., 2012; Pan and Chu, 2016).

Given the large number of pharmaceuticals in use and the fact that sorption data are only available for a small proportion of these, to adequately understand risks of these compounds, there is a need to enhance our understanding of sorption behavior. It would be cost prohibitive and time-consuming to experimentally determine sorption coefficients of all pharmaceuticals in the many soil types that exist in the natural environment. Modelling approaches have therefore been proposed for estimating the sorption affinity of pharmaceuticals in soils. These include poly-parameter Linear Free Energy Relationships and Artificial Neural Networks using chemical properties alone (Bronner and Goss, 2010; Barron et al., 2009) and models that use both chemical properties and soil parameters (European Union, 2003; Kah and Brown, 2007; Franco et al., 2009; Franco and Trapp, 2008; Droge and Goss, 2013).

Examples of models that use both chemical and soil properties include the models by Franco et al. (2009) and Franco and Trapp (2008) who used nonlinear regression analysis to explore the relationship between pharmaceutical properties and sorption behaviour in different soil systems. Linear regression approaches were also proposed in the study of Kah and Brown (2007) and European Union technical guidance document (European Union, 2003) to estimate the sorption behaviour of acidic organic compounds based on soil organic carbon content and pH corrected lipophilicity (Log D) or hydrophobicity (Log Kow). Droge and Goss (2013) developed a model that estimates the sorption of bases in soil by quantifying the impact of soil organic matter, clay minerals and pharmaceutical molecular structures on the contribution to sorption by both hydrophobic and electrostatic interactions. Unfortunately, most of these models have been developed using data published in the literature. The quality of these datasets may be questionable and the spread of pharmaceuticals used to train the models may not be reflective of the property distribution of all pharmaceuticals in use. There is therefore a need to evaluate these models against high quality datasets on sorption behaviour of pharmaceuticals representing the range of properties of pharmaceuticals in use more generally.

The aim of this study was therefore to evaluate the performance of existing models, that consider the effects of both chemical and soil properties, using a high-quality dataset on sorption of pharmaceuticals and, where the models are found to fail, develop improved models for estimating pharmaceutical sorption. The specific objectives were to: 1) generate sorption data for a wide range of pharmaceuticals and soil types covering the property space of pharmaceuticals more generally and soil characteristics of European agricultural systems; 2) evaluate existing models against the data; and 3) use principal components analysis and multi-regression methods to develop new models for pharmaceutical sorption and to evaluate these against published data.

2. Materials and methods

2.1. Study pharmaceuticals and reagents

Twenty-one study pharmaceuticals covering thirteen therapeutic classes were purchased from Sigma-Aldrich (Gillingham, UK) (purity ≥98 %). Pharmaceuticals were chosen to represent a broad range of both hydrophobicity characteristics (-0.08 < Log Kow < 4.79) and ionisation states at environmentally relevant pH values (-1.6 < pKa < 14.3). Study compounds were also selected whose half-lives in soil indicated that degradation would not occur over the duration of the sorption studies. Information on the physico-chemical properties, half-lives and CAS number of each compound is provided in Table SI 1. HPLC grade methanol (99.9 %), acetonitrile (99.9 %), acetone (≥99.5 %) and water as well as calcium chloride dihydrate, and potassium dihydrogen orthophosphate were obtained from Fisher Scientific (Loughborough, UK). Analytical grade phosphoric acid solution (≥85 %) and formic acid (≥95 %) were purchased from Sigma-Aldrich (Gillingham, UK).

2.2. Test soils

Five soils, covering a broad range of soil characteristics, were obtained from LandLook (Midlands, UK). On receipt, the soils were air-dried and sieved through a 2-mm mesh and stored in sterile sampling bags at 4°C before use in the experiments. The test soils were heated at 105°C for 3 h to minimize biological activity prior to use. The major properties of the five soils were analyzed by Forest Research Company (Surrey, UK). Detailed information on the characteristics and measurement procedures of each soil is shown in Table SI 2.

2.3. Sorption study

Sorption studies were carried out based on OECD guideline 106 for the testing of sorption of chemicals following a batch equilibrium method (OECD Guidelines for the Testing of Chemicals: Test No. 106 Adsorption Desorption Using a Batch Equilibrium Method, 2000). Preliminary sorption experiments for each study compound in the test soils were conducted to identify experimental conditions for use in the definitive study including the optimal soil to solution ratio, the time to reach sorption equilibrium, the experimental concentration range, the appropriate test vessel, and the filtration device. The optimal soil to solution ratio as well as specific concentration range of each compound for each soil type were selected depending on the aqueous concentrations at equilibrium and analytical method detection limits (Table SI 6). Details of the preliminary sorption experiment procedures are provided in the SI Section 2.

In the definitive sorption experiments, depending on the soil and test chemical in question, either 1, 2.5 or 5 g of soil (dry weight) was mixed with a specific volume of 0.01 M $CaCl_2$ solution (ranging from 10

to 1200 ml) to create the optimum soil to solution ratio (ranging from 1/1 to 1/1200, Table SI 4) in plastic or glass test vessels (selected based on stability tests for two vessel types, see Table SI 4). The mixtures were shaken over 12 h in the dark to pre-equilibrate. The soil solution mixtures were then spiked with stock solutions of the study compounds in either methanol, acetonitrile or HPLC water to give an initial concentration that ranged between 0.5 to 60 mg/L and a carrier solvent concentration of < 0.1 - 0.67 %. The concentration ranges of study analytes to create sorption isotherms generally differed by a factor from three to five (Table SI 4). Triplicate samples were prepared for each concentration. Control samples (containing analyte solution in 0.01 M $CaCl_2$ without soil), and one blank sample (containing $CaCl_2$ solution without study compound and soil) were prepared for each soil. All the samples were then agitated at 220 rpm in the dark at 4°C for 24 h or 48 h to reach sorption equilibrium (see Table SI 4). After this time, soil suspensions were centrifuged at 2500 rpm for 10 min and the resulting supernatant filtered, using 0.45 µm syringe filters, into amber glass vials for analysis.

2.4. Analytical method

Filtered samples were analysed by high performance liquid chromatography (HPLC) with diode array detection (DAD) using either a Perkin Elmer Flexar HPLC or an Agilent 1260 Infinity II HPLC instrument (The Agilent HPLC cannot be used with phosphate buffer). Separation was performed using an Agilent Zorbax Eclipse XDB C-18 column (4.6 mm × 250 mm, 5 µm pore size) at 30° C. The mobile phase comprised a solvent phase of either methanol or acetonitrile matched with an aqueous phase of either 0.1 % formic acid (pH = 2.7), 30 mM potassium dihydrogen orthophosphate (KH_2PO_4, pH = 3.3), 25 mM potassium dihydrogen orthophosphate (KH_2PO_4, pH = 3), 50 mM potassium dihydrogen orthophosphate (KH_2PO_4, pH = 4.5) or HPLC grade water adjusted to pH 2.7 with 85 % phosphoric acid. The flow rate of mobile phase ranged from 0.6 to 1.4 ml min^{-1}. The injection volumes and detection wavelengths for study compounds ranged from 10 to 40 µl and 200–260 nm, respectively. The retention times fell within the range 2–4 min. Concentrations in samples were calculated based on peak area using calibration curves developed using known standards of each pharmaceutical.

The analytical methods were evaluated in terms of linearity, intra- and inter-day repeatability, matrix recovery, limit of detection (LOD) and quantitation (LOQ). The Intra-/inter-day repeatability was measured at two concentrations (2 and 20 mg/L) over 3 days. The matrix recovery was determined in supernatant samples (centrifuged from the mixture of soil and 0.01 mol/L $CaCl_2$ (1/5 and 1/200 (w/v) soil/ solution ratio)) which was then fortified with the stock solution of target pharmaceuticals at the spiking level of 5 mg/L. The limit of detection (LODs) and limits of quantification (LOQs) were calculated as three and ten times the signal-to-noise ratio, respectively (Doretto and Rath, 2013). Satisfactory limits of detection (0.04-0.64 mg/L) and intra-/inter-day precisions (the relative standard deviation within the range of 0–20 %) were obtained for all twenty-one pharmaceuticals. With the exception of captopril, no apparent matrix interference was found for the majority of the pharmaceuticals with the average matrix recoveries of target compounds ranging from 91.25–103.79%. The details of the developed analytical methods and method validation results are summarised in Tables SI 5 and SI 6.

2.5. Derivation of sorption coefficients

Linear, Freundlich and Langmuir isotherms were fitted to the data using GraphPad Prism (version 7.00). The determination of Linear, Freundlich and Langmuir isotherm constants (K_d, K_f and K_L) as well as organic carbon normalized sorption coefficient (K_{oc}) are described in the SI section 2.

2.6. Evaluation of existing predictive models

Several models, which have been proposed to predict the sorption behaviour of different classes of acidic, basic and neutral organic compounds in soil (Table 2), were evaluated using the measured sorption coefficients. The applicability and accuracy of these models were assessed according to mathematical evidence by calculating root-mean squared deviation (RMSD) and Nash − Sutcliffe Efficiency (NSE) using the following equations (Eqs. 1, 2):

$$RMSD = \sqrt{\frac{\sum_{i=1}^{n}(Y_i^{Obs} - Y_i^{Pred})^2}{n}} \quad (1)$$

$$NSE = 1 - \left[\frac{\sum_{i=1}^{n}(Y_i^{Obs} - Y_i^{Pred})^2}{\sum_{i=1}^{n}(Y_i^{Obs} - Y^{Mean})^2}\right] \quad (2)$$

where Y_i^{Obs} and Y_i^{Pred} are the ith observed and predicted value, respectively. Y^{Mean} is the average of observed data and n is the number of observations. RMSD value of 0 indicates a perfect fit and less than half of the standard deviations of the observed represents a good prediction performance (Moriasi et al., 2007). NSE values which can range between − ∞ and 1 were used to evaluate how well the predicted values and the observed values fitted a 1:1 line. The closer that the NSE value is to 1, the better the model performance (Singh et al., 2005).

2.7. Development of new models and validation based on literature data

Principal components analysis (PCA) was performed in SPSS (version 25.0) to explore which physico-chemical properties of chemicals and soil characteristics appear to drive the sorption of each class of pharmaceuticals and to identify pharmaceutical and soil properties for use in the development of new models. The first three principal component axes were chosen to reduce the dimensionality of data according to the broken stick eigenvalue test (Legendre and Legendre, 1998).

New sorption models were then developed using 1) all soil and pharmaceutical properties identified from the PCA; and 2) using pharmaceutical properties and soil properties, identified by the PCA, that are commonly reported in literature studies that have measured sorption of pharmaceuticals. Taking into account the degree of dissociation, multiple-linear regression analysis in the Minitab software (version 18) was used to develop new models for estimating sorption of non-ionised (neutrals, Log Kow > 0.85) and fully ionised (bases, $pKa > 8.6$) pharmaceuticals based on their molecular descriptors and soil properties. The sorption of weak electrolytes is largely dependent on the degree of dissociation as the partitioning behaviours of dissociated and undissociated species involve different sorption mechanisms comprising different contributions to the overall sorption potential of the chemicals (Franco et al., 2009; Franco and Trapp, 2008). Non-linear models were then proposed for partially ionised pharmaceuticals (weak bases, $8 > pKa > 4.8$ and acids, $3.2 < pKa < 6.8$) by conducting the nonlinear least squares function in the R software (R version 3.4.1). The optimum model framework applied in R software is shown in Eq. 3:

$$Log\ Kd = Log(\Phi_n \bullet 10\hat{}(c_0 + c_1 \bullet X_1 + c_2 \bullet X_2 + \cdots c_i \bullet X_i) + \Phi_{ion} \bullet 10\hat{}(c_0 + c_1 \bullet X_1 + c_2 \bullet X_2 + \cdots c_i \bullet X_i)) \quad (3)$$

Where c_i and X_i represent the regression coefficients and soil and chemical parameters, respectively. Φ_n, Φ_{ion} are the neutral and ionic fractions and were derived from the Henderson-Hasselbalch equation (Henderson, 1908).

