A REVIEW ON INTEGRATED USE OF PHYSICO-CHEMICAL PARAMETER ESTIMATION TOOLS WITH MULTIMEDIA FATE MODELING

Barlas Nezahat Gulucuk[1] Imamoglu Ipek[1*],

[1]Department of Environmental Engineering Middle East Technical University, Ankara, Turkey, 06800, ipeki@metu.edu.tr

Introduction

Number of chemicals used in commerce is exponentially increasing and the task of identifying the fate of these chemicals and their impact on the environment becomes a task of ever increasing proportions. Traditional chemical testing necessitates a lot of time and money. Computer-based evaluation of physicochemical properties is an alternative for chemical assessment, and a variety of models are present under computational methods. Quantitative structure-activity/property relationship models (QSAR/QSPR) estimate a chemical property as a function of molecular structure. High predictability using these models depends on the high quality of experimental data, and suitable molecular descriptors[4]. QSAR models were suggested by Regulation for Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) to eliminate difficulties in traditional testing[1]. In the last decades, poly-parameter linear free energy relationships (pp-LFERs) are also gaining favor [2]. For all property estimation methods, the similarity of query compound to the calibration set's chemicals is the main strategy for applicability domain[3]. Multimedia mass balance (MM) models can integrate a variety of factors to investigate chemical concentrations and kinetics of transformation and transfer mechanisms in nature. Degradation rate constants, physicochemical properties of chemicals as well as information on emission are essential inputs for MM models[5]. Indicators such as long range transport potential (LTRP), characteristic travel distance (CTD), transfer efficiency (TE) and/or overall persistence (P_{ov}) of tested chemicals are are typical outputs of MM models[6].

Integration of QSAR/QSPR or pp-LFERs and MM models is becoming a new approach to evaluate the fate of ever-increasing number of synthetic organic chemicals. For example, property estimation models can be applied in MMs, where property information is unavailable for transformation products[7]. The objective of this study is to review existing research on the integrated use of such property estimation tools (e.g. making use of QSAR/QSPR or pp-LFERs) with MM models. These studies are increasing in number, especially in the last two decades and a critical evaluation of advantages as well as limitations of such studies would help for better chemical hazard assessment in the future.

Materials and Methods

This is a literature review performed using scientific databases, such as Science Direct and Web of Science. To find integrated modeling studies, keywords such as "consensus modeling of persistent organic chemicals," QSAR + MM models," and "integrated modeling for chemicals" were written in the search boxes of the database. A time frame was set for last two decades. Output of each search is evaluated whether it fits the criteria for MM modeling with integrated physicochemical property estimation tools. Each study that fits the description is examined in further detail and presented below. Papers examined in this study, by no means, constitute a complete list of all such studies, it is merely an effort to incorporate as many studies as possible which fit our aforementioned purpose.

Results and Discussion

Jagiello[4] underlines that combination of QSAR/QSPR models or pp-LFERs and MM models show promise with respect to risk management concerning chemicals. To test the effect of predicted inputs, Puzyn (2011) examined P_{ov} and LRTP estimations of an MM Model which uses experimental and predicted property information. The chief result from this study was that there was no statistically significant difference between the two[6]. Apart from integration of QSPR with MM models, a combination of pp-LFER with MM was suggested in place of single parameter-LFERs[8]. Authors underline the limitations of model parameterization as well as the impact of the use of sp-LFER or pp-LFER s[8]. A total of thirteen prominent studies was retrieved from the literature, to the best of our abilities, that incorporated predictive tools with MM modeling. Brief information regarding the studies are presented

in Table 1 and briefly discussed below.

Table 1. Summary information regarding the evaluated literature.

