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Bioaccumulation potential of air contaminants: combining biological allometry, chemical equilibrium and mass-balances to predict accumulation of air pollutants in various mammals

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## Abstract

In the present study we develop and test a uniform model intended for single compartment analysis in the context of human and environmental risk assessment of airborne contaminants. The new aspects of the model are the integration of biological allometry with fugacity-based mass-balance theory to describe exchange of contaminants with air. The developed model is applicable to various mammalian species and a range of chemicals, while requiring few and typically well-known input parameters, such as the adult mass and composition of the species, and the octanol-water and air-water partition coefficient of the chemical.

Accumulation of organic chemicals is typically considered to be a function of the chemical affinity for lipid components in tissues. Here, we use a generic description of chemical affinity for neutral and polar lipids and proteins to estimate blood-air partition coefficients ( $K_{ba}$ ) and tissue-air partition coefficients ( $K_{ta}$ ) for various mammals. This provides a more accurate prediction of blood-air partition coefficients, as proteins make up a large fraction of total blood components.

The results show that 75% of the modeled inhalation and exhalation rate constants are within a factor of 2 from independent empirical values for humans, rats and mice, and 87% of the predicted blood-air partition coefficients are within a factor of 5 from empirical data. At steady-state, the bioaccumulation potential of air pollutants is shown to be mainly a function of the tissue-air partition coefficient and the biotransformation capacity of the species and depends weakly on the ventilation rate and the cardiac output of mammals.

Keywords: bioaccumulation – volatile organic compounds – mammals – human – mechanistic model

## Introduction

Volatile organic compounds (VOCs) are ubiquitous contaminants of air in both the indoor environment and ambient, urban and rural environments. A large number of indoor-sources exist including consumer products, building materials, tobacco products, furniture, cleaning products, vehicles in attached garages, water supplies, and outdoor air (Kim et al. 2001; Wallace 2001). VOCs in ambient air largely originate from mobile and industrial sources, including vehicle emissions, industrial operations, gasoline fueling stations, landfills and storage facilities (Wallace 2001; Sexton et al. 2004a; Sexton et al. 2004b). Chronic exposure to relatively low levels of airborne VOCs is an inescapable reality for most people (Sexton et al. 2004a) and (urban) wildlife (Archbold et al., 2007). Many of these compounds are labeled as “hazardous” as they are known or suspected to cause chronic, adverse health effects in exposed populations (Sexton et al. 2004b). They are readily absorbed through the respiratory tract and then transported by blood to critical organs as the central nervous system. Ashley et al. (1996) have shown that for many VOCs, even when most of the internal dose of these compounds is quickly eliminated, there is a small fraction that is only slowly removed, resulting in potentially important bioaccumulation.

Bioaccumulation of persistent VOCs is therefore an issue that must be confronted in human and environmental risk assessment.

Two types of models have been developed to address human and environmental exposure to chemicals. Physiologically based pharmacokinetic (PBPK) models have been widely applied in risk assessment of human exposure to air and water contaminants (Andersen 2003). PBPK models describe the relationship between external exposures and internal concentrations of the biologically effective dose, e.g. the amount biotransformed or the concentration in a target organ (Clewell 1995). Characteristic features of these models are the mass-balance description of chemical distribution within the body based on knowledge of mammalian physiology (e.g. blood flows), biological processes (e.g. metabolic rates as ventilation rate and cardiac output) and physicochemical properties (e.g. tissue-blood partition coefficients). PBPK-models are particularly well-suited to calculate tissue doses of chemicals and their metabolites over a wide range of exposure conditions and can be scaled from one animal species to another (Andersen 2003). However, they are often chemical specific and empirically calibrated, and two major concerns have been the model-complexity and the large amount of biological data that is required to parameterize them (Chiu and White 2006).

A second type of exposure models consists of bioaccumulation models. These models are useful tools in the environmental risk assessment of chemicals because they relate external environmental exposures to internal, possibly toxic, concentrations and provide an estimate of accumulation when no empirical data are available (Hendriks et al. 2001). Bioaccumulation models have traditionally been developed for the aquatic environment, but applications have recently been extended to air-breathing mammals (Czub and MacLachlan 2004; Armitage and Gobas 2007; Kelly et al. 2007). Generally, these models are fugacity-based, one-compartment models, and their major advantage is their relative simplicity and their ability to be consistently applied to a wide range of chemicals. Yet, these models are often species-specific. Human and environmental risk assessment can benefit from a model that can be consistently applied to various species and a wide range of chemicals without case-specific calibration. Also, there are increasing calls for the integration of ecological and human risk assessment (Bridges, 2003; Suter et al., 2005; Schaafsma et al., 2009). This integration has been proposed as an efficient way to deal with a lack of information but, at present, there are only a few attempts in this direction (e.g., Vermeire et al., 2003; Suter, 2004; Hendriks et al., 2007).

One of the most important properties in determining the respiratory kinetics of volatile chemicals in mammals is the blood-air partition coefficient (Lin et al. 2002). In bioaccumulation modeling, it is common practice to assume that chemical affinity for tissues is a function of the octanol-water partition coefficient of the chemical and the fat content of the organism. Tissue-air partition coefficients are often estimated based on the chemical affinity for lipids only (Kelly and Gobas, 2003; Czub and MacLachlan, 2004; Armitage and Gobas, 2007). However, for blood, where proteins make up a large fraction of total blood components, it is important to consider protein-affinity in predictions of the blood-air partition coefficient. Recently, Hendriks et al. (2005) developed a general description for chemical equilibrium partitioning in various tissues, distinguishing between neutral lipids and polar lipids and including non-lipid fractions such

as proteins. It is important to investigate whether this generic approach can be used to accurately predict blood-air partition coefficients for various mammals and a range of chemicals.

The aim of this study is two-fold:

1. to develop and test, a generic, one-compartment bioaccumulation model for air exposure that describes uptake and elimination kinetics as a function of chemical specific properties, physiological processes, and species-based allometric scaling.
2. to investigate whether a generic description of substance affinity for various blood components can be used to predict blood-air partition coefficient for various mammalian species including humans, rats, mice, rabbits, pigs, guinea pigs and dogs.

To this end we combined steady-state equations of physiologically-based pharmacokinetic models for volatile chemicals with established allometric relationships for ventilation rate and cardiac output. Allometric scaling of these physiological processes as a power of body weight ( $^{-1/4}$ ) allows extrapolation from one species to another. This approach can therefore minimize the use of experimental animals. Although interspecies extrapolation can also be performed using body surface area relationships, we here use allometric scaling as a power of body weight ( $^{-1/4}$ ) as this is a well established method for extrapolation between species (see reviews by Peters, 1983; West et al., 1997; Hendriks, 2007 ). Additionally, (adult) species weight is an easy-to-measure parameter, which is available for most species. In contrast, body surface areas for a range of species are not as easily obtained. As the objective of the model is to predict accumulation of airborne contaminants for a range of species, based on well-known input parameters, we use allometric relationships on a body weight basis to extrapolate between species.

We use the resulting model to estimate chemical uptake from air as a function of species weight and the chemical-specific blood-air and tissue-air partition coefficients. These partition coefficients are estimated from physiological characteristics, such as the fraction of neutral lipids, polar lipids, proteins and the water content, and well-documented physicochemical properties such as the octanol-water and air-water partition coefficients. The model performance is evaluated in an external validation test, using independent, measured chemical inhalation rate constants and independent, measured exhalation rate constants for a variety of chemical substances and different mammals, including humans, rats and mice. Additionally, we compare predicted blood-air partition coefficients to empirical data collected from 29 studies.

## **Methods**

### **Internal chemical concentration**

At steady-state the chemical concentration in an organism can be estimated as the total uptake via air, divided by the total elimination via exhalation ( $k_{x,a,ex}$ ), excretion with urine ( $k_{x,w,ex}$ ), egestion with food ( $k_{x,n,ex}$ ), growth dilution ( $k_g$ ) and biotransformation ( $k_{x,m}$ ) (Hendriks et al. 2001).

$$C_i = \frac{k_{x,a,in} \cdot C_A}{k_{x,a,ex} + k_{x,w,ex} + k_{x,n,ex} + k_g + k_{x,m}} \quad \text{Equation 1}$$

$C_i$	=	Internal concentration [kg·kg <sup>-1</sup> <sub>wet wt.</sub> ]
$C_A$	=	Chemical concentration in air [kg·dm <sup>-3</sup> ]
$k_{x,a,in}$	=	Chemical inhalation rate constant [dm <sup>3</sup> ·kg <sup>-1</sup> ·d <sup>-1</sup> ]
$k_{x,a,ex}$	=	Chemical exhalation rate constant [d <sup>-1</sup> ]
$k_{x,w,ex}$	=	Chemical excretion rate constant [d <sup>-1</sup> ]
$k_{x,n,ex}$	=	Chemical egestion rate constant [d <sup>-1</sup> ]
$k_g$	=	Growth dilution rate constant [d <sup>-1</sup> ]
$k_{x,m}$	=	Chemical biotransformation rate constant [d <sup>-1</sup> ]

Bioaccumulation of chemicals via exposure to contaminated air can be characterized by a bioaccumulation factor, which equals the total internal concentration ( $C_i$ ) divided by the concentration in air ( $C_A$ ). In contrast to PBPK-models, the internal chemical concentration is not estimated at a specific site (i.e. liver, kidney, circulation), but represents the total internal chemical concentration in the body. The model objective is to estimate the bioaccumulation potential of VOCs and to provide insight in differences in magnitude of inhalation rate constants and exhalation rate constants across species and chemicals. For this purpose a one-compartment model is considered sufficient. If exposure occurs only via inhalation of air, this bioaccumulation factor can be estimated as the inhalation rate constant divided by the total elimination rate (Eqn. 2). The equations for excretion via urine, egestion with faeces and growth dilution have been developed by Hendriks et al. (2001) and are provided in the Supporting Information. The development of the inhalation and exhalation rate constants is described in the next section.

$$BAF = \frac{C_i}{C_A} = \frac{k_{x,a,in}}{k_{x,a,ex} + k_{x,w,ex} + k_{x,n,ex} + k_g + k_{x,m}} \quad \text{Equation 2}$$

At present, biotransformation rate constants ( $k_{x,m}$ ) cannot be predicted accurately enough based on species characteristics and chemical properties. Because several hazardous air pollutants are readily transformed it is important to take biotransformation into account as an elimination pathway. But it is also important to note that for the internal mass balance of many VOCs, elimination by exhalation might be very large compared to biotransformation. To address this issue, we tested model sensitivity to biotransformation by incrementally increasing the rate constants for biotransformation. This evaluation will give us information on how values for biotransformation range that will have a strong impact on model results. Biotransformation rates of volatile organic compounds are concentration dependent and are generally considered to follow Michaelis-Menten kinetics (Filser et al. 2000):

$$k_{x,m} = \frac{V_{\max}}{K_m + C_{liver}} \quad \text{Equation 3}$$

- $k_{x,m}$  = Chemical biotransformation rate ( $d^{-1}$ )  
 $V_{\max}$  = Maximum reaction rate ( $\text{mol}/\text{dm}^3 \cdot \text{d}$ )  
 $K_m$  = Apparent concentration ( $\text{mol} \cdot \text{dm}^{-3}$ )  
 $C_{liver}$  = Chemical concentration in the liver ( $\text{mol} \cdot \text{dm}^{-3}$ )

The biotransformation rate is constant in the two limits of linear metabolism ( $k_{x,m} = V_{\max} / k_m$  (first order kinetics)) and saturated metabolism ( $k_{x,m}$  is  $V_{\max}$ , zero-order kinetics). Here, we assume that biotransformation rates follow linear, first-order kinetics, which is often the case for environmentally relevant exposure concentrations (Chiu and White, 2006). This allows for the use of a concentration-independent biotransformation rate constant ( $k_{x,m}$ ).

### Chemical inhalation and exhalation rate constants

Chemical uptake and loss by respiration is inversely proportional to a series of resistances and flow delays. The equilibrium rate constant for chemical uptake via inhalation ( $k_{x,a,in}$ ) can be modeled as three transport processes occurring in series (Cahill et al. 2003) (Eqn. 3). First, the chemical is inhaled into/by the lungs. This airflow carries the chemical from the external air to the alveolar region in the lungs. The corresponding flow delay is quantified as the inverse of the alveolar ventilation rate ( $G_A$ ). The alveolar ventilation rate is the amount of air that reaches the alveoli and is available for gas exchange with the blood per unit time. Second, the chemical diffuses across the blood-air barrier and enters the capillaries. The diffusion resistance is a function of the thickness of the blood-air barrier ( $\beta_A$ ), the alveolar surface area ( $A_A$ ), the chemical diffusivity in the cytosol ( $d_w$ ) and the blood-air partition coefficient ( $K_{BA}$ ). Finally, the chemical is transported from the lungs to the main blood circulation. It is generally assumed that volatile chemicals equilibrate very rapidly with capillary blood in the lungs (Ramsey and Andersen 1984). This equilibrium ratio can be expressed by the blood-air partition coefficient of the chemical (Ramsey and Andersen 1984). The total flow delay is a function of the full cardiac output ( $G_B$ ) and the chemical-specific blood-air partition coefficient ( $K_{BA}$ ). Note that physiological parameters as the cardiac output, the ventilation rate and the alveolar surface area are expressed on a per kg body weight basis.

$$k_{x,a,in} = \frac{1}{\left( \frac{1}{G_A} + \frac{\beta_A}{d_w \cdot A_A \cdot K_{BA}} + \frac{1}{G_B \cdot K_{BA}} \right)} \quad \text{Equation 3}$$

- $k_{x,a,in}$  = Chemical inhalation rate constant [ $\text{dm}^3 \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ]  
 $w$  = Species wet weight [kg]



$G_A$	=	Alveolar ventilation rate [ $\text{dm}^3 \text{kg}^{-1} \cdot \text{d}^{-1}$ ]
$d_w$	=	Aqueous diffusion in cytosol [ $\text{dm}^2 \cdot \text{d}^{-1}$ ]
$A_A$	=	Alveolar surface area per kg body weight [ $\text{dm}^2 \text{kg}^{-1}$ ]
$\beta_A$	=	Diffusion distance across alveolar cells [dm]
$G_B$	=	Cardiac output [ $\text{dm}^3 \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ]
$K_{BA}$	=	Blood – air partition coefficient [ / ]

Chemicals entering the lungs in the venous blood stream can be transferred to lung air and be exhaled. This transport term is opposite of the inhalation and absorption process and works to remove chemicals from the blood stream. It works well for removing chemicals with a sufficiently high vapor pressure that are not accumulated in tissues such as body fat (Eqn. 4). The latter is expressed by the accumulation ratio ( $K_{TA}$ ), which reflects the affinity of substances for different body compartments, including neutral and polar lipids, protein fractions and water.

$$k_{x,a,ex} = \frac{1}{K_{TA}} \cdot \frac{1}{\left( \frac{1}{G_A} + \frac{\beta_A}{d_w \cdot A_A \cdot K_{BA}} + \frac{1}{G_B \cdot K_{BA}} \right)} \quad \text{Equation 4}$$

In the prediction of the inhalation and exhalation rate constants, the allometric relationships for the minute ventilation rate and cardiac output were taken from a review by Lindstedt and Schaeffer (2002) (Table 1). These relationships were selected as they are, to our knowledge, based on the largest available dataset, and include various mammalian species (including human, rats, mice, hamster, guinea pig, cat, dog, rabbit, mouse, monkey, horse, goat, sheep and pig). The methods to develop these relationships are well-documented and considered scientifically sound. Additionally, these relationships are consistent with classic allometric scaling laws that relate metabolic rate to adult body mass to the power  $-1/4$  ((Kleiber, 1930; Peters, 1983; West et al., 1997; Hendriks, 2007).

The alveolar ventilation rate is assumed to be 67% of the minute ventilation rate (EPA 1988). The mass-specific flow rates, such as ventilation rate and cardiac output, typically scale to body weight with a power  $-1/4$  (Peters 1983). The lung's diffusing capacity for  $O_2$  has, however, repeatedly been shown to be independent of body weight revealing no scale factor (Weibel 1979; Hughes 1984; Lindstedt 1984). Additionally, the alveolar surface area per kg body weight is independent of species weight (Weibel 1979; Hughes 1984) and the diffusion distance across the blood-air barrier is comparable across various mammalian species (Mania 2002; Maina and West 2005; Weibel 1979). Consequently, the diffusion resistance scales to the power of 1 instead of 0.75. The pure water diffusion coefficient ( $d_w$ ) for neutral organic substances is calculated following Schwarzenbach (1993) (SI).

### Physiological partition coefficients

The chemical affinity for both neutral lipids and polar lipids is approximately linearly related to the affinity for octanol (Hendriks et al. 2005). Substance affinity for proteins can also be related to the octanol-water partition coefficient, but the relationship is less than linear due to the polar nature of proteins (Hendriks et al. 2005). The blood-air partition coefficient can thus be estimated based on the physiological characteristics of blood and the affinity for these different blood components divided by the temperature-corrected air-water partition coefficient (Eqn. 5).

$$K_{BA} = \frac{p_{nl,bl} \cdot K_{ow} + p_{pl,bl} \cdot K_{ow}^{0.94} + p_{p,bl} \cdot K_{ow}^{0.63} + p_{H_2O,bl} \cdot K_{ow}^0}{K_{aw}} \quad \text{Equation 5}$$

$K_{BA}$	=	Blood-air partition coefficient
$K_{aw}$	=	Air-water partition coefficient (37°C)
$K_{ow}$	=	Octanol-water partition coefficient (25°C)
$p_{nl}$	=	Neutral lipid percentage of blood (bl) or tissues (t)
$p_{pl}$	=	Polar lipid percentage of blood (bl) or tissues (t)
$p_p$	=	Protein percentage of blood (bl) or tissues (t)
$p_{H_2O}$	=	Water percentage of blood (bl) or tissues (t)

Similarly, equation 5 can be used to estimate the tissue-air partition coefficient ( $K_{ta}$ ).

Predicted blood–air partition coefficients were compared to empirical blood–air partition coefficients. Species-specific blood parameters were used to predict the blood-air partition coefficient, except for mice, guinea pigs and pigs. For these species we used typical mammalian values (Table 2).

### Model evaluation

Model performance was evaluated using both visual goodness-of-fit observations and more quantitative model performance techniques, as well as a discussion of key sensitivities. In order to quantify model performance in terms of model error, the RMSE (root mean square error) was calculated (Eqn. 6).

$\log RMSE = r$  human, rat and mouse), methylchloride, 1-bromopropane and 1,3-butadiene (for both

humans and rats) and diethyl ether (for rats). Second, blood-air partition coefficients for humans are slightly, with a factor of 2-3, overestimated and measured partition coefficients for humans are generally lower than partition coefficients for rats.

The RMSE analysis shows that 68% of the predicted inhalation and exhalation rate constants are within a factor of 2.1 from empirical data (Figure 2a and 2b). All modelled inhalation rate constants are within a factor of five from measurements (fig. 2a) with exception of the predicted vinyl chloride inhalation rate constant for rats. The underestimation of the inhalation rate constant for this chemical can be attributed to the underestimation of the blood-air partition coefficient for low  $\log K_{ow}$ -high  $\log K_{aw}$ -chemicals, such as vinyl chloride. The  $K_{BA}$  of vinyl chloride is underestimated by a factor of 3.3 and model predictions are within a factor of 3 from empirical data if the measured  $K_{BA}$  for rats is used (results not shown). In Figure 2b it is shown that chemical exhalation rate constants are well predicted by the model.

The overall rate constant for chemical exchange with air is limited by the slowest process. Evaluation of the model equation for exchange via air shows that the diffusion resistance through the blood–air barrier is negligible compared to the combined resistance of the alveolar ventilation rate and blood flow. The chemical uptake and elimination via air is therefore flow-limited and the diffusion term can be neglected in the equations for inhalation and exhalation. In Figure 3a model predictions for chemical uptake in rats and empirical inhalation-data are plotted against the estimated blood-air partition coefficient ( $K_{BA}$ ). For vinyl chloride and 1,3-butadiene empirical values of the  $K_{BA}$  were used, as these substances belong to the group of chemicals with a low  $\log K_{ow}$  and high  $\log K_{aw}$ . The  $K_{BA}$ -model was shown to have less predictability for this chemical group. This figure shows that inhalation rate constants depend on the blood-air partition coefficient at values of  $K_{BA}$  lower than 1.6, whereas at high  $K_{BA}$  a maximum chemical inhalation rate constant is observed. This trend is partly confirmed by empirical data. A maximum chemical inhalation rate constant is observed, yet empirical data do not show a clear decline in inhalation rate constants with decreasing  $K_{BA}$ . However, insufficient empirical inhalation rate constant data for low  $K_{BA}$ -substances are available to evaluate model predictions in this range. The model slightly overestimates the maximum inhalation rate constant for rats by approximately a factor of 1.7. For most compounds exhalation rate constants are somewhat underestimated (by a factor of 2.2) compared to empirical rate constants of loss. Exhalation rate constants decrease with increasing  $K_{BA}$  and similarly, these rate constants decrease with increasing  $K_{TA}$  (Figure 3b).