Intercorrelated descriptors (e.g., the strong intercorrelation among hydrophobicity descriptors or the correlation between CEC and each exchangeable cation) were run separately in the regression analysis, as use of these could lead to double counting of the impact of cross-correlated parameters on the sorption.

The best performing model for each class was then identified based on 1) the number of observations used in the analysis (n), the standard

error of the estimate (S), the square of the correlation coefficient (R^2), the adjusted determination coefficient (R^2_{adj}), the predicted R^2 (R^2_{pred} calculated using the leave one out approach) as well as RMSD and NSE indices; and 2) the results of an evaluation of a models predictive capability using an external evaluation data set (including 152 Kd values covering 36 pharmaceuticals) resampled from the literature (details in Table SI 10). The external evaluation dataset was also used to explore how the best performing models compared to the existing sorption models.

3. Results and discussion

3.1. Overview of sorption results

In the definitive sorption experiments, interfering peaks were observed for captopril in the UV chromatograms of the soil samples (a matrix recovery of 79.62 % was obtained at the soil/ solution ratio of 1/5), which might be attributed to the organic and inorganic components existing in the soil matrix, leading to the apparent signal suppression of the analyte response (Yu et al., 2012). The obtained sorption coefficients of captopril were therefore not used in the evaluation of existing models and further model development. In the future, additional steps such as the use of isotopically-labeled internal standards with detection by mass spectrometry, sample dilution, or preparation of matrix-matched calibration curves are recommended to reduce the matrix effect prior to the analysis of captopril in solid samples (Campos-Mañas et al., 2017).

Results of the linear, Freundlich and Langmuir isotherms fitting are presented in Table SI 7. Freundlich and linear (R^2 of 0.89–1.00) isotherm models better described the sorption of the pharmaceuticals, across the concentration ranges tested, than the Langmuir model (R^2 of 0.0006–1.00).

Sorption coefficients varied greatly within each group. Acidic pharmaceuticals exhibited lower affinity to test soils as expected, with the sorption coefficients (Kd) ranging from 0.29 L/kg (ibuprofen) to 80.45 L/kg (naproxen). For the neutral compounds, Kd values ranged from 0.20 L/kg (antipyrine) to 117.4 L/kg (disulfiram). For the bases, Kd values ranged from 0.77 L/kg (metoprolol) to 393.10 L/kg (amitriptyline). For the weak bases, values ranged from 3.24 L/kg (lamotrigine) to 1249 L/kg (perphenazine) (Table SI 7). The sorption behaviour of pharmaceuticals also displayed large variability within each study soil. In soil 1, Kd values ranged from 0.57 L/kg (ibuprofen) to 1181 L/kg (perphenazine). In soil 2, Kd values ranged from 1.91 L/kg (captopril) to 1249 L/kg (perphenazine). In soil 3, Kd values ranged from 0.40 L/kg (antipyrine) to 501 L/kg (bisacodyl). In soil 4, Kd values ranged from 0.29 L/kg (ibuprofen) to 861.3 L/kg (bisacodyl). Finally, in soil 5, Kd values ranged from 0.20 L/kg (antipyrine) to 267.4 L/kg (perphenazine) (Table SI 7). Sorption affinities of pharmaceuticals in soil 1 and 2 were generally higher than in the other three soils, probably due to the higher organic carbon content of these soils (Fig. 1). Highest variability (covering two orders of magnitudes) was observed for acids among the five soils, which revealed that the soil properties (such as pH and organic matter) play an important role in determining sorption behavior of acidic pharmaceuticals (Tülp et al., 2009).

Comparison of our findings with previous findings (Kodešová et al., 2015; Drillia et al., 2005; Zhang et al., 2014; Williams et al., 2009; Barron et al., 2009; Monteiro, 2008; Xu et al., 2009a, b; Paz et al., 2016; Durán-Álvarez et al., 2014; Lin and Gan, 2011) showed that the measured linear sorption coefficients of pharmaceuticals from our study for atenolol, metoprolol, propranolol, amitriptyline, trimethoprim, furosemide, naproxen and carbamazepine were in a similar range to sorption coefficients previously reported in the literature (Table 1). For fluoxetine, our Kd values were towards the lower end of the ranges previously reported and for lamotrigine, ketoprofen, ibuprofen, our Kd values were at the higher end of those previously reported (Table 1). In these previous studies, a wider range of experimental concentrations was typically used ranging from 0.01 μg/L to 10 mg/L which includes more environmentally relevant treatments.

3.2. Evaluation of literature models against experimental sorption data

Ten existing models for estimating sorption of organic compounds were evaluated and prediction statistics are summarized in Table 2. The best performing model overall was the model developed by Franco and Trapp (2008) for neutral pharmaceuticals which estimates sorption from the Log Kow, and which gave a RMSD of 0.409 and NSE of 0.800. Models for acids and bases performed poorly with RMSD values being greater than the standard deviation of measured sorption coefficients and negative NSEs being obtained. Moderate performance was observed for models proposed for estimating sorption of weak bases with RMSDs below standard deviation of the observations and positive NSEs being obtained. The poorer performance of models proposed for ionisable compounds is likely explained by the fact that, with the exception of the Droge and Goss model, these models consider hydrophobicity and the degree of dissociation and soil organic content and, generally, do not account for other sorption processes known to be important for ionisable compounds such as hydrogen bonding as well as electrostatic interactions (ionic exchange, charge transfer, cation bridging, ligand exchange) (Kodešová et al., 2015; Vasudevan et al., 2009; Zhang et al., 2017). Therefore, in the next section, we describe work to identify key soil and pharmaceutical properties driving sorption and then move on to develop improved sorption models.