Title of the study	Physicochemical Parameter Prediction Tools	Multimedia Mass Balance Models	Study Aim	References
Comparison of Two Screening Level Risk Assessment Approaches for Six Disinfectants and Pharmaceuticals	EPIWIN	EUSES	To determine risk of pharmaceuticals and disinfectants	(Van Wezel & Jager, 2002)[16]
Expanding the Applicability of Multimedia Fate Models to Polar Organic Chemicals	sp-LFERs, pp-LFERs	Modified Level III Model	To show that implementation of pp-LFERs can reduce errors and uncertainty in multimedia fate modeling	(Breivik & Wania, 2003)[8]
Evaluating the Environmental Fate of Pharmaceuticals Using a Level III Model Based on Poly-parameter Linear Free Energy Relationships	EPIWIN	Modified Level III Model	To widen applicability of MM models for polar chemicals (i.e. pharmaceuticals) by integrating pp-LFERs	(Zukowska, Breivik, & Wania, 2006)[10]
Including Degradation Products of Persistent Organic Pollutants in a Global Multi-Media Box Model	CATABOL, EPIWIN	CliMoChem	To consider effects of degradation products on persistence, spatial range, and Arctic contaminant potential	(Schenker, Scheringer, & Hungerbühler, 2007)[12]
Development and Exploration of an Organic Contaminant Fate Model Using Poly-Parameter Linear Free Energy Relationships	pp-LFERs	CoZMo-POP2	Single parameter LFERs based CoZMo-POP2 was improved by changing sp-LFER to pp-LFER by testing on polar chemicals	(Brown & Wania, 2009)[11]
On the Replacement of Empirical Parameters in Multimedia Mass Balance Models with QSPR Data	EPI Suite, L-QSPR, PCA-kNN, QSPR	OECD Tool	Experimental based inputs of MM models were changed with QSPR derived inputs to reduce time and cost	(Puzyn, 2011)[9]
A New Metric for Long-Range Transport Potential of Chemicals	QSPR, LFER models	FATE	To evaluate the LRTP of chlorinated and brominated congeners of benzenes, furanes, diphenyl ethers, dibenzo-p-dioxins, biphenyls and naphthalenes by using QSPR-FATE model	(Kawai et al., 2014) [17]
Estimation of Physicochemical Properties of 52 Non-PBDE Brominated Flame Retardants and Evaluation of Their Overall Persistence and Long-range Transport Potential	EPI Suite, SPARC	OECD Tool	To evaluate the relationship between the properties on the molecular weight and chemical structure	(Kuramochi, Takigami, Scheringer, & Sakai, 2014)[18]
A Modeling Assessment of the Physicochemical Properties and Environmental Fate of Emerging and Novel Per- and Polyfluoroalkyl Substances	COSMOtherm, SPARC, EPI Suite	OECD Tool	Preevaluation of novel alternatives for long-chain perfluoroalkyl acids and their precursors	(Gomis, Wang, Scheringer, & Cousins, 2015)[19]
Novel Flame Retardants: Estimating the Physical-Chemical Properties and Environmental Fate of 94 Halogenated and Organophosphate PBDE Replacements	EPI Suite, SPARC, Absoly	OECD Tool	Testing persistence and long range transport potential of novel flame retardants replacing PBDEs	(Zhang et al., 2016)[20]
Estimation of Physicochemical Properties of 2-ethylhexyl-4-methoxycinnamate (EHMC) Degradation Products and Their Toxicological Evaluations	EPI Suite	OECD Tool	To determine physicochemical properties and fate of 2-ethylhexyl-4-methoxycinnamate (EHMC) and its transformation products	(Gackowska, Studziński, Kudlek, Dudziak, & Gaca, 2018)[21]
Organophosphate Ester Transport, fate, and Emissions in Toronto, Canada, Estimated Using an Updated Multimedia Urban Model	EPI Suite, CATALOGIC	Multimedia Urban Model (MUM)	To predict aggregate emissions of selected organophosphate ester to urban air and their fate in the urban area	(Rodgers, Truong, Jantunen, Helm, & Diamond, 2018)[22]
Can Poly-Parameter Linear-Free Energy Relationships (pp-LFERs) Improve Modelling Bioaccumulation in Fish?	sp-LFERs, pp-LFERs	One-compartment model, multi-compartment model	To understand the effect of applying pp-LFERs on the bioconcentration prediction in various types of fish model	(Zhao, Jones, & Sweetman, 2018)[23]

Integrated utilization of property estimation models with MM require modeling only of chemicals that are within the applicability domain (AD)[8]. AD is a hypothetical space that is bordered by structural similarity and range of endpoint. Predictions are credible only if chemicals are located in applicability domain[9]. Furthermore, many chemicals have complicated partitioning tendency. Extending AD could be achieved by adding experimental partitioning coefficients, multiple sp-LFER equations, or pp-LFERs integration to multimedia fate models. The last option can allow for assessing several types of chemicals with polar functional groups[8]. For example, Zukowska et al.[10] investigated three pharmaceuticals by implementing a pp-LFER based MM model. After the model was parameterized with respect to a real drainage basin, chemical based input requirement was satisfied by EPI Suite and the literature[10]. In addition to being able to model relatively polar chemicals, additional phases could also be considered without additional input requirement[8] by coupling MM models with property estimation tools. Also, the pp-LFER based models can supply mechanistic perspectives for several interactions and polar or nonpolar chemicals[10].

However, finding credible descriptors, effects of environmental conditions on pp-LFERs and inadequacies in empirical data necessary for generation of pp-LFERs were stated as challenges for combining pp-LFERs with MM models. In spite of these, Breivik et. al. (2003) envisioned that "chemical risk assessment tools of the future may ultimately require no other chemical input parameter than molecular structure" [8]. The results of pp-LFER based and sp-LFER based MM models were not significantly different as compared to model parametrization. Therefore, Brown et al. (2009) recommended that selection of sp-LFER or pp-LFER depended on the availability of input parameters. They evaluated that this was increasingly becoming possible owing to increasing available data[11]. Typically, hydrophobic persistent organic pollutants (POPs) were modeled by MM models[6]. Drugs that are similar to POPs can be evaluated by MM models that were originally generated for POPs[4]. Polar and/or ionized drugs can be relatively single media pollutants, so single medium based fate models such as water quality models may be enough[10]. However, the metabolization of pharmaceuticals by the human body and uncertainty due to loss mechanisms should be regarded when applying single medium based models[23]. Furthermore, equivalent aqueous based fate models can be preferred in place of fugacity based ones to determine fate of ionized compounds[4].

Schenker et al. (2007) investigated fate of original chemicals and their transformation products using a QSPR-MM scheme to estimate joint persistence, spatial range and Artic contamination potential. This allowed detecting environmentally-benign parent compounds that might have hazardous degradation products or vice versa[12]. