Estimation Models to Understand the Chemodynamics of Diverse Organic Pollutants for Organisms and Passive Sampler

By

Sana Naseem

NUST201700000206795

A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

In

Environmental Sciences

Institute of Environmental Sciences and Engineering (IESE) School of Civil and Environmental Engineering (SCEE) National University of Sciences and Technology (NUST)

Islamabad, Pakistan (2019)

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It is certified that the contents and forms of thesis entitled

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Submitted by

Sana Naseem

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Supervisor: _____

Dr. DeedarNabi

Assistant Professor IESE, SCEE, NUST

Member: _____

Dr. Muhammad Faheem Khokhar

Professor

IESE, SCEE, NUST

Member: _____

Dr. Zeshan

Assistant Professor

IESE, SCEE, NUST

THESIS ACCEPTANCE CERTIFICATE

It is certified that the contents and forms of the thesis entitled "**Estimation Models to Understand the Chemodynamics of Diverse Organic Pollutants for Organisms and Passive Sampler**" submitted by Ms. Sana Naseem, Reg. No has been found satisfactory of partial fulfillment of the requirements of the degree of Master of Science in Environmental Sciences

Supervisor: _____

Dr. DeedarNabi

IESE, SCEE, NUST

Head of Department: _____

Dr. Muhammad Arshad

IESE, SCEE, NUST

Principle: _____

Dr. Tariq Mahmood

SCEE, NUST

“I dedicate my dissertation work to my mother and my supervisor. Without whom none of my success would be possible. A special gratitude to my loving mother whose words of encouragement and push for tenacity ring in my ears”

ACKNOWLEDGEMENTS

I am thankful to Allah Almighty for his blessings which made it possible for me to complete this MS work.

First and foremost, I would like to express my sincere gratitude to my thesis supervisor ***Dr. Deedar Nabi (IESE)*** *for his continuous support throughout my thesis at IESE, for his patience, motivation, enthusiasm and immense knowledge. His guidance helped me through my research and writing of this thesis. I could not have imagined having a better advisor and mentor for my MS research work. I am also very thankful to* ***Dr. Faheem Khokhar (IESE)*** *and* ***Dr. Zeshan (IESE)*** *for their guidance and continuous support.*

I would like to acknowledge and thank my school (SCEE) for allowing me to conduct my research and providing any assistance requested.

I would also like to thank my parents for their wise counsel and sympathetic ear. They were always there for me. Finally, I am thankful to my friends. We were able to support each other by deliberating over our problems and findings, and also happy by talking about things other than just our research.

(Sana Naseem)

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LIST OF ABRIVATIONS

log $t_{1/2}$	Elimination half - life
K_{o-w}	Octanol- water partition coefficient
K_{a-w}	Air- water partition coefficient
K_{o-c}	Organic – carbon Partition coefficient
D_w	Diffusion in water
D_{eth}	Diffusion in ethanol
W_f	Weight of the fish
u_1	fist retention indces
u_2	Second retention indices
GC×GC	Two- dimensional gas chromatography
BCF	Bioconcentration factor
k_M	Biotransformation half – life
K_p	Skin permeability coefficient
PDMS	Polydimethylsiloxane
MLR	Multiple linear regression
PCA	Principle component analysis

RMSE	Root mean square error
PER	Prediction error rate
$\tau_{95\text{-PDMS}}$	Time to reach 95 % of equilibrium state
CV	Cross validation
LOO	Leave - one out

ABSTRACT

This thesis sheds light on the mechanistic aspects of chemodynamics of organic pollutants in three environmentally-important phases: fish, human skin and polydimethylsiloxane (PDMS) passive samplers.

Thesis starts with the probing of variability embedded in depuration half-life data for a diverse set of chemicals using different sets of inter-molecular interactions. I started with Abraham solvation parameters and found that together with fish weight information (W_f), molecular polarizability (E), hydrogen donating capability (B) and the size (V) of molecule play important role in describing more than 85% of variability in half-lives of a diverse set of chemicals. Models based on three types of descriptors-equilibrium coefficients (for air-water, octanol-water, organic carbon-water, and organism-water partitioning systems), rate-related coefficient (diffusion in water and ethanol, biotransformation rate), and allometric coefficient (W_f)- were used to estimate the depuration half-lives. The model using descriptors of bioconcentration factor (BCF), biotransformation rate constant (k_M), and W_f-referred to as BIOCEF model in this study-outperformed other models with R^2 of 0.87 and root-mean-square error (RMSE) of 0.44 log unit, when compared to experimental data. Finally, we showed that the estimates of depuration half-life can be directly applied to nonpolar chemicals detected on GC×GC chromatograms with an RMSE of 0.64 log units.

In the second part of this thesis, I developed a model to estimate skin – permeability coefficients (K_p), by modifying the previous approach. The training dataset was diverse and comprised of representatives of different chemical families. The new two-parameter (2p) model comprising of octanol – water (K_{o-w}) and air – water (K_{a-w}) partition coefficients. The 2p- model were able to explain 77% of variability

in the dataset with RMSE of 0.53 log unit. The performance of my new model was compared with previously used model, DERMWIN, which focus only on one partitioning property K_{o-w} and MW and Abraham solvation model have limitation of data accessibility for billions of chemicals.

In third phase, two models were developed to estimate the time for chemicals to reach 95 % of equilibrium state by using PDMS - log $\tau_{95\text{-PDMS}}$ Model based on inter molecular interaction parameters - (B, V) was best performed, while other model having partitioning descriptors- $K_{o-w}, K_{a-w}, K_{o-c}$, was also showing good predictive efficiency.

All studied aspects of chemodynamics explained that partitioning coefficients, diffusion coefficients and intermolecular interaction parameters are important descriptors to understand the transport of chemicals across or near different interfaces.

Chapter 1

INTRODUCTION

1.1 Background

Chemodynamics deal with the time dependent property of the chemicals. This primarily focuses on fate, transport and effect of chemicals leading various processes – transport, transformation, permeation, uptake and elimination by living organisms. These processes of chemical reactions and diffusion are regulated by existing ambient environment and conditions, such as, temperature, concentration of chemicals, reaction with others chemicals present in that medium and other physicochemical properties of chemicals. Environmental importance of chemodynamics explain by the fact that it is essential element to figure out the ecological and public health risk assessment because most of the chemicals are bioaccumulative in nature (Freed, Chiou, & Haque, 1977; Percuoco, Kalnejais, & Officer, 2015; ter Laak, Busser, & Hermens, 2008).

Understanding bioconcentration kinetics is important in the fields of ecotoxicology, bioaccumulation, and environmental risk assessment(Bayen, Ter Laak, Buffle, & Hermens, 2009; Escher & Hermens, 2004; Schwarzenbach & Gschwend, 2016).

Depuration rate constants have been described using the following diffusion-based mass transfer model(Bayen et al., 2009; Greenwood, Mills, & Vrana, 2007; Huckins, Petty, & Booij, 2006; Sijm & van der Linde, 1995; ter Laak et al., 2008).

$$k_d = \frac{A_f}{W_f(1-\gamma)+\gamma K_{m-w}} \quad \frac{1}{\frac{\delta_w}{D_w}+\frac{\delta_m}{D_m.K_{m-w}}} \qquad (1)$$

These rate constants can be converted into a more convenient form, for example,

depuration half-lives using following equation:

$$t_{1/2} = \frac{\ln(2)}{k_d} \quad (2)$$

Where A_f and W_f denote gill surface areas and weight (mass) of fish; δ, D and K are the diffusion path length, diffusion constant and partition coefficient, respectively. Subscripts *f*, *w*, and *m* indicate fish, water and biomembrane, respectively, and γ is fish lipid content.

The Abraham solvation model (ASM) is a 5- or 6-parameter equation (eq.3 $_{a\text{-}d}$) that has been widely explored in environmental chemistry to estimate several partitioning and transport properties(Michael H Abraham & Ibrahim, 2006; DiFilippo & Eganhouse, 2010; Endo, Brown, & Goss, 2013; Endo, Droge, & Goss, 2011; Endo, Escher, & Goss, 2011; Endo & Goss, 2011; Endo, Hale, Goss, & Arp, 2011; Endo, Mewburn, & Escher, 2013; Endo, Pfennigsdorff, & Goss, 2012; Geisler, Endo, & Goss, 2012; Hoover, Acree Jr, & Abraham, 2005; Kamprad & Goss, 2007; Lohmann, 2011; Poole, Ariyasena, & Lenca, 2013; Sprunger, Proctor, Acree Jr, & Abraham, 2007).

$$\log P_{xy,i} = c + eE_i + sS_i + aA_i + bB_i + vV_i \quad (3\ a)$$

$$\log P_{xy,i} = c + eE_i + sS_i + aA_i + bB_i + lL_i \quad (3\ b)$$

$$\log P_{xy,i} = c + sS_i + aA_i + bB_i + lL_i + vV_i \quad (3\ c)$$

$$\log P_{xy,i} = c + sS_i + aA_i + bB_i + vV_i \quad (3\ d)$$

Where, $P_{xy,i}$ is a partitioning property of a chemical i, dispersed between two phases xy, c denote the value of intercept; while e, s, a, b, v is the value of coefficient of each Abraham solvation parameters explain the importance of each

parameter. In addition to this, E_i explain the excess molar refractivity that use to check the polarizability of the solute (cm^3 per mole)/10, S_i describe the characteristics of polarity or dipolarity of the solute, A_i represent the hydrogen bond accepting capacity (hydrogen bond acidity) of the solute while B_i is the hydrogen bond donating capacity (hydrogen bond basicity) of the chemical, V_i is the McGowan characteristic of molecular volume of solute in specific unit of (cm^3 per mole)/100 and L is the gas- hexadecane partitioning coefficient of solute at 25ºC (Bradley et al., 2015).

In dermatotoxicology, skin sensitization and skin permeability is primarily controlled by several biological and physiological parameters, such as protein binding, quick response of dendrites, thermoregulation, anatomical configuration and genetic setup of organism.(Ghafourian, Samaras, Brooks, & Riviere, 2010b)

Dermal absorption mostly occurs by appendageal, transcellular and intercellular pathways**.** Monitoring of chemicals transfer by transcellular route is important in the chemical diffusivity model.(Chauhan & Shakya, n.d.; Moss, Wilkinson, & Sun, 2012; Tsakovska et al., 2017)**.** The mechanistic pharmacokinetic modeling of skin permeability demonstrate that dermal permeability coefficient is specifically correlated with ability of a chemical to pass from Stratum corneum (SC) to blood circulatory system, then ultimately into the vascular body system, where resorption of a chemical take place.(Michael H Abraham & Martins, 2004; Chen et al., 2013; Fatemi & Malekzadeh, 2012; Ghafourian, Samaras, Brooks, & Riviere, 2010a) Passive and active diffusion channels of the chemical occupied in epidermal and hypodermal region (follicle and sweat glands). It can be explained by the following Fick's first law of diffusion.(Magnusson, Anissimov, Cross, & Roberts, 2004; Pecoraro et al., 2019; Shen, Kromidas, Schultz, & Bhatia, 2014)

$$Q = \frac{DAT\Delta C}{h} \quad (4)$$

When stratum corneum act like a pseudo- homogenous membrane, chemical flux (mol/cm^2/s) in steady state condition will be expressed as:

$$J_{ss} = \frac{Q}{AT} = \frac{D\Delta C}{h} \quad (5)$$

Where J_{ss} - maximum flux of the chemical calculated by concentration of the chemical Q which is a product of diffusivity D and concentration gradient ΔC across the membrane, to the exposed area of skin A in a given time T which collectively describe as h - thickness of a biological membrane.(Pecoraro et al., 2019)

In equilibrium condition, concentrations of chemicals at path length depend upon following relationship:

$$C = K_m . C_V \quad (6)$$

In this equation, K_m is the partition coefficient between SC and the targeted delivery vehicle, C_V denote the concentration of drug vehicle. The final expression to describe skin –water permeability coefficient is given below.(Shen et al., 2014; Tsakovska et al., 2017)

$$K_p = \frac{J_{ss}}{C_v} \quad (7)$$

Where K_p is the skin permeability coefficient which depend upon J_{ss} and C_v, (cf – eq. 6, and 7).

Equilibrium constant – time to reach 95% of equilibrium state in PDMS - . log $\tau_{95\text{-PDMS}}$ is very useful for monitoring of truly dissolve and bioavailable concentrations of chemicals and it's time to be at equilibrium stage for a chemicals diffuse on passive sampler used to investigate the level of ecological risk, accumulation of chemicals in biological tissues and biomagnification as well.(Cui, Mayer, & Gan,

2013; Endo, Escher, et al., 2011; Jahnke, McLachlan, & Mayer, 2008; Schwarzenbach & Gschwend, 2016)

The aim of the study is understand the various aspects of chemodynamics for diverse set of chemicals by using simplest, inexpensive method of estimation by taking few important and easily accessible descriptors.

1.2. Problem Statement

Existing experimental methods to understand chemodynamics of diverse organic pollutant are laborious, expensive and also have ethical implications.

1.3. Objectives of the Study

- To estimate the bioconcentration kinetics in fish using LFER
- To map the skin permeability coefficient for human skin using simplest model
- To understand the variability in the diffusion coefficients in PDMS

1.4. Scope of study

Research work was divided into three phases,

- In the first phase, elimination half – life was estimated by developing various estimation models
- In the second phase, skin permeability coefficients were estimated for diversified set of chemicals.
- In the third phase, time for a chemical to reach 95 % of equilibrium stage was estimated by using different estimation approach.

Chapter 2

LITERATURE REVIEW

2.1 Chemodynamics

In the non- steady state conditions in different environmental medium, load of chemical pollutant fluctuate with time and response of each biological species varied accordingly (Nabi, Gros, Dimitriou-Christidis, & Arey, 2014). Experimental setup for the estimation of chemodynamics in soil and water medium depend upon ambient condition – temperature, concentration of chemical, amount of chemical adsorbed in case of soil and amount of chemical diffuse in the water and for the estimation purpose adsorption coefficient on soil and its correlation with kinetic at first order level (Felsot, Wei, & Wilson, 1982). Molecular dynamic simulation method was taken by an author to understand the chemodynamics of chemicals on metal surfaces and this study conclude that hydrogen bonding is a main binding forcing for a chemical to transport and adsorb on the metal surface in water medium (Li, Zhang, Liao, & Zhang, 2019).

For the estimation of chemodynamics in living organisms, exposed surface area has significant importance that how much chemical react at a given surface area, while residues of the chemicals also need to be asses for proper estimation of chemical transport and its effect (Rahman, Rahman, & Alam, 2015).

In the water treatment plant in USA, a study elaborate the role of chemodynamics for chemical risk assessment by taking values of solubility and octanol water partition coefficients theses estimation methods based on estimated values taken from Epi Suite for early risk assessment and the estimation of chemodynamics through partitioning coefficients and degradation estimators can assist in agriculture field for appropriate application of pesticide and for water treatment plants (Acharya &

Weidhaas, 2018).

2.2. Bioconcentration Kinetics

The experimental method to understand bioconcentration kinetics, environmental characteristics such as temperature, flow regime, biogeochemistry, and many other factors need more attentions, because it may perturb the steady-state conditions of environmental systems (Bayen et al., 2009; Schwarzenbach & Gschwend, 2016). Such dynamic aspects determine an organism's response to the fluctuating concentrations of contaminants in the environment. Responses to fluctuating environmental concentrations will depend on a fish's allometry; large organisms will integrate exposure concentrations over a longer time window and *vice versa* (Bayen et al., 2009).

In order to meet regulatory requirements, bioconcentration experiments must consume several test animals (Guideline, 1996). For instance, an estimated 2.6 million test animals are required (Van der Jagt, Munn, Tørsløv, & de Bruijn, 2004) to meet the requirements set out in the European chemical management program, REACH.("REACH," 2007) and experimental methods required labor intensive system.

Scientists have traditionally used linear first-order kinetics to model bioconcentration kinetics(Barber, 2003).

$$\frac{dC_f}{dt} = k_u C_w - k_d C_f \quad (8)$$

Where, C_f and C_w are the concentrations in fish and water respectively. k_u and k_d are the uptake and depuration rate constants, and t is the exchange time.

Release kinetics is functions of biological parameters, physicochemical parameters and hydrodynamic conditions. Scientists have developed these models to predict

bioconcentration kinetics using both biological and chemical parameters (Barber, 2003). Biological parameters include growth, size, age, gill surface area, and the composition of lipid and other constitutional units of fish (Brooke, Crookes, & Merckel, 2012). These biological parameters were empirically related to fish weight (Barber, 2003; Brooke et al., 2012; Hendriks, 1995; Hendriks & Heikens, 2001). Chemical parameters include diffusion coefficients in water and mucus layers, an equilibrium bioconcentration factor (i.e. whole-fish to water partition coefficient) and partition coefficients to compositional units such as biomembranes, lipids and proteins (Barber, 2003; Sijm & van der Linde, 1995). Such parameters were estimated using an octanol-water partition coefficient (K_{o-w}) (Brooke et al., 2012; Hendriks & Heikens, 2001; Sijm & van der Linde, 1995). Diffusion boundary layers δ_w and δ_p are controlled by the anatomical configurations of gills, therefore, theses parameters are assumed relatively constant (Sijm & van der Linde, 1995).This forms the rationale for using correlations based on K_{o-w} and species weight to predict kinetic rate constants.

In another studies, intermolecular interaction parameters derived from GC×GC (two dimensional gas chromatography) retention time information to develop a two-parameter-linear free energy relationship (LFER) for 37 environmental partitioning and transport properties for nonpolar contaminants (Nabi & Arey, 2017; Nabi et al., 2014).

$$\log P_{xy,i} = \lambda_1 U_{1,i} + \lambda_2 U_{2,i} + \lambda_3 \quad (9)$$

Where $P_{xy,i}$ describe the partitioning property of a chemical i in two different phases xy, while $U_{1,i}$ and $U_{2,i}$ can be explained by the following equation:

$$U_{1,i} = \log L_{1,i} \quad (9a)$$

$$U_{2,i} = \log L_{2,\mathrm{i}} - \beta_{\mathrm{orth}} \log L_{1,i} \quad (9b)$$

In these equations, $\log L_{1,\mathrm{i}}$ and $\log L_{2,\mathrm{i}}$ explain base-10 log-transformed gas-stationary phase partition coefficients (mol L^{-1} L) at 120°C for chemical i on two stationary phases 1 and 2. Furthermore the parameter β_{orth} has a constant value of 1.1353 for the stationary phases in the system; explain that the vectors $U_{1,i}$, $U_{2,i}$ are mutually orthogonal for assigned training set of nonpolar chemicals. The value of coefficients λ_1 , λ_2 , λ_3 are assigned to specific partitioning phases xy .Goss *et al.* suggested that depuration half-lives were much better metrics for bioaccumulation potential than biomagnification factor (BMF) (K. Goss, Brown, & Endo, 2013)**.** A short exposure phase can result in insufficient time for hydrophobic contaminants to reach the slower-clearing compartments of the fish.(Fisk, Norstrom, Cymbalisty, & Muir, 1998; Reinert, Giddings, & Judd, 2002) Furthermore, it is difficult to take into account such details as biotransformation (Arnot, Mackay, & Bonnell, 2008).

Hendriks developed the following relationship for the depuration constants in fish(Hendriks, 1995):

$$k_d = \left[\left(\frac{1}{4\times10^{-4}\, K_{o-w}+5}\right) + 4 \times 10^{-3}\right] \times W_f^{-0.19} \quad (10)$$

$n = 140, R^2 = 0.68$

However, K_{o-w} alone does not explain the interaction variability across different chemical families (Schwarzenbach & Gschwend, 2016). This calls for a set of descriptors that explore the whole spectrum of interactions across all chemical families.

2.3. Skin permeability coefficients

For any chemical to permeate through the skin, major factors - concentration,

solubility, exposure and sampling time of a chemical have considerable importance (Alves et al., 2015; Kupczewska-Dobecka, Jakubowski, & Czerczak, 2010). Various sub layers of epidermal layer from outer to inner side - stratum corneum (SC), stratum lucidium (SL), stratum granulusum (SG), stratum spinosum (SS) and stratum germinavtivum(SG) act as barrier to absorb and permeate any chemicals across the inner skin layers (Tsakovska et al., 2017)**.** SC describes as brick and mortar model, in which brick is a protein keratinized structure which enclosed in lipid lamella. This layer characterized by thickness of 10 to 50 µm, 5- 20% water content and it is free from any metabolic activity. Quantified chemical composition of SC is 40-50% of ceramides, 25% of lipoprotein with 5% of sulfate, ester group and other glucosylceramides, 15% of free fatty acids and long chain of hydoxylated alkyl group.

For calculation of skin- permeability coefficient, there are many problems in the case of in-vivo and in-vitro experimentation, As different data on permeability reported in literature ,but there is no standardize procedure of experimentation, so the variability in the data shows the importance of various subjective factors (species, genetic makeup and ages), dose application regime as well as occlusion that can easily effect the results in a direct way (Karadzovska & Riviere, 2013; Pecoraro et al., 2019; Tsakovska et al., 2017). All of these condition describe that experimental setup always operate in a sophisticated conditions. The actual value of diffusion coefficient in (SC) is very difficult to calculate, so in this condition, the value of diffusion coefficient in ceramic can be use as an estimate to calculate the relative value of skin permeability coefficient. In addition to this, slow diffusion and poor partitioning of anions make it difficult to figure out the value of permeability in case of ionic species (Zhang et al., 2012)**.**

Zhang et al develop a model by taking inter - molecular interaction parameters (Abraham solute descriptors) for estimating skin – water permeability coefficients and conclude that key physiochemical attributes, such as solute size, hydrophobicity and hydrogen bond donating capacity of a chemical assist in monitoring and estimation of K_p. Solute size of the chemical is directly proportional to permeability coefficient. This relationship has also being appropriate even at phase boundry level. Applicability of this model is restricted because of limited data of Abraham solute descriptors are available, therefore our proposed model introduced an easily computed proxies of Abraham solute descriptors that have enough potency to be fitted as suitable alternative assessment indicators in dermal risk assessment (Michael H Abraham & Martins, 2004; Kupczewska-dobecka, Jakubowski, & Czerczak, 2010; Zhang, Abraham, & Liu, 2017). Existing computational model (DERMWIN) of K_p returned us with less estimation efficiency by taking two descriptors - K_{o-w} and MW.

According to the guideline develop by OECD - organization for economic co-operation and development, modeling of pharmacokinetics is an emerging field that can resolve problem of ethical implication of human skin testing. The ultimate results from the dermal - chemo kinetic modeling mostly used for the early screening of chemical for dermal - application, risk assessment and the variability in the measurement process can also be reduce by it (Pecoraro et al., 2019).

According to the guideline of European chemical management guideline, regarding dermal exposure, Those chemicals which have MW of less than 500, then that chemical would be 100 % absorb by the living skin and if the MW of the chemical would be higher than 500. Only 10 % of the chemical would be absorbed by the skin. The standard range of octanol water partition coefficient $from < -1 \, to > 4$ has

allotted for minimum and maximum chemical absorption respectively (Berge, 2009).

2.4. Monitoring using PDMS

PDMS made up of various polymers and solvent having different capacities to perfume kinetic process. For monitoring of chemical in the perspective of partitioning of chemical between different interfaces, material made up of single polymer mostly consider as favorable option. Exchange rates and diffusion coefficients between sampler and water phase decide the amount of chemical move toward passive sampler PDMS can monitor PCBs with wide range of hydrophobicity and complex organic chemicals by taking integrated approach between exposure and time (J. Arey, Samanipour, Dimitriou-Christidis, Nabi, & Gros, 2015).

By simple diffusion model, equilibrium times are mapped out for hydrophobic compounds by consideration of surface – volume ratio of PDMS. in the field monitoring study using PDMS, sampling time and equilibrium constant need more attention to study the sorption behavior of chemical. (J. Arey, Samanipour, Dimitriou-Christidis, Nabi, & Gros, 2015).

At molecular level, affinity of a chemical to get absorbed at passive sampler depends upon van der Waals forces and hydrogen bond interaction parameters. Size and symmetry of the chemical, sampling area, mixing and turning of water and physiochemical properties of the chemicals decide the time to reach at equilibrium state. Uptake Kinetics can be affected by limiting factors, such as aqueous boundary layer that limit the transfer of chemicals between two mediums. (ter Laak et al., 2008).

Due to greater thickness and lipophilic nature of of PDMS, it mimic the inner epidermal layer of human skin SC so the permeation kinetics and it is affordable,

inexpensive and easy to available so experimental setup can be develop by it. Ionic species can permeate through PDMS membrane (Liu, Zhang, & Abraham, 2018).

2.5. Estimation Methods

Widely used existing estimation methods are Ab initio, LFER, Fragmental and Group methods that are used to screen chemicals at early stage.

Fragmental method of estimation has wide practical application to develop a QSAR model use to predict and estimate biological and physical properties of chemicals, site specific physiochemical profiling, active skeleton and functional group of the chemicals (Japertas, Didziapetris, & Petrauskas, 2003).

Solvent activity in polymer has assessed by group estimation method. At basic level contribution of first order group and at advance level, 2^{nd} order group get assessed and estimated by this method. Estimation and identification of isomers with accurate application used to identify properties (Constantinou & Gani, 1994). Poly parameter linear free energy relation model (PP- LFER) has higher efficiency to predict the partitioning coefficient in various technical systems and the applicability of this model has proven from the fact that the model describes the linear relationship between various environmental properties. Equation develops by LFERs model also describe the strong relationship between all mentioned descriptors (Endo & Goss, 2014; Endo, Grathwohl, Haderlein, & Schmidt, 2009).

Ab initio is a quantum mechanical modeling method use to identify mechanical structure of molecule at optimized level. This method based on simulation of the system to search different local approaches (Singh & Kollman, 1986). Structural dimension of the chemical with its ability to show uniqueness from other chemicals can be evaluated by this method.

Scattering data by ab initio method assist by various modeling methods, such as bead method and envelop function (Volkov & Svergun, 2003).

Chapter 3

METHODOLOGY

Details about materials and methods are described in this chapter which was used for the investigation purpose of the study. Analysis on available data was performed by authentic computational software on computer.

3.1 Data Source

Experimental values for depuration half-live $t_{1/2}$, $K_{o-w}$of contaminants, and fish weight data involving 192 chemicals were collected from literature (Fisk et al., 1998; Hendriks, 1995). To avoid over-representation, multiple values reported for a single chemical were averaged using arithmetic mean. This resulted in a final sample size of 82. Three compounds (DDT, permthrin and carbaryl) were excluded from the data because isomeric information was not given and the Cook's D values for these compounds were higher than the critical value. Diffusion coefficients in water (D_w) and in ethanol (D_{eth}) were estimated from the ASM-based relationships reported by Hills *et al*. (Hills, Abraham, Hersey, & Bevan, 2011). The values of K_{o-w} and K_{a-w} were estimated using Abraham solvation model equations (Michael H Abraham, Nasezadeh, & Acree Jr, 2008; K.-U. Goss, 2006) and from EPI Suite™ 4.1 – KOWWIN v1.68, HenryWin v3.20 (US-EPA, 2018). Estimated value of BCF and k_M were taken from EPI Suite™ 4.1 – BCFBAF v3.01. GC×GC retention parameters, u_1 and u_2, were taken from literature (Nabi & Arey, 2017; Nabi et al., 2014).

The diversity of the chemical set used in the study can be gauged in term of the wide ranges spanned by $t_{1/2}$(33 to 990 days), K_{o-w} (9 order of magnitude), K_{a-w} (5 order

of magnitude), and by broad-spectrum ASM descriptors. The spread for other descriptors such as D_w , D_{eth} , BCF, k_M , W_f is given in table S15. Structurally, the dataset includes compounds from families such as chlorinated - and brominated-benzenes (CBs), chlorophenols, pesticides, insecticides, polycyclic aromatic hydrocarbons (PAHs), heterocyclic aromatic compounds, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), polyhalogenated dibenzo-*p*-dioxins (PHDDs), dibenzofurans (PHDFs), and polychlorinated naphthalenes (PCNs).

Experimental values of skin permeability coefficient K_p, comprises of 275 chemicals were taken from literature (Zhang et al., 2017). It has been reported in the previous studies (Zhang et al., 2012) that ionized species penetrate less deeper than neutral species, and follow lateral diffusion due to steric resistance exert by interlinked lipid layer in the deeper region of the skin and estimated values of partitioning coefficients was very limited Therefore, we exclude ionic species from the data set. A final sample size for further computational modeling was 175 (n=175).

The experimental data set of K_p taken in this study spanned by 7 orders of magnitude. The estimated, experimental, and Abraham solvation derived values of $K_{o-w,}$ $K_{a-w,}$ also have diversified range. Data set contain compounds from structurally different chemical families, such as steroids, alcohol, acids, amines, amides, carbonyls, esters, urea, carboxylic acids, ether, halides, nitriles and nitro compounds (Baba, Takahara, & Mamitsuka, 2015; Zhang et al., 2017)

Experimental and estimated values of $K_{o-w,}$ $K_{a-w,}$ was extracted from easily accessible software - EPI Suite^{TM} 4.1 – (KOWWINv 1.68), (HenryWin v 3.20) respectively.(US-EPA, 2018) Another estimated data set of $K_{o-w(ASM),}$ $K_{a-w(ASM),}$

was develop by Abraham solvation model equation (Michael H Abraham et al., 2008; K.-U. Goss, 2006).

For monitoring of chemical diffusion by PDMS, experimental value of log $\tau_{95\text{-PDMS}}$ for PCBs and CBs are taken as (n=21) was taken from literature(Rusina, Smedes, Koblizkova, & Klanova, 2009). This data set also diversified over 5 order of magnitude and the values of Abraham solute descriptors are taken from absolve data base, which also spanned over diversified range (Ulrich S.; Brown, T.N.; Watanabe, N.; Bronner, G.; Abraham, M.H.; Goss, K.-U., 2017). In this case also, values of partitioning coefficients $K_{o-w,}$ $K_{a-w,}$ and $K_{o-c,}$were also taken from EPI Suite™ 4.1 – (KOWWINv 1.68), (HenryWin v 3.20) and (KOCWIN v2.00) respectively.(US-EPA, 2018).

3.2. Statistical Analysis

Statistical analyses such as multiple linear regression, Principle Component Analysis (PCA) and cross-validation were performed using R statistical environment (version - 3.5.3) (R(3.5.3), n.d.) and XLSTAT (2018) (xlstat, 2018). Contribution of a variable in the model was considered statistically significant if the computed t-value of the variable coefficient is less than or equal to the critical t-values reported at the significance level (p-value <0.05) for a given degree of freedom (Dempster, 1969). The Akaike Information Criterion (AIC) was used to select the optimum number of variables in the model. AIC penalizes the model upon adding new variables that do not impart sufficient information to the model.(Bozdogan, 1987). Hence, a model with minimum AIC value was selected. Analysis of correlation was also performed to check any overlapping information bring by different descriptors

After selection of variables, regression diagnostic (Studentidized Residuals, Hat Values and Cook's Distance) were analyzed to identified influential values in each

model or approach proposed in this study. Standard errors of the fitting coefficients in each model were computed using bootstrapping algorithm. Following cross-validation tests were performed to assess the predictive capability of models: K- Nearest Neighbor, K-Fold, repeated K- Fold (r =10), Leave-One-Out (LOO), and bootstrapping (n=1000). For the external-validation of each model, the dataset was randomly split into training and test sets. Principle Component Analysis (PCA) was performed on model descriptors to investigate the dimensionality in the final data set.