3.3. Potential factors influencing the sorption of four classes of pharmaceuticals in soil

The main factors including chemical and soil properties associated with the degree of sorption of pharmaceuticals in each class were explored by using principal components analysis (PCA) and were then used for further model development. (Details are provided in Fig. 2 and Table SI 8).

3.3.1. Basic pharmaceuticals (bases, $pKa > 4.8$ and weak bases, $8 > pKa > 4.8$)

For basic pharmaceuticals, the PCA indicated that hydrophobicity descriptors (Log Kow, Vx, Log Dow) and soil TOC had a strong positive effect on sorption and that the degree of ionisation of the pharmaceutical (F_{ion}) and soil CEC, clay and cations (Na, K, Ca) content had a weak positive effect on sorption (Table SI 8). These results suggest that bonding mechanisms such as hydrophobic effects, van der Waals interactions as well as hydrogen bonding interactions with organic matter, dominate the overall sorption of basic pharmaceuticals in soil. Similar observations have been made in previous studies (Kah and Brown, 2007, 2006; Al-Khazrajy and Boxall, 2016). Moreover, most basic pharmaceuticals are predominantly in the protonated form at soil pH, so some additional influence through electrostatic attraction to electronegative charged soil surfaces (clay or organic matter) is likely (Klement et al., 2018). Indeed, a weak positive association of CEC and clay on sorption was observed across the basic and weak basic groups that supports the existence of cation exchange processes for cationic species of bases on negatively charged surfaces (clay or organic matter) occupied by metal cations (Kodešová et al., 2015; Vasudevan et al., 2009; Hyland et al., 2012).

3.3.2. Acidic pharmaceuticals ($3.2 < pKa < 4.5$)

For acidic pharmaceuticals, the degree of dissociation (F_n) of the molecule, soil TOC and Al^{3+} and Fe^{3+} had a positive effect on sorption while pH and clay content had a negative effect on sorption (Table SI 8). These findings are consistent with observations from previous studies where the sorption behaviour of acidic compounds was found to be strongly dependent on the soil acidity (Chefetz et al., 2008; Revitt et al., 2015; Foolad et al., 2016). The non-ionised species of acidic

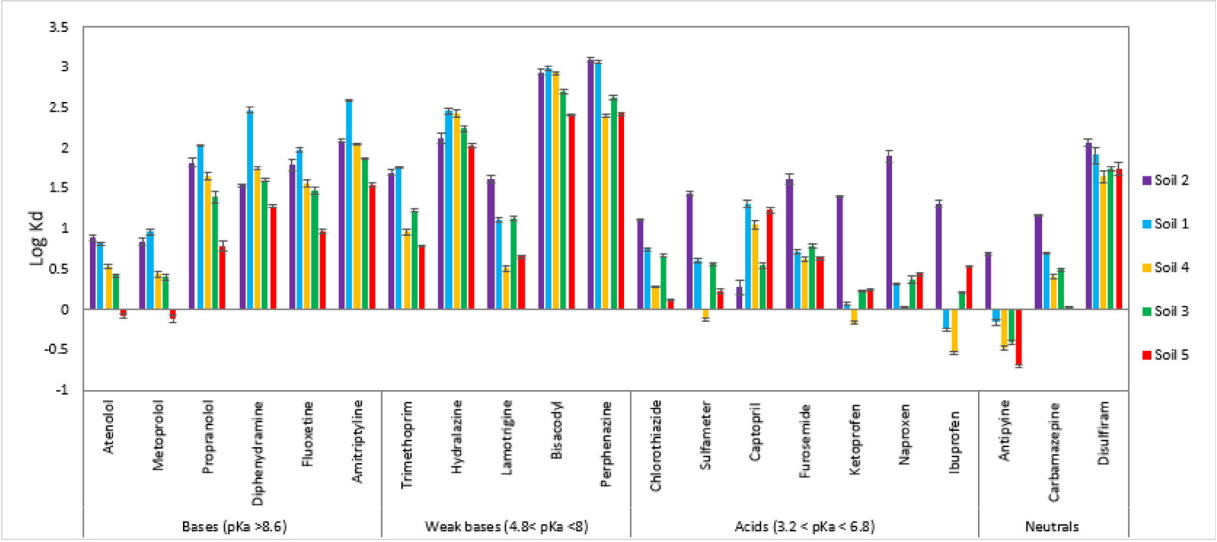

Fig. 1. Logarithm of the linear sorption coefficient (Log Kd values) (± SE) for all the investigated pharmaceuticals in the five study soils. Compounds within a group ordered from low to high Log Kow. Soil organic carbon content increased in the order of soil 2 > soil 1 > soil 4 > soil 3 > soil 5.

Table 1
Comparison of the sorption coefficient (Kd) measured in present study and reported Kd values of pharmaceuticals in soil environments.

Compound	Measured Kd (L/kg)	Literature Kd (L/kg) (Reference)
Atenolol	0.85-7.81	1.61-7.08 (19); 15 (23); 1.88–4.8 (10)
Metoprolol	0.77-9.16	25.4-75 (19); 20 (23); 1.36–3.83 (10)
Propranolol	6.16-108.7	58 (23); 16.3–199 (13)
Diphenhydramine	19.3–299.2	n.d.
Fluoxetine	9.38–95.78	146-234.8 (38)
Amitriptyline	35.29-393.1	138 (23)
Trimethoprim	6.15-58.16	4.67-109(19); 26 (23); 1.16 (10); 7.06–9.21 (18); 7.42 (43)
Hydralazine	109.70–290.36	n.d.
Lamotrigine	3.24-41.45	0.73-2.64 (41)
Bisacodyl	261.1–986.2	n.d.
Perphenazine	252.9-1249	n.d.
Chlorothiazide	1.31-13	n.d.
Sulfameter	0.76-27.65	0.09-0.17 (18)
Captopril	1.91-20.34	n.d.
Furosemide	4.22-42.3	27 (23)
Ketoprofen	0.69-25.59	0.09-9.59 (19); 9 (23); 1.26–8.24 (39)
Naproxen	1.07-80.45	0.23-17.5 (19); 11(23); 10.1–252.9 (38); 1.24–16.49 (40); 2.39–4.41 (12)
Ibuprofen	0.29-20.32	0.15-3.01(19); 21 (23); 0.56–3.71(40); 1.18(42); 1.08–1.14 (43)
Antipyrine	0.20-4.92	n.d.
Carbamazepine	1.08-14.88	0.53-16.7(19); 13 (23); 0.43 (10); 0.49–37 (13); 4.7–32.8 (38); 0.53–1.25 (41)
Disulfiram	45.28–117.4	n.d.

n.d.: no data.

pharmaceuticals is prevalent at low pH (e.g. soil 2) where the hydrophobic partitioning of neutral counterparts with organic matter via van der Waals and hydrogen bonding interactions dominate the extent of sorption of acids (Leal et al., 2013; Zhang et al., 2017; Klement et al., 2018; Revitt et al., 2015). In addition, the strong dependence of Kd on trivalent cations suggest that cation bridging between anionic form of acids and negatively charged sites and surface complexation of carboxyl group to exchangeable trivalent cations on soil metal oxides and aluminosilicate edge sites may be important processes for these molecules (Vasudevan et al., 2009; Kah and Brown, 2006; Bui and Choi, 2010). However, an electrostatic repulsion interaction between the anionic form of acidic pharmaceuticals and negatively charged soil surface (clay) could substantially attenuate the sorption of acids at neutral and alkaline pH (Kodešová et al., 2015; Maoz and Chefetz, 2010).

3.3.3. Neutral pharmaceuticals (Log Kow > 0.85)

For the neutral molecules, the PCA analysis indicated a strong positive effect of hydrophobicity and soil organic carbon on sorption (Table SI 8). This supports the hypothesis that sorption of neutral molecules is due to hydrophobic partitioning into organic matter via van der Waals and electron donor-acceptor interactions (Klement et al., 2018; Williams and Adamsen, 2006).

3.4. Regression model development and validation

A linear regression model containing two explanatory variables (Log Kow and TOC) was generated with a good predictive capability (R^2_{pred} of 0.872) for estimating sorption coefficients for neutral pharmaceuticals (Table 3). For bases, a two-parameter model (Log Dow combined with TOC) explained 75.2 % of the variation in the experimental Log Kd values. Incorporation of an additional soil property (exchangeable Na^+) into the model for bases resulted in an increase in the R^2_{pred} from 0.703 to 0.782 (Table 3). These results suggest that both hydrophobic interactions and cation exchange processes for cationic species on negatively charged surfaces occupied by metal cations drive the sorption of the basic pharmaceuticals.

Two non-linear regression models were developed for weak bases, which provided satisfactory predictive performance with the explained variance higher than 91.7 % (Table 3). Molecular weight (MW) was applied to describe hydrophobic partitioning of undissociated species of weak bases, while hydrophilic factor (HF is a hydrophilicity descriptor which is calculated based on the number of carbon atoms and the number of hydrophilic groups in a molecule) was superior to other hydrophobicity descriptors in predicting the sorption of the ionic molecule species. Besides, charged surface area (simplified by the number of hydrogens bound by the charged nitrogen, Nai) and TOC were selected in explaining the sorption of ionic species, which revealed that electrostatic sorption of weak bases might be influenced by the charged surface area of the different amine types and soil organic carbon content. Furthermore, inclusion of the Ex Na^+ as model input (Model 5) yielded an improvement in the predictions of Log Kd for weak bases, the R^2_{pred} increased from 0.856 to 0.892 (Table 3). The hydrophilic factor (HF) combined with TOC that were found to be able to capture the variance in sorption of non-ionic molecules of acids (Model 6). Molecular weight (MW) combined with soil properties (CEC and soil

Table 2
Evaluation of existing regression models for estimating the sorption behaviour of neutral, basic and acidic organic compounds in soil (The predicted organic carbon-normalised sorption coefficients (Log Koc) were converted to Log Kd to allow comparison to experimental data).

Class	Regression model		N	R^2	SD	RMSD	NSE
Neutrals	Franco and Trapp (2008)	$Log\ Koc = 0.5*LogP + 1.13$	N = 15	0.907	0.947	0.409	0.800
Bases	Droge and Goss (2013)	$Kd = K_{CEC,Clays}(CEC_{Soil} - 3.4f_{oc}) + f_{oc}*D_{oc,IE}$	N = 25	0.091	0.745	1.311	−2.230
	Franco and Trapp (2008) base model A	$Log\ Koc = Log\ (\phi n*10^{0.21*LogP+2.24}\phi ion*10^{0.42*LogP+2.19}$	N = 30	0.709	0.710	0.780	−0.247
	Franco and Trapp (2008) base model B	$Log\ Koc = Log\ (\phi n*10^{0.37*LogP+1.7}\phi ion*10^{pKa^{0.65}*f^{0.14}}$	N = 30	0.529	0.710	1.077	−1.376
Weak Bases	Franco and Trapp (2008) base model A	$Log\ Koc = Log\ (\phi n*10^{0.21*LogP+2.24}\phi ion*10^{0.42*LogP+2.19}$	N = 25	0.473	0.816	0.691	0.253
	Franco and Trapp. (2008) base model B	$Log\ Koc = Log\ (\phi n*10^{0.37*LogP+1.7}\phi ion*10^{pKa^{0.65}*f^{0.14}}$	N = 25	0.309	0.816	0.686	0.263
Acids	Franco and Trapp (2008)	$Log\ Koc = Log\ (\phi n*10^{0.54*LogP+1.11}\phi ion*10^{0.11*LogP+1.54}$	N = 30	0.166	0.576	0.640	−0.276
	Franco et al. (2009)	$Koc = \frac{10^{0.54*LogP+1.11}}{1+10^{(pH-0.6-pKa)}} + \frac{10^{0.11*LogP+1.54}}{1+10^{(pKa-pH+0.6)}}$	N = 30	0.115	0.576	0.694	−0.503
	Kah and Brown (2007)	$Log\ Kd = 0.13*\log D + 1.02\,Log\ OC - 1.51$	N = 30	0.282	0.576	0.655	−3.359
	European Union (2003)	$Log\ Koc = 0.6*\log P + 0.32$	N = 30	0.001	0.576	1.127	−2.961

f_{oc}: fraction organic carbon in soil.
Log P: the octanol–water partition coefficient.
pKa: acid-dissociation coefficient.
ϕn, ϕion: fraction of neutral and ionic species.
f : fraction of compound in the lipophilic phase, f = Kow/(Kow + 1).
Log D: lipophilicity corrected to soil pH.
$K_{CEC,Clay}$ and $D_{OC,IE}$ are CEC-normalized and soil organic matter-normalized sorption coefficients, respectively. Log $K_{CEC,Clay}$ = 1.22 Vx - 0.22Nai + 1.09; Log $D_{oc,IE}$ = 1.53Vx + 0.32Nai – 0.27.
Vx: molecular volume was determined following the approach described in Abraham and McGowan's, (1987).
Nai: number of hydrogens bound by the charged nitrogen.
N: Number of observations.
SD: Standard deviation of the observation.
RMSD: Root mean square deviation.
NSE: Nash-Sutcliffe Efficiency.

organic carbon content) could explain the contributions of ionic species to the overall sorption of acids.

The predictive performance of our developed models and existing predictive models from the literature were evaluated against the literature data, which are summarised in Tables 3 and 4. Briefly, four developed models from each group all yielded good predictions ($RMSD_{test}$ range from 0.416 to 0.577, NSE > 0). The variability in predicted sorption coefficients by Model 1 agreed satisfactorily with 65 Log Kd values in the external data sets for neutral pharmaceuticals across the various soil types ($RMSD_{test}$ of 0.448). In comparison, the model for neutral organics proposed by Franco and Trapp (2008) performed more poorly and showed an underestimation of Log Kd values for hydrophobic neutrals (Log Kow > 3.36) over one order of magnitude ($RMSD_{test}$ of 0.601) (see Table 4 and Fig. 3). For the basic group, both the proposed regression (Model 3) relying on Log Dow and TOC and the published model by Franco and Trapp (2008) derived from Log Kow generated the reasonable predictions and gave an accuracy of a factor of 10 (N = 23, Fig. 3). The Model 4 proposed for weak bases displayed an accurate prediction ($RMSD_{test}$ of 0.483), which outperformed the models described by Franco and Trapp (2008) (RMSD of 0.903 and 0.811, respectively). This revealed that amine types (Nai) combined with HF provided a better estimation of the sorption of weak bases compared to the single hydrophobicity descriptor (Log Kow). A satisfactory prediction of sorption was feasible with Model 6 for acidic pharmaceuticals ($RMSD_{test}$ of 0.577) which yielded a performance significantly superior to the two existing models proposed by Kah and Brown (2007) and the European Union (2003) ($RMSD_{test}$ of 0.870 and 0.611, respectively), which suggested that sorbate speciation is an important factor in predicting the sorption of acidic pharmaceuticals in soil. Similar predictions were also observed with the models developed by Franco et al. (2009) and Franco and Trapp (2008), with the average errors of 0.558 and 0.573, respectively.

Overall, the model evaluation results based on the independent data set demonstrates that the sorption affinity of the partially ionised pharmaceuticals could be estimated accurately by weighting the contributions of neutral and ionic molecule species separately. The multiple-linear regression models to estimate the sorption coefficient of the nonionised and fully ionised pharmaceuticals yielded appropriate predictions by incorporating molecular and soil properties (all predicted Log Kd values within a factor of 10). However, the better Models 2 and 5 for basic and weak basic pharmaceuticals and sorption model developed by Droge and Goss (2013)containing the soil descriptors (exchangeable Na^+ and CEC) could not be evaluated due to the incomplete record of soil properties being reported in many studies in the literature. The predictive performance of these models is worthy of further validation through the generation of additional experimental data on a wider range of pharmaceuticals and soil types and employing more environmentally-relevant concentrations.

4. Conclusion

In this study, the sorption behaviour of twenty-one pharmaceuticals across thirteen therapeutic classes was investigated in five test soils with different properties. Use of the data to evaluate existing sorption models, relying solely on Log Kow, for estimating sorption of neutral pharmaceuticals indicated that these models worked well. However, comparison of the sorption coefficients, obtained in the experiments, with predictions from existing models for estimating sorption of ionisable compounds showed that the models performed poorly for pharmaceuticals. Work was therefore done to develop new modelling approaches. An initial PCA analysis indicated that the sorption of the study pharmaceuticals was driven by hydrophobic forces as well as electrostatic interactions and a range of soil parameters. Using this knowledge, new models were developed for estimating sorption coefficients for pharmaceuticals. Evaluation of these new models against an independent dataset obtained from the literature showed that the models were on par with (model for bases and acids) or superior to (model for neutrals and weak bases) existing models.

While our study was more extensive than previous investigations of this type in terms of the range of pharmaceuticals and soil investigated,

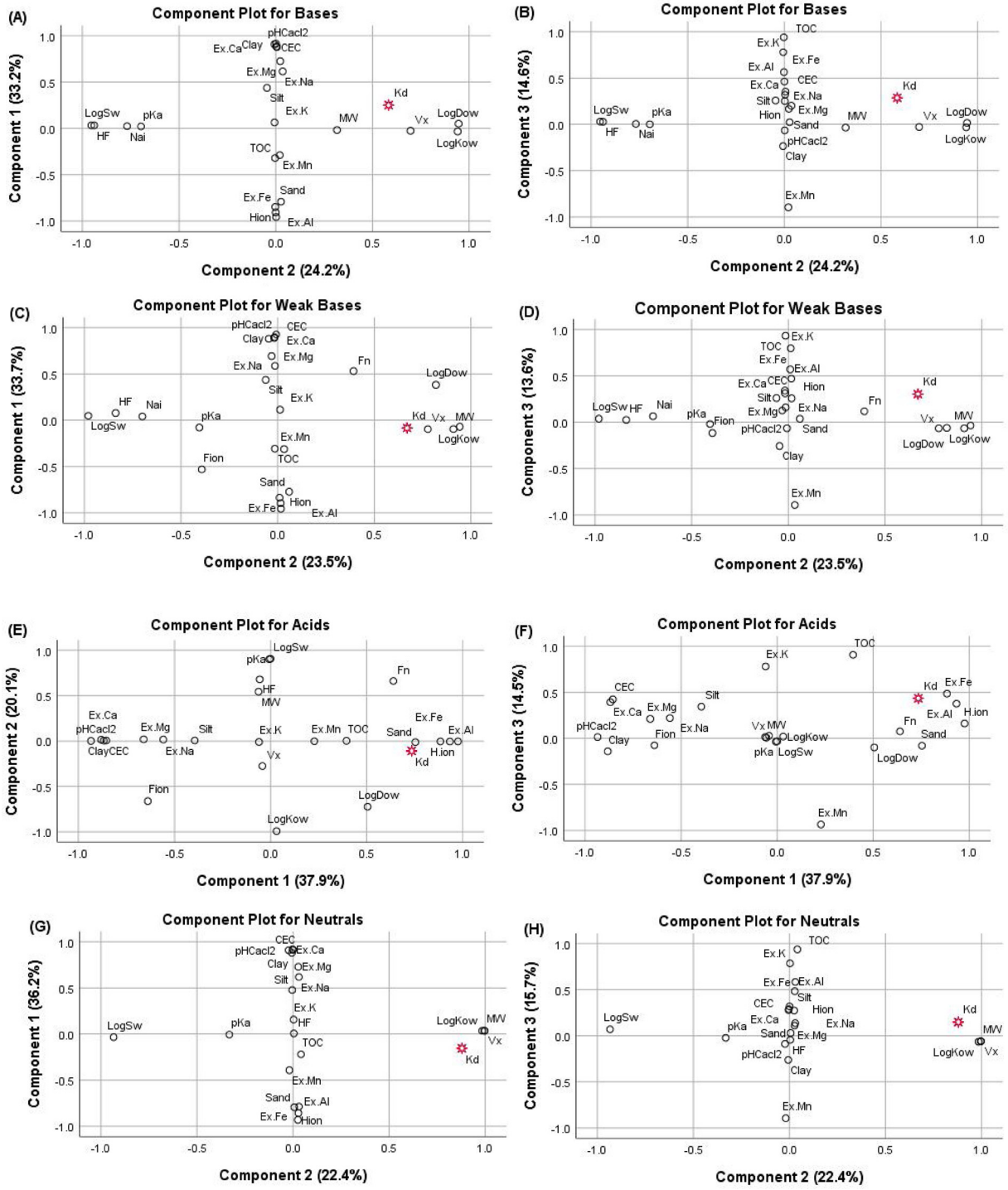

Fig. 2. Principal component analysis loading plots for Kd, soil and pharmaceutical properties for basic compounds (A,B); weak basic compounds (C,D); acidic compounds (E,F); and for neutral compounds (G,H).

it still only focused on a subset of the pharmaceuticals in a small number of soils. The study also employed concentrations greater than concentrations typically observed in the environment. In the future, we recommend that further work is done at lower concentrations that are environmentally relevent and using a wider concentration range to further evaluate the models and, if appropriate, further refine the relationships. These models would allow us to predict sorption behavior of pharmaceuticals under realistic environmental conditions and could be invaluable for not only characterizing the environmental risks of pharmaceuticals in soil environments but also in sediment-water systems.

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Table 3
Multiple linear and non-linear regression equations for predicting sorption coefficients of pharmaceuticals in soils.

Class	Model	Equation	Training						Test				
			N	SE	R^2	R^2_{adj}	R^2_{pred}	$RMSD_{train}$	N	SD	R^2_{test}	$RMSD_{test}$	NSE
Neutrals (Log Kow > 0.85)	1	$Log\ Kd = 0.779*Log\ Kow + 0.211*TOC - 1.729$	15	0.265	0.933	0.921	0.872	0.237	65	0.637	0.543	0.448	0.497
Bases ($pKa > 8$)	2	$Log\ Kd = 0.312*Log\ Dow + 0.171*TOC + 4.164*ExNa + 0.336$	30	0.306	0.834	0.815	0.782	0.284	n.d.				
	3	$Log\ Kd = 0.315*Log\ Dow + 0.188*TOC + 0.585$	30	0.367	0.752	0.733	0.703	0.348	23	0.447	0.721	0.416	0.094
Weak bases ($pKa < 8$)	4	$Log\ Kd = Log(\phi n*10^{0.021*MW-4.7} + \phi ion*10^{-0.535*HF+0.345*Nai+0.145*TOC+1.559})$	25	0.264	0.917	0.895	0.856	0.230	20	1.082	0.816	0.483	0.790
	5	$Log\ Kd = Log\ (\phi n*10^{0.021*MW-4.979} + \phi ion*10^{-0.54*HF+0.331*Nai+3.208*Ex\ Na+0.139*TOC+1.389})$	25	0.228	0.942	0.922	0.892	0.193	n.d.				
Acids ($6.8 > pKa > 3.2$)	6	$Log\ Kd = Log\ (\phi n*10^{-0.313*HF+0.191*TOC+0.417} + \phi ion*10^{0.0083*MW-0.038*CEC+0.301*TOC-2.36})$	30	0.198	0.906	0.886	0.842	0.174	44	0.733	0.456	0.577	0.366