Bioaccumulation of chemicals in an organism occurs if the rate of uptake from air is higher than the total rate of elimination, i.e. the sum of excretion with urine, egestion with faeces, growth dilution and biotransformation. A quantitative analysis of the different elimination rate constants shows that persistent volatile organic compounds are predominantly eliminated via exhalation. This finding is illustrated in Figure SI3 of the Supporting Information. The contribution of other pathways of loss, such as excretion with water, egestion with faeces and growth dilution, to the total elimination rate is typically less than <10%. Therefore, the steady-state bioaccumulation factor ( $C_i/C_A$ ) of air pollutants can be estimated as the inhalation rate constant divided by the exhalation rate constant. Figure 4 shows that persistent air pollutants with a blood-air partition coefficient of 5 or higher, have a high bioaccumulation potential ( $BAF \geq 60 \text{ dm}^3 \cdot \text{kg}^{-1} \text{ wet wt.}$ ) unless they are biotransformed at a sufficiently rapid rate (i.e.  $k_m > 500 \text{ d}^{-1}$  obtains a

BAF of 1). This ratio equals the equilibrium tissue-air partition coefficient, if the biotransformation rate is negligible.

## **Discussion**

### **Blood-air partition coefficients**

One of the objectives of the present study was to investigate whether a generic description of substance accumulation in various blood components can be used to predict blood-air partition coefficient for various mammalian species including humans, rats, mice, rabbits, pigs, guinea pigs and dogs. Our results suggest that in general blood-air partition coefficients can be reliably predicted for various mammals. However, blood-air partition coefficients of substances with a combination of a relatively low octanol-water partition coefficient,  $\log K_{ow} < 2$ , and a relatively high air-water partition coefficient,  $\log K_{aw} > 0.32$  are underestimated. DeBruyn and Gobas (2007) concluded that low  $K_{ow}$ -chemicals have a higher affinity for blood proteins such as albumin than expected based on their  $K_{ow}$ . Our results suggest that especially chemicals with a combination of a low  $K_{ow}$  and a high  $\log K_{aw}$  have a higher affinity for blood proteins than expected.

Also blood-air partition coefficients for humans are slightly overestimated and measured partition coefficients for humans are generally lower than partition coefficients for rats. This observation is consistent with results from several studies (Lin 1998; Gargas et al. 1989; Lam et al. 1990) and has been attributed to a weaker binding to plasma-proteins such as albumin and/or hemoglobin in humans compared to rats (Lin 1998; Gargas et al. 1989; Wiester et al. 2002; Lam et al. 1990). This suggests that the sorptive capacity of human blood proteins is overestimated by our model.

Other deviations between model predictions and empirical values may be due to variation in blood parameters, especially in neutral lipid content of blood, and due to differences in experimental techniques between studies. Although inter-species differences in blood composition are relatively small (Nelson 1972; Nelson 1967), partition coefficients have been found to vary with changes in hematocrit and blood lipids (Fiserova-Bergerova 1983; Lin et al. 2002). There is considerable variation in reported blood-air partition coefficients of a chemical between studies as indicated by 90% confidence intervals in Figure 1. Differences in experimental techniques, for example differences in equilibration time may also contribute to the observed variability in empirical blood-air partition coefficients (Wiester et al. 2002).

### **Contaminant exchange via air**

The blood-air partition coefficient is often assumed to be one of the most important properties in determining the respiratory kinetics of volatile chemicals in humans (Lin et al. 2002). Evaluation of the model equations for contaminant exchange with air shows that inhalation rate constants are  $K_{BA}$ -dependent at low values for  $K_{BA}$ , whereas at high  $K_{BA}$  values a maximum chemical inhalation rate constant is observed. This is due to a flow-limitation imposed by the ventilation rate, which results in comparable inhalation rate constants for different chemicals. Compared to inhalation rate constants, exhalation rate

constants are a more complex function of the tissue-air partition coefficient ( $K_{TA}$ ), the blood-air partition coefficient ( $K_{BA}$ ) and the flow delays imposed by ventilation and cardiac output. Consequently, the exhalation rate constants show more variation than inhalation rate constants, depending on chemical-specific properties and species characteristics.

Our results show that the maximum inhalation rate constant for rats is generally slightly overestimated. There are two possible explanations for this overestimation. First, model performance for high  $K_{BA}$  substances strongly depends on an accurate prediction of the ventilation rate. A ventilation rate of  $180 \text{ dm}^3 \cdot \text{d}^{-1}$  is predicted for a 250 gram rat. This prediction is in close agreement (within a factor of 1.1) with standard physiological parameters for ventilation ( $168 \text{ dm}^3 \cdot \text{d}^{-1}$  for a 250 gram rat) (Arms and Travis 1988). Second, in our modelling approach we assumed that there is no exchange of substances between air and tissue in parts of the respiratory tract other than the alveolar region. However, gases with a high water-solubility will also be absorbed to the tissues of the conducting airways during inhalation and desorbed upon exhalation, so-called wash-in/wash-out effects. This may result in lower uptake rate constants than expected based on the ventilation rate, cardiac output and blood-air partition coefficient of the chemical (Johanson and Filser 1995). This wash-in/wash-out effect is particularly important for rodents, and is thought to be less important in humans, due to the relative smaller surfaces of the human nasal cavity (Filser et al. 1993). In contrast, exhalation rate constants may be underestimated compared to measured rates of loss due to wash-out of chemicals from tissues in the respiratory tract. This may explain our observation that exhalation rate constants for rats are slightly underestimated.

### **Bioaccumulation potential of air pollutants**

It is shown that air pollutants with a blood-air partition coefficient of 5 or higher, have a high bioaccumulation potential ( $\text{BAF} \geq 60 \text{ dm}^3 \cdot \text{kg}^{-1}$  wet wt.) unless they are biotransformed at a sufficiently rapid rate. This bioaccumulation potential is similar in humans and rodents as variation in tissue-composition is relatively small across mammals (Hendriks et al. 2005). However, as is shown in Figure 4 the bioaccumulation potential strongly depends on the biotransformation capacities. This biotransformation capacity is largely chemical- and species-specific and differences in bioaccumulation potential between humans and rodents will arise due to variation in biotransformation rates (Pastino et al. 2000).

### **Model applicability in human and environmental risk assessment**

Here, we present a mechanistic bioaccumulation model for chemical exchange via air, which is applicable to neutral organic chemicals and various mammals. This model uses chemical- and species-specific inhalation rate constants and exhalation rate constants that are estimated based on chemical properties, physiological partition coefficients and species characteristics. The advantage of the model is the relative simplicity and the minimum amount of input-data required, i.e. adult mass of the species, and the octanol-water and air-water partition coefficient of the chemical. We have evaluated the performance of this model for accumulation kinetics of volatile organic compounds in rats, mice and humans. The model produces a

fit within a factor of 2-5 from empirical data (RMSE = 2.1). This is considered satisfactory for a generic model, as both the external validation data and used model parameters (chemical properties and allometric relationships) are subject to inherent uncertainties. At present, options to evaluate the model for other animal species and for other chemicals were limited and this is an important direction for further research.

Our model can be of added value in a number of current human and environmental risk assessment procedures. For example, national and international regulatory agencies, and the chemical industry, are facing a significant challenge from new chemical legislation that requires risk assessment of thousands of chemicals on the market (Bradbury et al., 2004; Schaafsma et al., 2009). To achieve this objective more efficient risk assessment procedures are needed, i.e. risk assessment should focus more on groups of chemicals and move away from a labor-intensive and animal consuming approach (Bradbury et al., 2004; Schaafsma et al., 2009). A tiered approach is considered with the first tier providing a conservative system of easy-to-use models followed by a more elaborate and precise higher tier assessment when necessary (Bradbury et al., 2004; Schaafsma et al., 2009). There is an urgent need for simple, transparent tools that can be used to assess exposure for a range of chemicals and a range of species, without increasing input parameter requirements. Additionally, chemical risk assessment should ensure a high level of protection of both humans and the environment, and tools are needed that integrate human and environmental risk assessment as much as possible (e.g., Bridges, 2003; Suter, 2004, Suter et al., 2005; Schaafsma et al., 2009). Here, we propose such a model: the combination of biological allometry with chemical fugacity theory in a consistent and mechanistic framework makes it feasible to extrapolate the model to a range of mammalian species, including humans, and a range of organic chemicals, while requiring a minimum amount of input-data. Another example of model application comes from the indoor environment field. McKone et al. (2007) have used biomarker data together with an indoor fugacity based mass-balance model to better understand cumulative exposures to pesticides. Their work uses biomarker data to demonstrate for pesticides that occupants attain some level of chemical equilibrium with the household environment. In an assessment of the indoor fate of semi-volatile organic chemicals (SVOCs), Weschler and Nazaroff (2008) have also demonstrated that SVOCs are transported from indoor air to occupants, resulting in measurable body burdens. But neither McKone et al. (2007) nor Weschler and Nazaroff (2008) have explicitly modeled this transfer of chemicals from indoor air to humans. This study fills that gap.

At present, the availability of information on biotransformation rates is and will be a limiting factor for the model. This applies, however to all risk assessment models in this field. While improvements of “in vivo”, “in vitro” and “in silico” methods for predicting metabolism are promising, the present model can, just as other risk assessment models be useful for a conservative screening-level risk assessment, in which comparisons are made between large sets of substances and various species.

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## Tables

Table 1: Physiological parameters and allometric relationships for ventilation rate ( $\text{dm}^3 \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ), cardiac output and alveolar surface area of mammals

Parameter		Value	$r^2$	$n$	Unit	Reference
Minute ventilation rate (per kg body weight)	$G_M$	$6.7 \cdot 10^2 \cdot w^{-0.25}$	0.96	19	$\text{dm}^3 \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$	Lindstedt and Schaeffer, 2002
Full cardiac output (per kg body weight)	$G_B$	$3.2 \cdot 10^2 \cdot w^{-0.25}$	0.99	21	$\text{dm}^3 \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$	Lindstedt and Schaeffer, 2002
Alveolar surface area (per kg body weight)	$A_A$	$293 \cdot w^{-0.03}$	0.99	11	$\text{dm}^2 \cdot \text{kg}^{-1}$	Weibel, 1979
Blood-air barrier	$\beta_A$	$2.7 \cdot 10^{-6} \cdot (w \cdot 1000)^{0.06}$	0.81		dm	Mania and West, 2005

$n$  is the number of species included, species weight ( $w$ ) in kg. Alveolar ventilation rate ( $G_A$ ) equals 67% of minute ventilation rate ( $G_M$ ) (EPA, 1988). Note that physiological parameters as the minute ventilation rate, the full cardiac output and the alveolar surface area are expressed on a per kg body weight basis.

Table 2. Species-specific blood and tissue parameters and for mammals: water content ( $p_{H_2O}$  in  $g \cdot ml^{-1}$ ), neutral lipid content ( $p_{nl}$  in  $g \cdot ml^{-1}$ ), polar lipid content ( $p_{pl}$  in  $g \cdot ml^{-1}$ ) and protein content ( $p_p$  in  $g \cdot ml^{-1}$ ) of whole blood and tissues (SI).

<b>Species</b>	<b>Body part</b>	<b><math>p_{H_2O}</math></b> $g \cdot ml^{-1}$	<b><math>p_{nl}</math></b> $g \cdot ml^{-1}$	<b><math>p_{pl}</math></b> $g \cdot ml^{-1}$	<b><math>p_p</math></b> $g \cdot ml^{-1}$	<b>References</b>
Human	Blood	80.6%	0.33%	0.24%	17.4%	Altman, 1961, Davies and Morris, 1993, Haddad et al., 2000
Rat	Blood	81.6%	0.23%	0.23%	17.9%	Altman, 1961, Davies and Morris, 1993, Nelson, 1967, Nelson, 1972
Rabbit	Blood	81.7%	0.23%	0.19%	17.9%	Altman, 1961, Davies and Morris, 1993, Nelson, 1967, Nelson, 1972
Dog	Blood	80.1%	0.34%	0.28%	19.3%	Altman, 1961, Davies and Morris, 1993, Nelson, 1967, Nelson, 1972
Mammals <sup>b</sup>	Blood	80.4%	0.23%	0.20%	19.8%	Altman, 1961, Davies and Morris, 1993, Nelson, 1967, Nelson, 1972, Haddad et al., 2000
Mammals <sup>b</sup>	Tissue	70%	9%	1%	21%	Hendriks et al., 2005

<sup>b</sup>The values for “mammals” are average values for mammal blood and tissues (SI)

### Figure Legends

Figure 1. Predicted blood-air partition coefficients ( $K_{BA}$ ) versus independent empirical blood-air partition coefficients

Figure 2. Model predictions of exchange with air compared to measurements

Figure 3. (a) Empirical inhalation rate constants for rats plotted against predicted  $K_{BA}$  (b) Empirical exhalation rate constants for rats plotted against predicted  $K_{TA}$ .

Figure 4. Predicted bioaccumulation factors (BAF) using different biotransformation rate constants ( $k_M$  in  $d^{-1}$ ) plotted against the blood-air partition coefficient.

## Figures

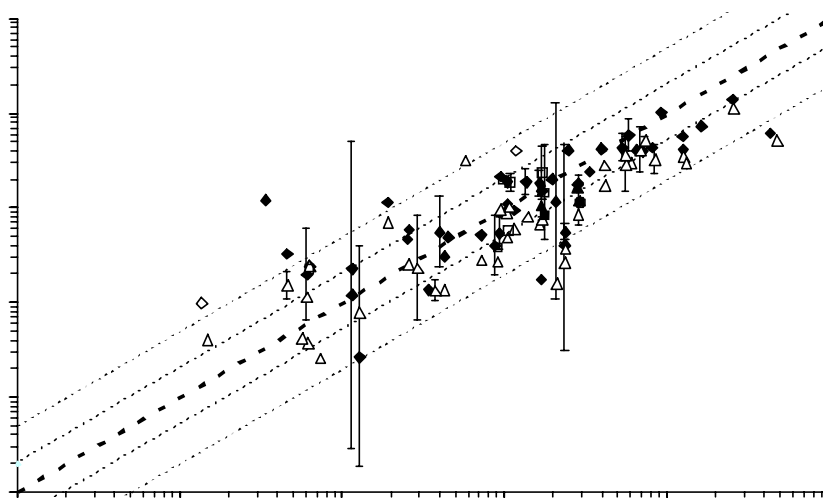


Figure 1. Predicted blood-air partition coefficients ( $K_{BA}$ ) versus independent empirical blood-air partition coefficients

