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Estimating *n*-octanol-water partition coefficients for neutral highly hydrophobic chemicals using measured *n*-butanol-water partition coefficients

Kaila B. Hanson^a, Dale J. Hoff^b, Tylor J. Lahren^b, David R. Mount^b, Anthony J. Squillace^c, and Lawrence P. Burkhard^{b,*}

^aOak Ridge Association University Student Services Contractor to U.S. Environmental Protection Agency, National Health and Environmental Effects Research Laboratory, Environmental Public Health Division.

^bMid-Continent Ecology Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, 6201 Congdon Blvd, Duluth, MN 55804 USA.

^cStudent Services Contractor to U.S. Environmental Protection Agency, National Health and Environmental Effects Research Laboratory, Environmental Public Health Division.

Abstract

Direct measurement of the *n*-octanol partition coefficients (K_{OW}) for highly hydrophobic organic chemicals is extremely difficult because of the extremely low concentrations present in the water phase. *n*-Butanol/water partition coefficients (K_{BW}) are generally much lower than K_{OW} due to the increased solubility of solute in the alcohol saturated aqueous phase, and therefore become easier to measure. We measured the K_{BW} for 25 neutral organic chemicals having measured $\log K_{OW}$ s ranging from 2 to 9 and 4 additional highly hydrophobic chemicals, with unmeasured K_{OW} s, having estimated $\log K_{OW}$ s ranging from 6 to 18. The measured $\log K_{BW}$ and $\log K_{OW}$ values were linearly related, $r^2 = 0.978$, and using the regression developed from the data, K_{OW} s were predicted for the 4 highly hydrophobic chemicals with unmeasured K_{OW} s. The resulting predictions were orders of magnitude lower than those predicted by a variety of computational models and suggests the estimates of K_{OW} in the literature for highly hydrophobic chemicals (i.e., $\log K_{OW}$ greater than 10) are likely incorrect by several orders of magnitude.

Keywords

n-octanol/water partition coefficients (K_{OW}); Collander equation; *n*-butanol/water partition coefficients

*Corresponding Author: Lawrence P. Burkhard, burkhard.lawrence@epa.gov, TEL: 218-529-5164, FAX: 218-529-5003.

Appendix A: Supplementary Data

Supplementary data to this article can be found online at doi: 10.1016/j.chemosphere.2018.11.141.

Introduction

Regulatory authorities and other stakeholders across the globe are tasked with assessing the risks of new and existing chemicals to human health and the environment. In many circumstances, these assessments must be made without the benefit of measured values for important environmental fate and effect processes, such as soil/sediment partitioning, or bioaccumulation by fish. For neutral organic chemicals, the *n*-octanol/water partition coefficient (K_{OW}) has been shown to be quantitatively related to many processes important to risk assessment. Early bioaccumulation models for fish were based entirely on K_{OW} (e.g., $\log BCF = 0.85 \log K_{OW} - 0.70$; (Veith et al., 1979)), and K_{OW} has remained a fundamental parameter for estimating bioaccumulation in more recent and more sophisticated models (Connolly, 1991; Thomann et al., 1992; Arnot and Gobas, 2004; Barber et al., 2017). K_{OW} is also used within PBTK (Physiologically Based Toxicokinetic) models to predict blood-water partitioning (Poulin and Krishnan, 1995) and partitioning among tissues (Bertelsen et al., 1998). K_{OW} has also been shown to be the largest source of uncertainty in applying food-web models to predict residues in fish tissues for chemicals with K_{OW} larger than 10^4 (Burkhard, 1998; Ciavatta et al., 2009).

Measurement of K_{OW} s for highly hydrophobic organic chemicals, i.e., $\log K_{OW}$ greater than 10, is difficult, in part, due to the exceedingly low concentrations of the chemicals in the aqueous phase. For example, decachlorobiphenyl (PCB-209) with a $\log K_{OW}$ of 8.22 (Tolls et al., 2003) can be measured successfully using a slow stir procedure (OECD, 2006) with an aqueous phase sample of 0.5 L, based on a water concentration mean of 32 ppb and a detection limit of approximately 0.2 ppb. Assuming the same analytical sensitivity, a chemical with a $\log K_{OW}$ of 12.22 would require the equilibration, extraction, and analysis of an aqueous phase sample of 5,000 L-- clearly, a very difficult if not impossible experimental measurement to perform.

Measurement of K_{OW} s for highly hydrophobic organic chemicals using the generator column technique (Devoe et al., 1981; Tewari et al., 1982; Woodburn et al., 1984; US-EPA, 1996) has similar difficulties. In general, these methods use HPLC pumps and column hardware, and are configured for flowrates of 5 mL/min and less. With a 5 mL/min flowrate, collection of a 5,000 L sample would take 694 d. Scaling columns up in size to 0.1 and 1.0 L/min flowrates would result in collection times of 34.7 and 3.47 d for a 5,000 L sample, respectively. In addition, as noted by Kuramochi et al (Kuramochi et al., 2007), micro-emulsions can be a problem with the generator column technique for chemicals with higher K_{OW} s. These issues make the experimental measurements with generator column problematic for highly hydrophobic chemicals.

Another issue with both the slow stir and generator column techniques is the low solubility of highly hydrophobic chemicals in *n*-octanol saturated with water. With lower solubility in the alcohol phase, concentrations in the aqueous phase are further lowered. For example, assuming similar K_{OW} s between two chemicals, one with ppm solubility and another with ppb solubility in *n*-octanol, the concentrations in the aqueous phase are three orders of magnitude lower for the latter chemical from solubility considerations alone.

Because of these measurement difficulties, most highly hydrophobic organic chemicals lack measured K_{OW} values, forcing assessments of environmental behavior and bioaccumulation potential to be based on computationally derived estimates. Unfortunately, estimated K_{OW} s for highly hydrophobic chemicals vary substantially across commonly used K_{OW} estimation algorithms. For example, decabromodiphenyl ethane (BDEthane-209) has predicted K_{OW} values spanning 6 orders of magnitude: log K_{OW} of 7.72 (OPERA (<https://comptox.epa.gov/dashboard/>)), 7.87 (Tetko et al., 2005), 8.70 (Wania and Dugani, 2003), 9.16 (Yue and Li, 2013), 9.68 (NICEATM via <https://comptox.epa.gov/dashboard/>), 10.56 (Admire et al., 2015)), 11.1 (ACD via <http://www.chemspider.com/Chemical-Structure.82781.html> (accessed 15:39, Apr 6, 2017)), 12.4 (Chemaxon via CSID:82781, <http://www.chemspider.com/Chemical-Structure.82781.html> (accessed 15:39, Apr 6, 2017)), 12.3 (Carreira et al., 1994; Hilal et al., 1995), and 13.6 (US-EPA, 2012). From these estimates, BDEthane-209 is most likely highly hydrophobic with a log K_{OW} of greater than 9. Nevertheless, the resulting uncertainty in selecting a K_{OW} is folded into the uncertainties associated with environmental behavior and bioaccumulation models used in risk assessments of such chemicals.

The intractability of using slow-stir methodologies to directly measure K_{OW} for highly hydrophobic chemicals and the issues associated with scaling the generator column methodology to high flowrates, e.g., 0.10 to 10 L/min, has led to the exploration of other approaches that use empirical chemical measurements to estimate K_{OW} . One such approach is to use a correlation between HPLC retention times/capacity factors and measured K_{OW} s (OECD, 2004). Currently, due to the lack of chemicals with measured log K_{OW} s greater than 10, this method requires extrapolations well beyond the chemicals with known K_{OW} s, i.e., the retention times/capacity factors are much longer/larger than those for chemicals with known K_{OW} s, and leads to large uncertainties in the forecasted K_{OW} s.

Recently, Jonker (Jonker, 2016) developed a method using polydimethylsiloxane-coated solid-phase microextraction fibers for measuring K_{OW} . In the method, the K_{OW} is determined from slow-stirring dual-flask/solid phase extraction system where concentrations of the chemical in the fiber and octanol phases after equilibration are measured. With chemical concentration in the fiber and fiber-water partition coefficient, the concentration in the aqueous phase is estimated and subsequently, used to calculate the K_{OW} of the chemical. The method requires the fiber-water partition coefficient and for highly hydrophobic chemicals, their determination will be challenging. Additionally, the method required equilibration times of 18–20 weeks. Overall, the fiber method extends the range where experimental measurements are possible but does have limitations (Jonker, 2016).