Chapter 4

RESULTS AND DISCUSSIONS

4.1.Bioconcentration Kinetics in Fish (PHASE 1)

4.1.1. Elimination half - life

Different approaches used to explore the variability in depuration half-lives, and develop predictive models are discussed in the following sections.

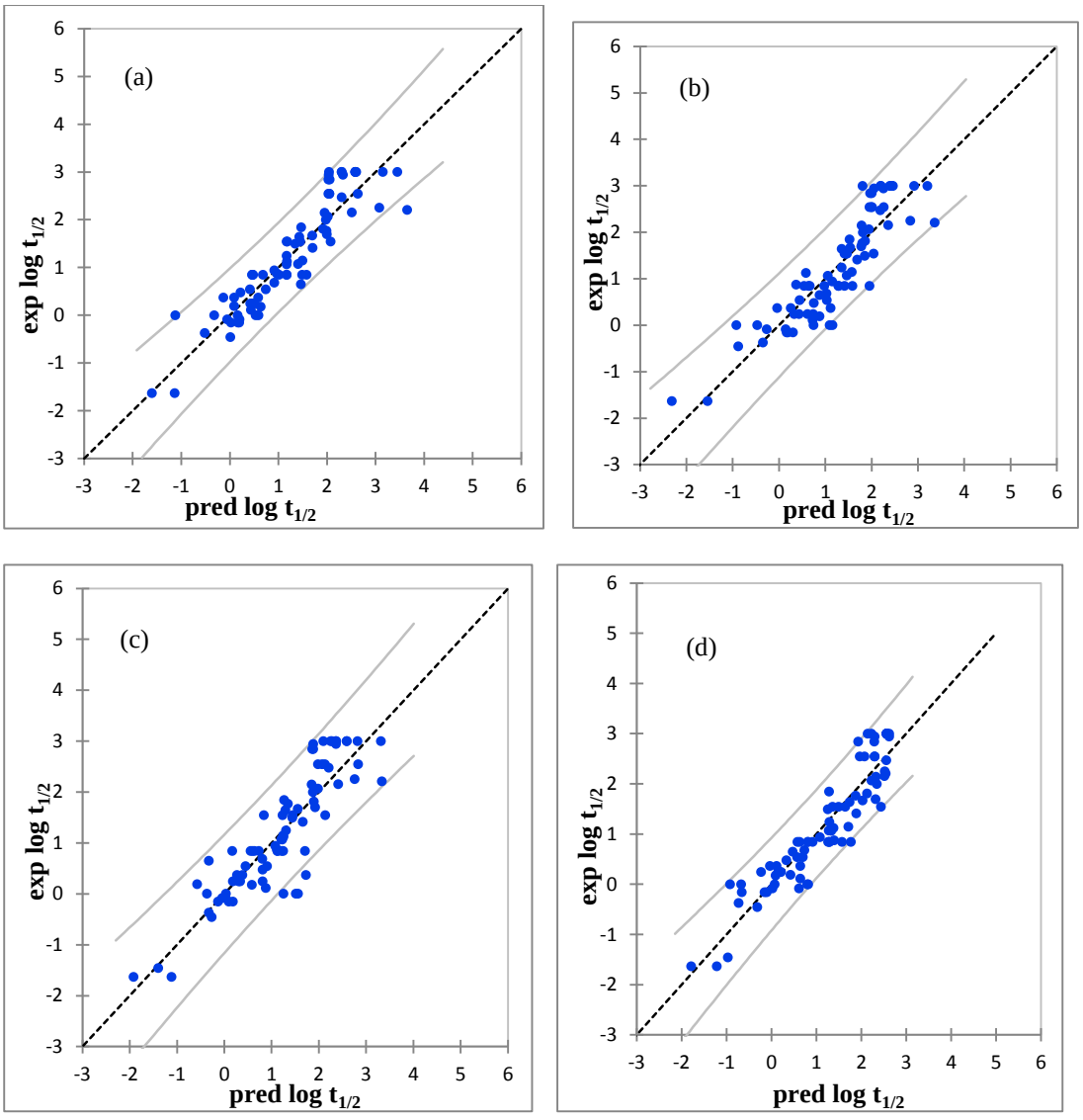

Figure1. Plots of experimental versus predicted depuration half-life using (**a**) Abraham solvation model (eq.11), (**b**) Triad Bioconcentration Kinetic Model (eq 12),

(**c**) Diffusivity Model (eq 13), and (**d**) BIOCEF model (eq. 14). At upper and lower line show 95% of confidence interval.

4.1.1.1. Abraham Solvation Model

A multiple linear regression of depuration half-lives against Abraham solvation parameters and fish weights resulted in eq.7. $A_i$and S_i descriptors were not statistically significant ($p > 0.05$), and the Akaike information criterion (AIC) was not reduced further by adding these descriptors; therefore A_i and S_i were removed from the model. The removal of these descriptors may be justified chemically. The magnitude of descriptor A_i generally tends to be small (for the depuration half-life data set $A_i \leq 0.66$). Solute descriptors E_i and S_i are found to be strongly correlated; this correlation is attributed to the fact that polarizability is embedded, to a greater or lesser extent, in the definitions of E_i andS_i (J. S. Arey, Green, & Gschwend, 2005; Gritti, Felix, Achard, & Hardouin, 2001; Vitha & Carr, 2006). Polarizability also tends to increase with solute size, V_i. This covariance magnifies because all solute molecules are aromatic in the data set (Vitha & Carr, 2006). The Pearson product-moment correlation coefficients between E_i and S_i, and between V_i and S_i, were 0.82 and 0.81, respectively. This is further corroborated by the PCA of ASM descriptors. Hence, in the presence of one variable, the other becomes almost redundant and statistically insignificant.

$$\log t_{1/2} = -1.29(\pm 0.37) - 0.91(\pm 0.16)E_i - 2.25(\pm 0.33)B_i$$

$$+2.97(\pm 0.24)V_i + 0.14(\pm 0.04)\log W_f \qquad (11)$$

$$n = 80, \quad RMSE = 0.47, \quad PRESS\ RMSE = 0.50, \quad R^2 = 0.85$$

$$Adj.R^2 = 0.83, \quad Q^2 = 0.82$$

Eq. 11 explains the 85% of variability in depuration half-live data with $RMSE$ of 0.47 log unit. The model is internally valid as indicated by the closeness of RMSE and $PRESS\ RMSE$ values, and of R^2 and Q^2 values. This is further supported by other cross-validation tests. We trained eq.11 using estimated values of Abraham solute descriptors E_i B_i V_i and fish weight information W_f (n=80) computed $R^2 = 0.85$ and $RMSE = 0.46$ log unit

In both cases (exp. and est. model) 85% of variability with RMSE in the range of 0.46 to 0.47 log unit explained by eq.11.

Eq. 11 depicts that the solute size is the most influential descriptor in controlling the exchange kinetics: bigger molecules tend to depurate slowly. Compounds with hydrogen-bonding interactions were fast in the exchange process. This was expected, as other rate-related properties, such as the skin permeation and the human intestinal absorption rate constants, have been found to have a similar dependence on solute size and hydrogen-bonding interactions (Michael H Abraham & Martins, 2004; Michael H Abraham et al., 2002; Zhang et al., 2012). Similarly, the weight of the fish species is positively correlated with the depuration half-lives, which can be rationalized based on the fact that heavier fish takes longer times to integrate the fluctuations in chemical concentration.

4.1.1.2. Three-Parameter Kinetic (TPK) Model.

As evident from equation 11, the depuration half-life is dictated by Van der Waals forces and hydrogen bond-donating trait of the chemicals- which may be constrained sufficiently using K_{o-w} and K_{a-w} for the types of chemicals present in the training dataset. This motivated us to develop TPK model.

$$\log t_{1/2} = -0.91\ (\pm 0.39) + 0.17\ (\pm 0.05) \log W_f + 0.59 (\pm 0.05) \log K_{o-w(ASM)}$$

$$+0.27\ (\pm 0.05)\ \log K_{a-w(ASM)} \qquad (12)$$

$n = 82, \quad RMSE = 0.54, \quad PRESS\ RMSE = 0.57, R^2 = 0.79$

$Adj.R^2 = 0.78, \quad Q^2 = 0.77$

Here, eq 12 is trained with K_{a-w} and K_{o-w} values (n=82) estimated using ASM equations,(Michael H Abraham et al., 2008; K.-U. Goss, 2006) which are known to provide accurate estimations compared to EPI-Suite (Du, Valko, Bevan, Reynolds, & Abraham, 2001; Reppas-Chrysovitsinos, Sobek, & MacLeod, 2016) However, we report model (eq 12) training on values obtained from different estimation approaches in SI. Training of eq 12 on experimental values of K_{a-w} and K_{o-w} (n=61) returned $R^2 = 0.73$ and $RMSE = 0.62$ log unit. We also trained eq 12 using values of K_{a-w} and K_{o-w} (n=82) estimated from easily-accessible EPI-Suite, which resulted in of $R^2 = 0.78$ and $RMSE = 0.56$ log unit.

In all cases of trainings, eq 12 explains 73-79% of variability with RMSE in range of 0.54-0.62 log unit. The fitting coefficients in all cases of trainings are not significantly different from each other. The nearness of values of $RMSE$ and $PRESS\ RMSE$, and of R^2 and Q^2 values shows the internal validity of eq. 12, which is further elaborated by other cross-validation analyses.

Eq. 12 shows that octanol-water partitioning property strongly influences the depuration behavior of chemical. The chemicals with higher K_{o-w}, being hydrophobic and persistent, tend to depurate slowly. The chemicals with higher K_{a-w} tend to depurate at low rate. As in case of eq 11, W_f shows a positive relationship with $t_{1/2}$.

4.1.1.3. Prediction based on diffusivities

Different studies showed that diffusion through stagnant layers, such as mucus layer on biological tissues, is a rate-limiting step in the mass transfer process (Michael H Abraham et al., 2002; Sijm & van der Linde, 1995). A mucus layer is composed of glycoprotein and sialic acid, with 95% water. Abraham *et al.* found that transport properties, such as diffusion constants in water and in ethanol, are closely related to such mass transfer processes (M H Abraham, 2003). However, due to the presence of glycoprotein and sialic acid, the actual diffusion constants of contaminants in mucus layers are higher than those in water (Verhaar et al., 1999). Hill *et al.* found that ethanol is a good model solvent for mimicking the mucus layer. This provided the rationale for these parameters to be considered in MLRs together with the K_{o-w}, diffusion coefficient in water (D_{w}), diffusion constant in ethanol (D_e), and fish weight information to estimate the elimination half lives of the contaminants. This exercise resulted in the following model.

$$\log \mathrm{t}_{1/2} = -2.13(\pm 0.35) + 5.6\ (\pm 2.111)\log D_e + 0.391\ (\pm 0.068)\log K_{o-w}$$
$$+ 0.125\ (\pm 0.048)\log W_f - 3.759(\pm 1.031)\log D_w \qquad (13)$$

$$n = 82, \quad RMSE = 0.56, \quad PRESS\ RMSE = 0.63, \quad R^2 = 0.78,$$

$$Adj.R^2 = 0.77, \quad \mathrm{Q}^2 = 0.77$$

Eq. 13 explains 78 % of variability ($R^2 = 0.78$) with $RMSE$ of 0.63 log unit - Figure 1(c). As evident from the values of $RMSE$, $PRESS\ RMSE$, R^2, Q^2 and other cross-validation tests (Table S5.3 and Table S9) for eq 13, this model is deemed valid and robust for predictive purpose. The success of eq. 13 can be mapped back to eq.2 where D_e , K_{o-w} and W_f act as proxy of D_m , K_{m-w} and A/V respectively.

Eq 13 shows that diffusivities have a profound effect in controlling the exchange kinetics: D_e is positively related, and D_w is negatively related to $t_{1/2}$.

4.1.1.4. BIOCEF Model

The BIOCEF model, which is trained on BCF and k_M descriptors, resulted in the following eq.

$$\log t_{1/2} = -1.08(\pm 0.262) + 0.084\ (\pm 0.035) \log W_f + 0.43(\pm 0.088) \log \mathrm{BCF} - 0.6\ (\pm 0.084) \log k_M \quad (14)$$

$$n = 82, RMSE = 0.44, \quad PRESS\ RMSE = 0.46, \quad R^2 = 0.87$$

$$Adj.R^2 = 0.86, \quad Q^2 = 0.85$$

BIOCEF model (eq14) outperformed all estimation approaches developed in this study, and was able to explain 87 % of variability in the dataset with $RMSE$ 0.44 log unit (Figure 1d). The model is internally and externally valid as evident from the validation statistics

Eq.14 shows that all variables bring significant information but k_M is the most dominating parameter in the model. The model indicates that a chemical with low biotransformation rate constant and high BCF value will depurate slowly. The better performance of BIOCEF may be attributed to the fact that BCF and k_M are closer relative of K_{m-w} and K_d, respectively (cf. eq.2) than the descriptors used for other models.

4.1.1.5. Mapping elimination – half-lives onto GC×GC

Previous studies (Nabi & Arey, 2017; Nabi et al., 2014) showed that eq. 9 is capable of estimating partitioning and transport properties. It was thus expected that, together

with weight information on fish, eq. 9 would be able to explain the variance in the depuration constant data for nonpolar chemicals. This exercise resulted in the following eq.

$$\log \mathrm{t}_{1/2} = -1.80\ (\pm 0.77) + 1.037\ (\pm 0.156)\, u_1 - 8.01\ (\pm 1.125)\, u_2$$

$$+0.22\ (\pm 0.091) \log W_f \qquad (15)$$

$$n = 27, \qquad RMSE = 0.51, \qquad PRESS\ RMSE = 0.63, R^2 = 0.80,$$

$$Adj.R^2 = \ 0.78, \qquad Q^2 = \ 0.70$$

The regression and validation statistics for eq 15 shows that the estimates of half-lives for nonpolar chemicals can be mapped onto GC×GC chromatograms with sufficient accuracy.

The experimental dataset (n=27) used to train eq. 9 is diverse and has the representation of chemical families such as chlorinated aliphatic hydrocarbon, PAHs, PCBs, chlorobenzenes, PCN, OCPs and toxaphenes. Abraham solute descriptors for this dataset constitute quite a representative multidimensional space. However, for small sized dataset correlation among explanatory variables may adversely affect the predictive capability of the model (Golbraikh & Tropsha, 2000). Even though smaller in size (n=27), the experimental dataset used to calibrate eq.15 is representative of nonpolar contaminants, and was modeled parsimoniously with the orthogonal variables; therefore, we can deem eq.15 to be statistically robust for its predictive capability.

However, another approach may also be taken that circumvents the issue of data size and representativeness. In this approach eq. 9 is trained against the values of $t_{1/2}$ that were estimated using eq. 11, which resulted in the following eq.

$$\log t_{1/2} = -2.46\ (\pm 0.122) + 1.15\ (\pm 0.064)\, u_1 - 7.4\ (\pm 0.314)\, u_2$$

$$+ 0.141(\pm 0.041) \log W_f \qquad (16)$$

$$n = 41, \qquad RMSE = 0.34, \qquad PRESS\ RMSE = 0.37$$

$$R^2 = 0.93, Adj.R^2 = 0.93, \quad Q^2 = 0.92$$

When the experimental values of $logt_{1/2}$ (n=27) were compared to the predicted values by eq.12, an RMSE of 0.57 log unit was obtained. This slightly higher value of RMSE of eq 16 compared to that of eq 14 was expected as the model was calibrated against ASM-estimated values. However, given the uncertainty in the experimental data this slightly higher RMSE values may still be acceptable. Nonetheless, eqs.14 and 15 satisfactorily explained the variability in depuration half-lives

4.1.1.6. Comparison with the Hendriks model

The predictive performance of the estimation models developed in this study were compared with that of Hendriks model (eq.10) using the common experimental dataset Hendriks model returned an RMSE value of 0.64 and R^2 = 0.71. In comparison eq 11 explained 12% more variance in the depuration half-lives with lower RMSE. This was expected as K_{o-w} only explores the variability for solutes that are structurally similar or belong to the same chemical family. Abraham solute descriptors capture the interactions across different chemical families

with diverse structures and properties.

4.2. Human Skin Permeability Coefficient (Phase 2)

Different Models and approaches used to describe the importance and utilization of descriptors that were involved in the estimation of K_p (cm/s) described in the following section:

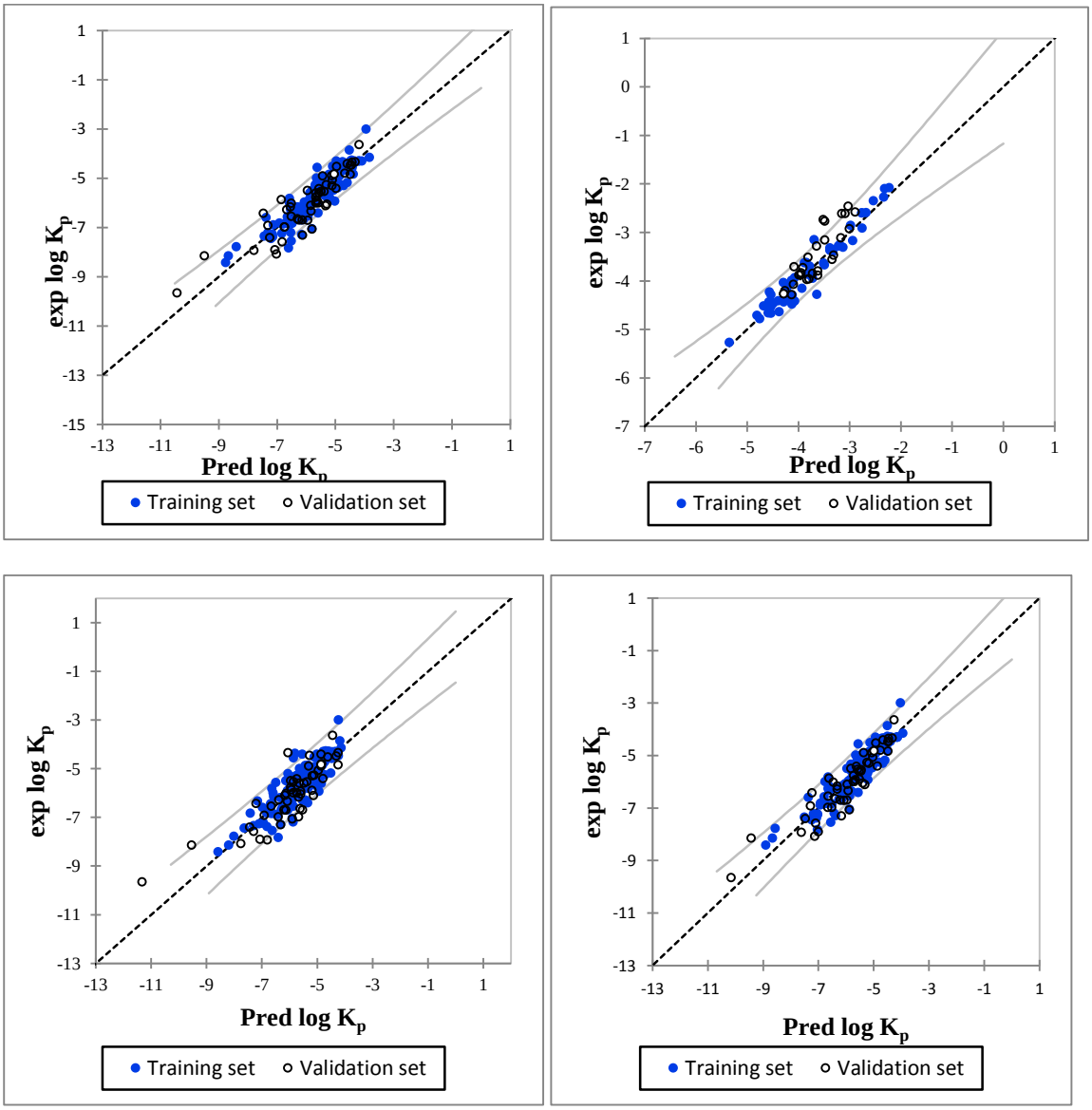

Figure 1 Plots of predicted versus experimental values develop by splitting of data in to training and test data sets to describe robustness of all models. a) Two Parameter Model, b) GC×GC based Model, c) DERMWIN Model, d) Zhang Model

4.2.1 Two - Parameter Model

In this model we regressed by observed values of K_p against the estimated values of descriptors - K_{o-w}, K_{a-w}, which results in eq.6.

$$\text{Log}\, K_p = -5.21(\pm 0.12) + 0.39\ (\pm 0.03) \log K_{o-w} + 0.16\ (\pm 0.01) \log K_{a-w} \quad (16)$$

$n = 175, \quad R^2 = 0.71, \quad \text{Adj.}\, R^2 = 0.71, \quad Q^2 = 0.70, \quad RMSE = 0.59,$

$PRESS\ RMSE = 0.60$

Equation 16 portrait 71% of variability in the final permeability data set with $RMSE$ of 0.59 log units. Internal validity of the model highlighted by the nearness of RMSE and PRESS RMSE values and by another indication – closeness of R^2 and Q^2 values. Furthermore, results of cross validation tests also confirm that model is robust with internally and external valid for predictive purpose

In term of theoretical explanation, and both partitioning coefficients - K_{o-w}, K_{a-w} are positively related, while MW is negatively correlated with K_p. The most significant variable in the model is K_{o-w}. Thickness of epidermal region - SC in context with chemical diffusion is correlated with K_{o-w} and this characteristic is interlinked with water- liposome partition coefficient (Zhang et al., 2012) and those chemicals would transport through Existing link between MW and K_p has justified by free - volume theory, that diffusion or permeability coefficient is inversely proportional to molecular weight (Kupczewska-dobecka et al., 2010)**.** So the chemical with higher value of partitioning coefficients and lower value of molecular weight will permeate with faster rate through an exposed area of skin.

In another multi- dimensional approach at inter-molecular interaction level, partitioning descriptors - $K_{o-w\,(ASM)}$, $K_{a-w\,(ASM)}$ with MW was derived by Abraham solvation equation to provide the alternative pitch with better efficiency, which results in eq. 17.

$$\log K_p = -5.41\ (\pm 0.08) + 0.46(\pm 0.03) \log K_{o-w\,(ASM)}$$

$$+0.14\ (\pm 0.007)\log K_{a-w\ (ASM)} \qquad (17)$$

$n = 175,\quad R^2 = 0.82,\qquad \text{Adj.}\, R^2 = 0.82,\qquad Q^2 = 0.81,\quad RMSE = 0.47,$

$PRESS\ RMSE = 0.48$

In eq.17, 82% of variability explained with $RMSE$ of 0.47 log unit. Evidence of internal validity (nearness of $RMSE$ and $PRESS\ RMSE$, R^2 and Q^2) with cross validation of the model have indicated in the results

As evident in eq.17 that both partitioning descriptors are showing positive relationship with K_p.

In the case of experimental values of partitioning coefficients, we have very limited data (n=68) for targeted chemicals in our study, we have trained an equation 6 by using experimental values to check the estimation power of resulting eq.18.

$$\log K_p = -5.43(\pm 0.17) + 0.5\ (\pm 0.05)\log K_{o-w} + 0.16\ (\pm 0.02)\log K_{a-w} \qquad (18)$$

$n = 68,\qquad R^2 = 0.85,\qquad \text{Adj.}\, R^2 = 0.84,\qquad Q^2 = 0.83,\qquad RMSE = 0.34,$

$PRESS\ RMSE = 0.36$

In eq.18, 85 % of variability with RMSE of 0.34 log unit explains that experimental values of descriptors have enormous potential to map - out the permeability coefficient.

Statistical indicators of this model also depict that model is internally valid to calculate the value of K_p, and the results of cross validation also qualify the same

Equation 18 also draw same conclusion that K_{o-w} is highly influential to calculate skin-permeability coefficient and these partitioning properties of chemical are positive related with K_p , which indicate that electrostatic interactions with hydrogen bond related properties are momentous at intermolecular level

4.2.2. GC×GC based Model

To monitor the skin permeability of complex non polar organic chemicals, we trained the eq.6 to estimate the value of time retention indices by ASM equations (Table 16 and 17). The values of retention indices act as efficient proxies of partitioning descriptors, so the permeability of complex mixtures can be mapped by u_1 and u_2.

$$\log K_p = -5.35\ (\pm 0.07) + 0.58(\pm 0.02)u_1 - 3.51\ (\pm 0.19)u_2 \qquad (19)$$

$n = 79, \quad R^2 = 0.90, \qquad \text{Adj.}\, R^2 = 0.89, \qquad Q^2 = 0.89,$

$RMSE = 0.23$ (wrt ASM − redicted values),

$PRESS\ RMSE = 0.24$

Eq.19 depicts 90% of variability with RMSE of 0.23 log units that explain higher prediction power of the model. This model was trained on model data set derived from analytes separate by GC×GC chromatogram. When we compare the values of K_p estimated for analytes with the values derived from eq.19, we get higher RMSE of 0.39 log units wrt ASM-predicted values. (Table S15). Whereas, for the same analytes set, DERMAWIN exhibited RMSE value of 0.83 log unit wrt ASM-predicted values.

Statistical indicator - closeness of $RMSE$ and $PRESS\ RMSE$ and of R^2 with Q^2 confirm that model is internal valid for prediction purpose, which is supported by cross validation results (Table 17.4, 16.4, 20).

Eq.8 explains that u_1 and u_2 bring significant information to map K_p, while u_2 is influential variable in the model. The descriptor - u_2 is negatively correlated with K_p, which shows that those chemicals that retain fro longer time in the first dimension and for less time in second dimension of GC×GC will penetrate with faster speed across the deeper region of the skin

4.2.3. DERMWIN

The dermal permeability modeling program (Dermvin v2.02) for the estimation of skin permeability coefficient (cm/h) was develop for a diverse set of chemicals This is freely available in the EPI Suite package (Alves et al., 2015). The practicing model for dermal risk assessment rely on K_{o-w} and MW, so we trained a model using same descriptors,

which are fitted in dermin model. After this training of variables, we get a following equation.

$$\log K_p = -5.58 + 0.61(\pm 0.03) \log K_{o-w} - 0.006(\pm 0.00)\, MW \qquad (9)$$

$$n = 175, \quad R^2 = 0.74, \quad \text{Adj.}\, R^2 = 0.74, \quad Q^2 = 0.73, \quad RMSE = 0.56,$$

$$PRESS\ RMSE = 0.57$$

In eq.9, explained model's variability is 74% with $RMSE$ of 0.56.moreover, when we compare $RMSE$ ofeq.9 with result derived by equation of Dermwin module of Epi Suite, we get higher $RMSE$ of 0.78 log units,so it can be concluded that a small advancement by the addition of new descriptor definitely enhance the prediction proficiency of the model.

4.2.3. Comparison with zhang model

Zhang's model was based on Abraham solute descriptors – E, S, A, B, V) which result in $RMSE$ of 0.44 log units. Primary focus of this model was to highlight interaction parameters at molecular level, which play an important role in the permeation of chemicals, specifically the structure and size of the molecule. Applicability of this model is restricted because of limited data of Abraham solute descriptors are available, therefore our proposed model introduced an easily computed proxies of Abraham solute descriptors that have enough potency to be fitted as suitable alternative assessment indicators in dermal risk assessment.

4.3. Equillibrium constant by PDMS (PHASE 3)

Estimation of the time to reach 95 % of equilibrium state can be estimated by various models. Highly efficient models were selected.

4.3.1. ASM Model for diffusivity

$$\log \tau_{95-PDMS} = -1.80\ (\pm 0.34) - 3.87\ (\pm 0.51)B\ +\ 3.38(\pm 0.15)\mathrm{V} \qquad (19)$$

$$n = 21, \qquad RMSE = 0.15, \qquad PRESS\ RMSE = 0.18, R^2 = 0.99$$

$$Adj.R^2 = 0.99, \quad \mathrm{Q}^2\ = 0.98$$

Equation 19 is showing 99 % of variability to estimate the time to reach at equilibrium state.

Nearness of RMSE with PRESS RMSE also shows that model is internally valid to explain the diffusion constant.

Eq.19 also showing that hydrogen bond accepting capacity and size of the molecule play an important role to monitor diffusivity constant. And those chemical that are smaller in size will diffuse speedly in less time.

4.3.2. Partitioning Model

In another model, value of partitioning descriptors were taken to develop a model

$$\log \tau_{95-PDMS} = -2.87(\pm 0.46) + 0.53\ (\pm 0.1)\log K_{o-w} + 0.43\ (\pm 0.15)\log K_{a-w}$$
$$+ 0.86\ (\pm 0.29)\log K_{o-c} \qquad (20)$$

$$n = 21, \qquad RMSE = 0.15, \qquad PRESS\ RMSE = 0.23, R^2 = 0.99$$

$$Adj.R^2 = 0.99, \quad \mathrm{Q}^2\ = 0.97$$

Eq.20 is showing that model is able to explain ability of partitioning descriptors with explaining the variability of 99% with RMSE of 0.15 log unit. Nearness of the RMSE with PRESS RMSE showing the internal validity of the model and the result of cross validation also confirm the same.

Eq. 20 explaining that are hydrophobic in nature and have high absorbant capacity will diffuse quickly and reach at 95 % of equilibrium in less time.

Chapter 5

CONCLUSION AND RECOMMENDATION

5.1. Conclusions

Our models were successfully able to describe the factor governing chemical dynamics for Fish, Human and Passive Sampler Use of multi-parameter intermolecular interactions considerably improved results when compared to the use of alone. All computational models are efficient for predictive purpose but BIOCEF outperformed other models.

Proposed 2- parameter partitioning model have scientific and theoretical justification with best predictive efficiency. These proposed LFERS models are easily accessible than complicated multi- parameter model

Both approaches to estimate the time for chemicals to reach 95 % of equilibrium state was performing well, but model having inter molecular interaction parameter is simplest one.

Our models are not applicable for ionic, metallic and organo-metallic compounds. In case of ASM, we have limited data of all descriptors that is for only 8000 Chemicals.

5.2. Recommendations

We need to be extended for inorganic and ionized chemicals. It should be integrated with Epi Suite as separate module. Similar chemodynamics on other rate related properties, such as Intestinal absorption, Blood brain barrier, Diffusion for bio and synthetic membrane draw solutions.

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Supporting information of my thesis comprises of all tables, plots, figures and other relevant detailed description of analytical tools.

Supporting information of my thesis can be access by the following link:

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