△ Human □ Mice ◇ Dog ◆ Rat ● Pig ▲ Rabbit, ■ Guinea pig

Geometric means with 90% confidence intervals are presented where possible

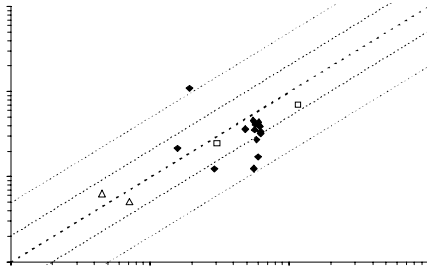
Dashed line represents the theoretical 1:1-relationship

Dotted lines represent a factor of 2 and a factor of 5 above and below the 1:1 line

RMSE = 2.8,  $n = 100$  Regression analysis was performed on the total dataset for log-transformed values of empirical  $K_{BA}$  vs. predicted  $K_{BA}$



a. Inhalation rate constants ( $k_{X,a,in}$ ) [ $\text{dm}^3 \cdot \text{kg} \cdot \text{d}^{-1}$ ]: model predictions compared to empirical data



b. Exhalation rate constant ( $k_{X,a,ex}$ ) [ $\text{d}^{-1}$ ]: model predictions compared to empirical data

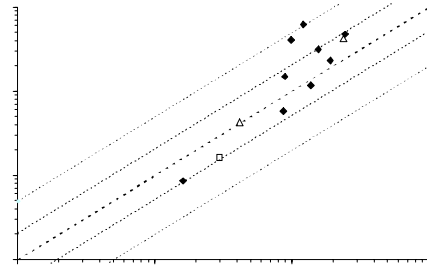
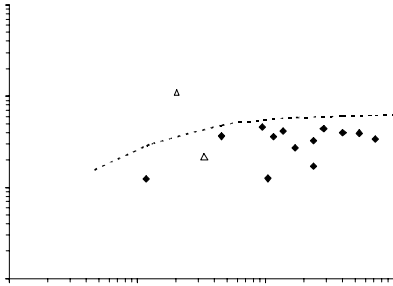


Figure 2. Model predictions of exchange with air compared to measurements

$\triangle$  Human  $\square$  Mice  $\blacklozenge$  Rat. Dashed line represents the theoretical 1:1-relationship, Dotted lines represent a factor of 2 and a factor of 5 above and below the 1:1 line. A regression analysis was performed of log-transformed inhalation and exhalation rate constants versus log-transformed empirical rate constants. For inhalation rate constants (Fig. 2a): RMSE = 2.1, n = 19 and for exhalation rate constants (Fig. 2b) RMSE = 2.1, n = 13

a. Inhalation rate constants for rats ( $k_{X,a,in}$  in  $\text{dm}^3 \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ) plotted against the predicted blood-air partition coefficient ( $K_{BA}$ )



b. Predicted and measured exhalation rate constants for rats ( $k_{X,a,ex}$  in  $\text{d}^{-1}$ ) plotted against the predicted tissue-air partition coefficient ( $K_{TA}$ )

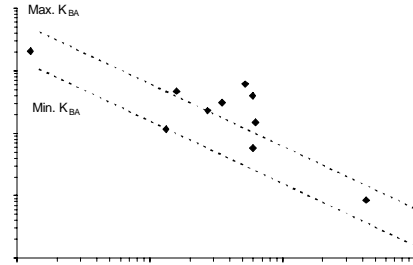


Figure 3 (a) ◆ Empirical inhalation rate constants for rats plotted against predicted  $K_{ba}$ , △ Empirical inhalation rate constants of vinyl chloride and 1,3-butadiene are plotted against measured blood-air partition coefficients as these substances belong to the class of chemicals with a low  $\log K_{OW}$  and high  $\log K_{aw}$ . The  $K_{BA}$ -model has less predictability for this class of chemicals. (b) ◆ Empirical exhalation rate constants for rats plotted against predicted  $K_{TA}$ . Model predictions are shown for a minimum and maximum value of the blood-air partition coefficient, i.e. a value of 0.46 and 71, respectively. This minimum and maximum  $K_{BA}$  are representative for the included substances.

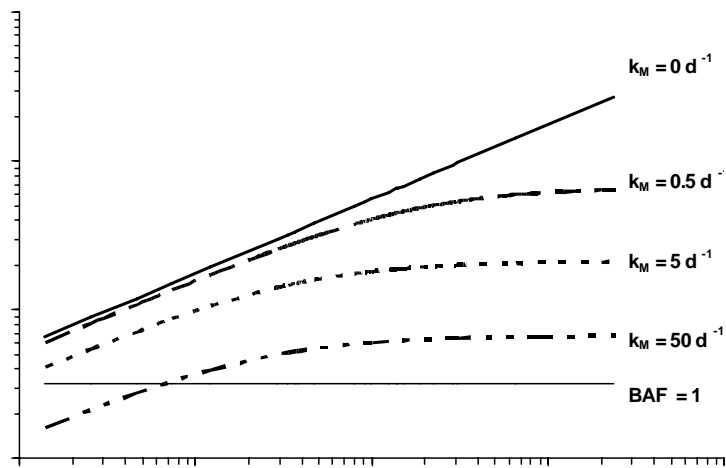


Figure 4. Predicted bioaccumulation factors (BAF) using different biotransformation rate constants ( $k_M$  in  $\text{d}^{-1}$ ) plotted against the blood-air partition coefficient.