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High-throughput in-silico prediction of ionization equilibria for pharmacokinetic modeling

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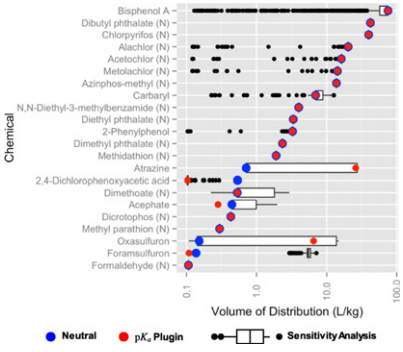
HIGHLIGHTS

- We have replaced a proprietary human variability model with an open-source EPA tool for high throughput risk prioritization.
- Introduced the ionizable atom type (IAT), a high-throughput method for assessing the effects of ionization on compound PK.
- Identified broad differences in the ionization of chemicals intended for pharmaceutical use, near-, and far-field sources.
- pKa was estimated for 8132 pharmaceuticals and 24,281 other compounds to which humans might be exposed in the environment.
- Explored the pKa prediction uncertainty for 22 NHANES chemicals using IATs and how errors in predictions impact PK models.

GRAPHICAL ABSTRACT



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ABSTRACT

Chemical ionization plays an important role in many aspects of pharmacokinetic (PK) processes such as protein binding, tissue partitioning, and apparent volume of distribution at steady state (Vd_{ss}). Here, estimates of ionization equilibrium constants (i.e., pK_a) were analyzed for 8132 pharmaceuticals and 24,281 other compounds to which humans might be exposed in the environment. Results revealed broad differences in the ionization of pharmaceutical chemicals and chemicals with either near-field (in the home) or far-field sources. The utility of these high-throughput ionization predictions was evaluated via a case-study of predicted PK Vd_{ss} for 22 compounds monitored in the blood and serum of the U.S. population by the U.S. Centers for Disease Control and Prevention National Health and Nutrition Examination Survey (NHANES). The chemical distribution ratio between water and tissue was estimated using predicted ionization states characterized by pK_a. Probability distributions corresponding to ionizable atom types (IATs) were then used to analyze the sensitivity of predicted Vd_{ss} on

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predicted pK_a using Monte Carlo methods. 8 of the 22 compounds were predicted to be ionizable. For 5 of the 8 the predictions based upon ionization are significantly different from what would be predicted for a neutral compound. For all but one (foramsulfuron), the probability distribution of predicted Vd_{ss} generated by IAT sensitivity analysis spans both the neutral prediction and the prediction using ionization. As new data sets of chemical-specific information on metabolism and excretion for hundreds of chemicals are being made available (e.g., Wetmore et al., 2015), high-throughput methods for calculating Vd_{ss} and tissue-specific PK distribution coefficients will allow the rapid construction of PK models to provide context for both biomonitoring data and high-throughput toxicity screening studies such as Tox21 and ToxCast.

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1. Introduction

Regulatory agencies worldwide are tasked with characterizing the safety of tens of thousands of commercial chemicals, yet only a small subset have been fully characterized with respect to hazard and exposure (Egeghy et al., 2012; Judson et al., 2009; USGAO, 2009; USGAO, 2013). As thousands of new chemicals are introduced into commerce each year (Judson et al., 2009; USGAO, 2009; USGAO, 2013; Wilson and Schwarzman, 2009), it becomes much more challenging to set research priorities for determining what risk, if any, these chemicals in our environment pose to human and ecological populations (Thomas et al., 2013).

High throughput, in vitro testing programs such as Tox21 (Tice et al., 2013) and ToxCast (Kavlock et al., 2012) have been screening thousands of chemicals for potential bioactivity. However, interpretation of these data relies on nominal tested concentration unless the results can be extrapolated to in vivo conditions (e.g., Wetmore et al., 2015). The Centers for Disease Control and Prevention (CDC) National Health and Nutrition Examination Survey (NHANES) includes measurements of hundreds of xenobiotic chemical concentrations in blood and serum in the U.S. population (CDC, 2012). But, without knowing how these chemicals distribute within the body, blood concentrations cannot be related to potential concentrations in tissues that might be targets of toxic effects. Further, without knowing tissue distribution, neither the total body burden of the chemical nor the rate of exposure can be estimated.

Tissue distribution of chemicals remains an important aspect of pharmacokinetics (PK) that is not rapidly measured using in vitro or in vivo techniques. Tissue PK methodologies exist in the PK literature for the prediction of chemical distribution into specific tissues or the whole body (e.g., volume of distribution at steady-state or Vd_{ss}) but require specific information on physico-chemical behavior. In silico prediction of such chemical tissue distribution is heavily influenced by three key parameters: binding to tissue and plasma, hydrophobicity, and ionization (Peyret et al., 2010; Schmitt, 2008). Hydrophobicity (quantified by the octanol-water partition coefficient, logP) drives distribution of neutral compounds; however, a neutral compound at one pH can become ionized, for example, at a physiological pH. Thus, chemical ionization is key in estimating distribution (illustrated in Fig. 1). For predicting tissue distribution, tissues can be broadly described as consisting of components with differing affinities for chemicals depending on the charged state of the organic chemical molecule, as shown in Fig. 1 (Peyret et al., 2010; Schmitt, 2008). The resulting ratio between the total concentration (ionized and un-ionized) of chemical in the tissue and the plasma is the distribution coefficient (logD) (Manners et al., 1988). In PK, logD is described through tissue-specific partition coefficients (PC) (Peyret et al., 2010; Schmitt, 2008).

At a given pH, some atoms of a compound can donate (dissociation) to or receive (association) protons from one or more atoms or sites within the compound (Fig. 2). Chemical association/dissociation changes the overall molecular charge, with the potential for coexistence of multiple microspecies (i.e., different charge states of the same parent molecule). The chemical association/dissociation equilibrium constant (pK_a) characterizes the pH at which concentrations of protonated or deprotonated chemical microspecies associated with an ionizable atom or site are in equilibrium. The aim of the present work was to generate ionization profiles of chemicals at an atomic level using a rapid approach suitable for thousands of chemicals.

pK_a is often reported in scientific literature as a single numerical value, sometimes categorized as “acid” or “base”. This is sufficient for a compound that undergoes a single ionization, but in many cases there are multiple ionizations, and each pK_a needs to be characterized in the range of $0 < pH < 14$, as shown in Fig. 2. This information is vital for PK because the overall charge and the fraction extant at a certain pH follows the Henderson-Hasselbalch equation (Hasselbalch, 1916; Henderson, 1908), which has a different behavior for acidic (negative to neutral) and basic (neutral to positive) events as pH is increased. Therefore, ionization cannot be characterized by a scalar pK_a value only, nor is it possible to compare predictions of quantitative structure–activity relationship models without further characterizing the ionization kinetics.

Understanding chemical-specific ionization properties is critical for predicting tissue distribution. As new data sets of chemical-specific information on metabolism and excretion for hundreds of chemicals are being made available (e.g., Wetmore et al., 2015), high-throughput methods for calculating Vd_{ss} and tissue-specific PK distribution coefficients will allow the rapid construction of compartmental and physiologically-based PK models. PK distribution describes how chemicals can accumulate preferentially in certain tissues, producing higher

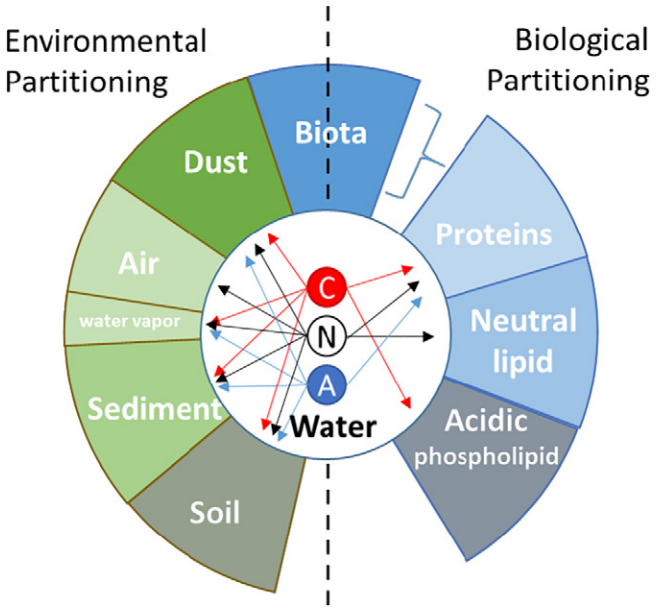

Fig. 1. Neutral and ionized species of the same molecule can partition differently into environmental and biological media (C = cation, N = neutral, and A = anion). Ecologically only neutral species partition into air, while only ions partition onto water droplets (Franco and Trapp, 2008); all species can partition into dust, sediment, and soil (Doucette, 2003; Franco et al., 2009). Biologically both neutral and ionized forms can bind to proteins, while cations can partition into acidic phospholipids and neutral species can partition into neutral lipids (Peyret et al., 2010).