All the regression descriptors were statistically significant at the 0.05 level.
Log Kow, *pKa*, MW, Log Dow are the partition coefficient of the neutral molecule, dissociation constant, molecular weight, pH-dependent octanol-water distribution coefficient, respectively, which were calculated by the software ACD/Labs(http://ilab.cds.rsc.org/). HF (hydrophilic factor) was obtained from alvaDesc (v1.0.8).
ϕn, ϕion are the fraction of neutral and ionic species, respectively.
Nai: number of hydrogens bound by the charged nitrogen.
Ex Na^+ and CEC are exchangeable sodium and cation exchange capacity (cmol+/kg), respectively. Clay and TOC are clay content and total organic carbon content (%) in soil, respectively.
N_{train}, N_{test} are the number of the experimental sorption coefficients and published sorption coefficients, respectively.
SE, SD_{test} are the standard error of the fitted model and standard deviation of published sorption coefficients.
R^2_{adj}, R^2_{pred} is the adjusted R^2, predicted R^2 of developed models.
$RMSD_{train}$, $RMSD_{test}$ are root mean square deviation of experimental data against predicted data and test data against predicted data, respectively.
NSE is the Nash − Sutcliffe Efficiency value.
n.d.: no data.

Table 4
Predictive performance of existing models against literature data.

Evaluation data set	N	SD	Existing model	R^2_{test}	$RMSD_{test}$	NSE
Neutral	65	0.637	Franco and Trapp (2008)	0.521	0.601	0.096
Bases	23	0.447	Franco and Trapp (2008) base model A	0.789	0.417	0.088
			Franco and Trapp (2008) base model B	0.628	0.647	−1.194
Weak bases	20	1.082	Franco and Trapp (2008) base model A	0.512	0.903	0.267
			Franco and Trapp (2008) base model B	0.504	0.811	0.409
Acids	44	0.733	Franco and Trapp (2008)	0.547	0.573	0.375
			Franco et al. (2009)	0.513	0.558	0.406
			Kah and Brown (2007)	0.499	0.870	−0.441
			European Union (2003).	0.348	0.611	0.288

N is the number of the observations.
SD is the standard deviation of the observations.
$RMSD_{test}$ is the root mean square deviation.
NSE is the Nash − Sutcliffe Efficiency value.

CRediT authorship contribution statement

Jun Li: Conceptualization, Methodology, Formal analysis, Investigation, Software, Visualization, Writing - original draft. **Laura J. Carter:** Methodology, Writing - review & editing. **Alistair B.A. Boxall:** Supervision, Conceptualization, Methodology, Writing - review & editing, Funding acquisition.

Declaration of Competing Interest

The authors have no competing interests to declare.

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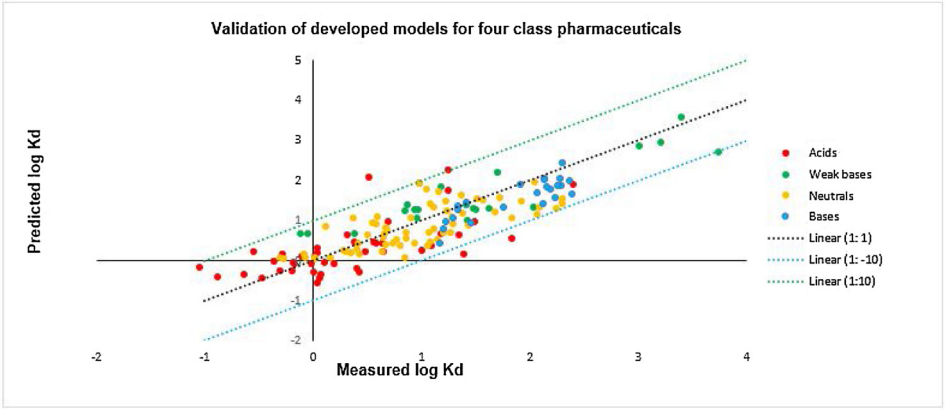
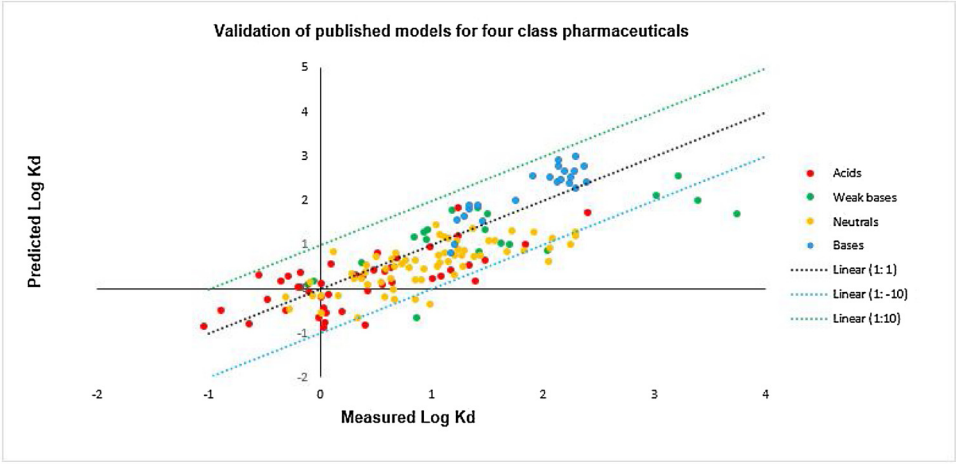
Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jhazmat.2020.122469.



(A)



(B)

Fig. 3. Comparison of predictive performance between the developed models in the current study and existing models in the literature. The selected models for the comparison were the model showing the best performance in each class (The model performance results are presented in Tables 3 and 4). A) Validation of models 1, 3, 4, 6 developed in present study for neutrals (Log Kow > 0.85), bases ($pKa > 8$), weak bases ($8 > pKa > 4.8$), acids ($6.8 > pKa > 3.2$), respectively; B) Validation of the existing models for bases, weak bases and neutrals proposed by Franco and Trapp (2008) and the model for acids proposed by Franco et al. (2009). The black dashed line represents perfect model fit (1:1 line) and the green and blue dashed lines represent a difference of 1 order of magnitude. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

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