Another approach is to use extrathermodynamic relationships (linear free-energy relationships) (Wold, 1974; Leffler and Grunwald, 2013) between partition coefficients in different solvents. Collander (Collander, 1951) demonstrated that relationships of the form:

$$\log K_{\text{solvent} - 1 / \text{water}} = A + B \times K_{\text{solvent} - 2 / \text{water}} \quad (1)$$

exists for numerous solvent pairs where $K_{\text{solvent-1/water}}$ and $K_{\text{solvent-2/water}}$ are solvent-1/water and solvent-2/water equilibrium partition coefficients for organic chemicals. Leo et al. (Leo et al., 1971; Leo and Hansch, 1971) provided further follow-up comparisons and developed 20 solvent pair relationships with *n*-octanol/water partition coefficients (K_{OW}) being the independent variable in all cases (solvent-2/water in equation 1). Like the HPLC method, the lack of chemicals with measured $\log K_{\text{OW}}$ s greater than 10 limits this approach for estimating the K_{OW} s of highly hydrophobic chemicals. Therefore, further development of the Collander relationship will simply provide an extended approach for estimating highly hydrophobic chemical's $\log K_{\text{OW}}$ s via measured $\log K_{\text{BW}}$ s.

In the relationships developed by Leo et al. (Leo et al., 1971; Leo and Hansch, 1971), the slopes of the *n*-butanol/water (K_{BW}) and *n*-pentanol/water (solvent-2/water) against K_{OW} (solvent-1/water) were 1.43 and 1.24, respectively. With slopes greater than 1.0, the *n*-butanol/water and *n*-pentanol/water partition coefficients are less than K_{OW} s. As discussed by Chiou (Chiou, 2003), *n*-butanol is much more polar than *n*-octanol and therefore has a greater solubility in water which causes nonpolar solutes to have a lower affinity for water-saturated *n*-butanol compared to water-saturated *n*-octanol resulting in $K_{\text{BW}} < K_{\text{OW}}$. In Figure 1, $\log K_{\text{OW}}$ data from BioByte (BioByte, 2017), Leo and Hansch (Leo and Hansch, 1971), and Westall (Westall, 1983) are plotted against their $\log K_{\text{BW}}$ s, and range of $\log K_{\text{OW}}$ s extends from -3.21 to 4.92. The data in Figure 1 spans a wide variety of chemical classes and includes sugars, alcohols, phenols, aromatic and aliphatic acids, amines, drugs, and chlorinated benzenes.

The K_{BW} - K_{OW} correlation shown in Figure 1 demonstrates a strong linear relationship over a series of chemicals with $\log K_{\text{OW}}$ s < 5. However, the range of the available data does not provide much support for confidently applying this regression to chemicals with $\log K_{\text{OW}}$ s > 5. Based on this, the objective of this study was 4-fold. The first objective was to measure additional K_{BW} s for chemicals with measured $\log K_{\text{OW}}$ s ranging from 2 to 9 and for chemicals with estimated $\log K_{\text{OW}}$ s exceeding 10. The second objective was to expand the K_{BW} - K_{OW} correlation shown in Figure 1 using the newly measured K_{BW} s and subsequently evaluate the relationship. The third objective was to measure K_{OW} s for a few highly hydrophobic chemicals to further evaluate the K_{BW} - K_{OW} relationship. The fourth objective was to make predictions for highly hydrophobic chemicals, i.e., estimated $\log K_{\text{OW}} > 10$, with K_{BW} - K_{OW} relationship and compare these predictions to estimates from $\log K_{\text{OW}}$ calculators.

Materials and Methods

Reagents and Glassware Cleaning

See Supplementary Data: Tables S1-S4 for details on all chemicals and solvents used. Prior to use, *n*-octanol and *n*-butanol were further purified by distillation, with distillate collection between the alcohol boiling point and 5 °C beyond.

To eliminate cross contamination and minimize background, after washing with soap and water, all glassware was combusted at 450 °C for 4 h prior to use. The Teflon stir-bars used

were cleaned with a Dionex 300 Accelerated Solvent Extractor using dichloromethane:acetone (1:1, v/v).

Slow Stir Measurement Methodology

n-Butanol and *n*-octanol/water partition coefficients were measured following the OECD slow stir technique (OECD, 2006). Glass jacketed reservoirs (2 L and 5 L Radnoti reservoirs, Covina, CA, USA) were set up on magnetic stir plates with water jacket spouts connected to a recirculating bath with a controlled temperature of 25.00 ± 0.05 °C. Deionized (DI) water (saturated with *n*-butanol or *n*-octanol) was added to the reservoirs and allowed to reach temperature. Chemical dissolved in *n*-butanol or *n*-octanol (saturated with DI water) was then slowly added to the reservoirs carefully avoiding emulsion formation. After chemical was added to the reservoirs, slow-stirring was started with a vortex at the water/*n*-alcohol interface of less than 2.0 cm in depth and the reservoirs were covered with aluminum foil to avoid any possible photodegradation. Start times for sample collections were based solely on an estimated chemical equilibration time. Prior to sampling the reservoirs, stirring was stopped and the reservoirs were allowed to rest until quiescent conditions were obtained.

Sampling of the *n*-alcohol phase was done using a Pasteur pipette through the neck of the reservoir. After sampling, a subsample of *n*-alcohol phase was diluted using toluene or ACN, and the dilution was spiked with surrogate chemical.

For the aqueous phase, sampling was performed by draining 10–20 mL of the aqueous phase through sampling line and value to waste, and then, collecting 0.1–2 L of sample into a flask. The collected aqueous sample was analyzed using one of two methods. The first method involved the direct dilution of a subsample of the aqueous solution with ACN for analysis with HPLC instrumentation. This method was used for the polyaromatic hydrocarbons, see Supplementary Data: Table S5 for specific chemicals analyzed using this method.

The second method involved the collection of the aqueous sample into a tared volumetric flask containing the surrogate standard after evaporation of its solvent. The pre- and post-sample collection mass of the volumetric flask was used to determine the sample volume. Aqueous phase samples were liquid-liquid extracted 3x with hexane in the volumetric flasks. Prior to extraction, DI water saturated with Na₂SO₄ was added (1% sample volume) to the flask to prevent emulsion formation during extraction. Extraction flasks were mixed vigorously using a Teflon stir-bar for at least 30 minutes and then allowed to settle. The hexane layer was pipetted off into a 60 mL test tube and evaporated using a N-Evap 111 nitrogen evaporator (Organomation, Berlin, MA) with a heated water bath maintained at a temperature range of 50–90 °C or a Rocket solvent evaporator (Thermo Scientific, Waltham, MA). Once hexane reached a volume < 1 mL, it was transferred to a micro-GC-vial via Pasteur pipette. The 60 mL test tube was rinsed 3x with hexane and pooled into the micro-vial. Samples were concentrated under N₂ to a final volume of 20–200 µL, spiked with appropriate internal standard, and vortex mixed.

Quantification

Depending upon the chemical, analytes were quantified using one of the following systems: Agilent 6890N/5975C Gas Chromatography/Mass Spectrometry (GC/MS), Thermo Scientific Q-Exactive Orbitrap coupled with a Trace 1310 Gas Chromatograph (QE-GC/MS), Thermo Scientific DFS High Resolution GC/MS, or an Agilent 1100 series High Performance Liquid Chromatography (HPLC) coupled to fluorescence (FLD) or Diode Array (DAD) detector. Selected-ion monitoring (SIM) for target and confirming masses was used for mass spectrometer detection. Quantification was performed using the isotopic dilution method for chemicals that required liquid extraction. For the samples resulting from the direct dilution of the aqueous phase, they were analyzed using HPLC. See Supplemental Data: Table S5 for additional analytical details.

The *n*-butanol/water partition coefficients ($\log K_{BW}$) and *n*-octanol/water partition coefficients ($\log K_{OW}$) were computed using the equation:

$$\log K_{AW} = \log \frac{C_A}{C_W} \quad (2)$$

In equation 2, $\log K_{AW}$ is the alcohol/water partition coefficient that represents either *n*-butanol or *n*-octanol, C_A is the concentration in the alcohol phase, and C_W is the concentration in the water phase. *n*-Butanol and *n*-octanol/water partition coefficients are plotted against collection days, and for a successful $\log K_{AW}$ measurement experiment, the slope of the regression of $\log K_{AW}$ against time must be not significantly different from zero ($\alpha = 0.05$) with a minimum of 4 collections over time (criteria in OECD 123 methodology (OECD, 2006)). Additional samples were collected where necessary to satisfy the equilibrium criterion.

An aqueous phase saturated with *n*-butanol or *n*-octanol was used as the method blank. Blanks were processed with each slow stir collection to monitor possible hexane extraction and sample preparation contamination. Aqueous phase sample concentrations were method blank corrected using the blank for the corresponding collection days.

Generator Column Measurement Methodology

An additional approach for measuring *n*-octanol/water partition coefficients was using the generator column technique (Woodburn et al., 1984; US-EPA, 1996). Stainless steel HPLC columns (25 cm in length with 2.0 μ m frits) were packed with diatomaceous earth (Celite 545, Celite 560 or sieved >100 mesh Celite 560) with 1/2 cm of 100–120 mesh glass beads on the downstream end of the column. After measuring the concentration of the chemical in the water saturated *n*-octanol solution, the columns were coated with the solution using a gentle vacuum to draw the solution through the column. For each measurement, columns were placed in series in a water jacket connected to a recirculating bath with a temperature of 25.0 ± 0.05 °C. Using Gilson HLPC 303 and 306 pumps, water saturated with *n*-octanol was passed through the columns and the exiting water passed through activated octadecyl solid phase extraction (SPE) columns (Bakerbond 7020–06). After sample collection, SPE

columns were dried with nitrogen gas, spiked with the analytical surrogate solution, and then, eluted using hexane followed by toluene. The eluted extracts were concentrated using Rocket Evaporator to approximately 1 mL and then, to 200 μ L using N-Evap nitrogen evaporator. The extracts were transferred to micro-GC-vials via Pasteur pipette with 3x rinses of hexane. Extracts were concentrated to a final volume of 20–200 μ L, spiked with appropriate internal standard, and vortex mixed. Analytes were quantified using selected-ion monitoring with GC/MS systems described above.

Partition coefficients were computed using equation 2. For an individual chemical, partition coefficients were measured using different columns and different flowrates through the columns to demonstrate equilibrium conditions with the measurements (See Supplemental Data: Table S8 for experimental conditions).

Results and Discussion

In addressing the first objective of this study, we measured the K_{OW} for three chemicals (benz[a]anthracene, benzo[a]pyrene, and PCB-209) for the purpose of insuring comparability between our measurement methods and the literature since we intended to combine our measure K_{BW} values with K_{OW} values. The measurements of PCB-209 by the two methods were essentially identical (average of 8.17 by slow stir and 8.18 by generator column; Table S6) and both values agree well with the literature value of 8.22 (Table 1). For further method validation, our measured slow stir value for benz[a]anthracene was 5.77 versus a literature average of 5.85. For benzo[a]pyrene, our measurement; is higher than the literature average (6.77 vs. 6.09; Table 1), though, our slow stir value is in good agreement with the recently reported slow stir value of 6.69 ± 0.02 by Jonker (Jonker, 2016). Taken together we believe these results affirm the comparability of measurement methods, and support the use of literature K_{OW} values in building a K_{BW} - K_{OW} relationship.

We also measured log K_{OW} for decabromodiphenyl ether (BDE-209; 8.37 by generator column) and bis-(2-ethylhexyl)-3,4,5,6-tetrabromophthalate (TBPH; 9.21 by slow stir), to provide additional data to help extend the K_{BW} - K_{OW} relationship at high log K_{OW} . From a methodological perspective, measuring the K_{OW} s of these highly hydrophobic chemicals was very demanding. The challenges for slow stir method included the extraction of large volumes of aqueous phase, long equilibration times, low solubilities of the chemicals in the alcohol phase, insuring that the chemical was dissolved in alcohol phase, and having analytical instrumentation optimized for the lowest detection limits possible. The OECD guidance (OECD, 2006) discusses these issues, and we cannot over-emphasize their importance to making these measurements. The challenges for the generator column method included pumping large volumes of water through the columns, getting the columns to come to equilibrium, dissolving the chemicals to coat the diatomaceous earth, and demonstrating that K_{OW} was independent of flowrate conditions.

The log K_{BW} s for 29 chemicals were measured using the OECD slow stir technique (Table 1 and Table 2). Among these chemicals, literature K_{BW} values were available for benzene and chlorobenzene (Westall, 1983; Hansch et al., 1995; Table 1) and these agreed closely with our measurements (Table 1). The collected log K_{BW} s from this study only and their available

log K_{OW} s data are shown in Figure 2. The data are plotted with the following regression equation:

$$\log K_{OW} = 1.7769(\pm 0.0560)\log K_{BW} - 1.5158(\pm 0.2365) \quad r^2 = 0.978 \quad n = 25 \quad (3)$$

Chemical classes were categorized to qualitatively show that there is no significant bias relating to compound structure (Figure 2). Additional data within each class would be needed to resolve any bias concerns.

In Figure 3, our K_{BW} (Table 1; Supplementary Data: Table S7) are plotted with literature values (shown in Figure 1) and supports/continues the linear trend previously depicted in Figure 1. The regression equation is:

$$\log K_{OW} = 1.5020(\pm 0.0221)\log K_{BW} - 0.5327(\pm 0.0448) \quad r^2 = 0.964 \quad n = 173 \quad (4)$$

The residuals for the regressions are plotted in Supplementary Data: Figure S1-A-B. For the all data regression, there is a slight negative bias in residuals for chemicals with log K_{BWs} ranging from 2 to 4 and a slight positive bias in residuals for chemicals with log K_{BWs} above 4 (Supplementary Data: Figure S1-A). There is no thermodynamic basis, we believe, for the relationship to be nonlinear between K_{OW} and K_{BW} . The fit of the regression for the data collected within this study (Figure 2) is better in terms of the residuals, i.e., more evenly distributed across the range of K_{BWs} in the measurements (Supplementary Data: Figure S1-B), and regression is based solely upon neutral hydrophobic organic chemicals. Therefore, the developed regression from this study i.e., Equation 3, will be used for estimating the K_{OW} s for the 4 selected chemicals within this study, and will be beneficial for estimating additional K_{OW} s for highly hydrophobic chemicals via their measured log K_{BWs} .

In Table 1, the quantitative structure-activity relationship (QSAR) estimated log K_{OW} s are relatively consistent to our Eq. 3 regression K_{OW} estimations for less hydrophobic chemicals. However, as chemicals become more hydrophobic, difference between Eq. 3 and other QSAR predictions increase greatly. This is noticeable around PCB-155 and beyond for QSAR log K_{OW} estimations. Our Eq. 3 regression predictions are relatively comparable to the measured literature log K_{OW} s for more hydrophobic chemicals, thus producing a reliable regression for estimating log K_{OW} s where measuring K_{BW} is feasible.

To address the fourth objective, we used the K_{BW} - K_{OW} regression formed within this study (Figure 2) to predict log K_{OW} s for highly hydrophobic chemicals in which there are no literature data available. The log K_{BWs} for tetradecachloro-*m*-terphenyl (*m*-TCP), tetradecachloro-*p*-terphenyl (*p*-TCP), and octadecachloro-*p*-quaterphenyl (*p*-QTCP) were successfully measured (Table 2). To meet the OECD equilibrium criteria of slopes not significantly different from zero with a minimum of four sampling points over time in the slow stir measurements, equilibration times ranging from 2 to 4 weeks were required for these chemicals. Shown in Table 2, log K_{OW} s estimates using several different QSAR algorithms are provided ranging between 6–19.

The predicted log K_{OW} s using equation 3 from our collected K_{BW} data for the 4 highly hydrophobic chemicals are substantially lower than most of the K_{OW} s forecasted by the selected QSAR models (Table 2). As an example, EPISuite, SPARC, and ACD prediction models are estimated up to 10 orders of magnitude higher compared to this study's log K_{OW} predictions for BDEthane-209, *m*-TCP, *p*-TCP, and *p*-QTCP. There is no clear reason for this, though, EPISuite, SPARC, and ACD algorithms use molecular fragmentation methods that are calibrated based on empirical datasets (Hilal and Karickhoff, 2004; Cabalo and Knox, 2014; Stenzel et al., 2014) and substantial extrapolation are needed due to the lack of measured data for highly hydrophobic chemicals. How the experimental data is assigned to a set of sub-structural fragments differ in the extent of correction factors, use of secondary regressions, and applied intermolecular interactions parameters. The majority of QSAR K_{OW} estimations are primarily dependent on limited empirical parameters and the quality of empirical data available. Therefore, it becomes difficult to pinpoint what chemical parameters may cause log K_{OW} over-predictions aside from the shortage of empirical data for highly hydrophobic chemicals. Other factors within QSAR models may include but are not limited to overbearing correction factors stimulated by compound symmetry (Cabalo and Knox, 2014), absence of quantum mechanic contributions such as molecular distortion/orbital hybridization, steric effects, etc., or molecular thermodynamic assumptions between similar chemical classes and sub-structures (Maggiore, 2006; Scior et al., 2009). OPERA log K_{OW} predictions are relatively low for the 4 selected hydrophobic chemicals (Table 2), and the OPERA model estimates for log K_{OW} s are based on a reviewed dataset of over 14,000 chemicals (Mansouri et al., 2018). Similarly, EPISuite predictions also implement a similar number of reviewed chemicals (e.g. 13,700) (US-EPA, 2012). Consequently, the estimations for highly hydrophobic chemicals lack experimental validation and therefore true accuracy is indefinite.

Conclusions

We have successfully expanded the K_{BW} - K_{OW} correlation shown in Figure 1 over a wider range of organic chemicals including several having log K_{OW} s greater than 9. It was proven that K_{BW} s are measurable for highly hydrophobic chemicals using the OECD slow stir technique for chemicals with estimated log K_{OW} s greater than 10. With the developed linear correlation between K_{BW} and K_{OW} , measured K_{BW} s can be used to estimate a chemical's K_{OW} and provide a more accurate estimate of K_{OW} for chemicals. To illustrate the importance of having an unbiased estimate for a highly hydrophobic chemical, consider the K_{OW} estimates ranging from 8.48 to 15.0 for *p*-TCP (Table 2). Using BCFBAF algorithm of EPISuite (US-EPA, 2012), log BAFs (bioaccumulation factor) for upper trophic level fish predicted for these K_{OW} estimates range from 6.82 to 0.72 (L/kg (ww)), respectively. Assuming an environmentally low concentration of *p*-TCP in water of 1 pg/L (part per quadrillion), predicted residues in fish would range from 6,607,000 to 5.24 pg/kg (ww). This example demonstrates the importance of using accurate K_{OW} measurements with predictive models for assessing a chemical's environmental behavior and bioaccumulation.

To estimate log K_{OW} s for highly hydrophobic chemicals, we recommend that one simply use the developed regression given in Eq. 3 with a K_{BW} measured using the OECD slow stir methodology; i.e., the methodology used within this study. It is highly advised to measure

K_{BW} s for one or more less hydrophobic chemicals with known $\log K_{OW}$ s for method validation. Additionally, predictions of $\log K_{OW}$ s above 10 are extrapolations, and their accuracy are a bit tenuous without further experimental measurements. At this time, we have no basis for determining biases with Eq. 3, if any, related to differences in chemical classes. Additional K_{BW} measurements and K_{OW} measurements for additional highly hydrophobic chemicals are needed to address this question, to span Eq. 3 to higher K_{OW} s, and to further validate the K_{OW} – K_{BW} relationship.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- *n*-Butanol/water partition coefficients are measurable for hydrophobic chemicals
- Plot of log K_{OW} vs log K_{BW} is linear, $r^2=0.98$, for K_{OW} s extending into 10^9 range
- K_{OW} s were estimated using K_{OW} - K_{BW} relationship and measured K_{BWs}
- K_{OW} s estimated for highly hydrophobic chemicals are lower than their QSAR estimates

Fig. 1.
Log K_{OW} vs. Log K_{BW} for existing literature data. Regression coefficients ($\pm$ standard error).

Fig. 2.
Log K_{OW} s vs. log K_{BW} s measured in this study. Regression coefficients ($\pm$ standard error).

Fig. 3.
All $\text{Log } K_{\text{OW}}$ s vs. $\text{log } K_{\text{BW}}$ s values. Regression coefficients ($\pm$ standard error).

Table 1.

n-Butanol/water (K_{BW}) and *n*-octanol/water partition coefficients (K_{OW}).

Chemical	Measured Log K_{BW}		Measured Log K_{OW}		Estimated Log K_{OWs}			
	This Study ^a	Literature	This Study ^a	Literature ^{b, d}	Eq. Regression ^c	EPISuite ^e	SPARC	ACD
Benzene	1.92 (0.02; 2)	1.85 [1], 1.90 [2]		2.13	1.90	1.99	2.06	2.22
Chlorobenzene	2.43 (0.02; 2)	2.38 [2]		2.84	2.81	2.64	2.53	2.81
Bromobenzene	2.53 (0.02; 2)			2.99	2.98	2.88	2.67	2.99
Naphthalene	2.76 (0.02; 3)			3.40 (0.17; 33)	3.39	3.17	3.41	3.45
Acenaphthene	3.21 (0.04; 2)			3.97 (0.21; 6)	4.18	4.15	4.06	4.19
Fluorene	3.28 (0.02; 2)			4.14 (0.12; 11)	4.31	4.02	4.20	4.16
Phenanthrene	3.46 (0.01; 3)			4.49 (0.14; 22)	4.63	4.35	4.74	4.68
Anthracene	3.56 (0.06; 3)			4.63 (0.25; 21)	4.82	4.35	4.69	4.68
PCB-1	3.64 (0.06; 3)			4.54 (0.15; 4)	4.95	4.40	4.65	4.45
Fluoranthene	3.73 (0.13; 3)			5.00 (0.28; 17)	5.11	4.93	5.29	5.17
Pyrene	3.74 (0.05; 3)			5.10 (0.21; 14)	5.12	4.93	5.25	5.17
Chrysene	4.07 (0.02; 4)			5.69 (0.27; 13)	5.72	5.52	5.90	5.91
Benz[a]anthracene	4.11 (0.02; 4)		5.76 (0.14; 2)	5.85 (0.08; 7) ^e	5.79	5.52	5.85	5.91
Hexachlorobenzene	4.19 (---; 1)			5.53 (0.25; 17)	5.93	5.86	6.04	4.89
Benzo(g,h,i)perylene	4.21 (0.20; 3)			6.62 (0.51; 7)	5.97	6.70	7.04	6.89
Indeno(1,2,3-cd)pyrene	4.23 (0.16; 3)			6.65 (0.43; 4)	6.00	6.70	7.09	6.89
Benzo[a]pyrene	4.28 (0.03; 4)		6.77 (0.21; 2)	6.09 (0.31; 7) ^e	6.08	6.11	6.54	6.40
PCB-77	4.68 (0.04; 3)			6.58 (0.34; 3)	6.80	6.34	6.28	6.00
PCB-155	4.72 (0.10; 3)			7.23 (0.28; 4)	6.87	7.62	7.66	6.83
Di- <i>n</i> -hexyl phthalate	4.91 (0.04; 2)			6.82 (0.10; 6)	7.20	6.57	6.29	6.95
PCB-209	5.20 (0.04; 5)		8.18 (0.12, 4)	8.22 (0.17; 10) ^e	7.72	10.2	10.5	8.10
BDE-209	5.47 (0.04; 4)		8.37 (0.21, 2)		8.21	12.1	12.0	11.2
Di- <i>n</i> -octyl phthalate	5.52 (0.04; 2)			8.15 (0.04; 3)	8.28	8.54	8.03	9.08
Di- <i>n</i> -decyl phthalate	5.95 (0.05; 2)			9.05 (0.31, 2)	9.06	10.5	9.71	11.2
TBPH	6.21 (0.19; 2)		9.21 (0.19; 2)		9.52	12.0	10.9	10.8

^a average (propagated error, n).

^b average (standard deviation, n).

^c Predicted using Equation 3 and measured KBW's.

^d See Supplementary Data: Table S7 for sources of the literature log KOW values.

^e Measured log KOW from this study not included in literature average. 1 - (Westall, 1983), 2 - (Hansch et al., 1995).

Table 2. Measured *n*-butanol/water (K_{BW}) and estimated *n*-octanol/water partition coefficients (K_{OW}).

Chemical	Measured Log K_{BW}		Estimated Log K_{OW} s							
	This Study ^a	Eq. 3 Regression ^b	OPERA ^c	Tetko et al. ^e	NICEATM ^c	Upper ^f	ACD ^g	Chemaxon ^h	SPARC ⁱ	EPISuite ^e
BDÉthane-209	5.60 (0.14; 2)	8.43 (7.78 – 9.09)	7.72 ^d	7.87	9.68	10.6	11.1	12.4	12.3	13.6
<i>m</i> -TCP	5.78 (0.06; 4)	8.76 (8.09 – 9.45)	8.47 ^d	9.79	9.73	13.2	11.7	12.7	15.1	14.5
<i>p</i> -TCP	5.82 (0.08; 4)	8.82 (8.16 – 9.49)	8.48 ^d	9.80	10.3	13.2	11.2	12.7	15.0	14.5
<i>p</i> -QTCP	6.47 (0.13; 3)	9.98 (9.29 – 10.67)	6.06 ^d	10.4	11.9	16.7	14.3	16.4	19.6	18.9

^a average (propagated error, n).

^b This study, predicted using Equation 3 and (95% prediction interval).

^c US-EPA via <https://comptox.epa.gov/dashboard> (accessed August 15, 2018).

^d Prediction unreliable: Outside of global applicability domain and low local applicability domain.

^e ALOGPS 2.1 (Tetko et al., 2005).

^f Upper (Adimire et al., 2015).

^g ACD via <http://www.chemspider.com/Chemical-Structure.82781.html> (accessed August 15, 2018).

^h Chemaxon via <http://www.chemspider.com/Chemical-Structure.82781.html> (accessed August 15, 2018).

ⁱ (Carreira et al., 1994; Hilal et al., 1995).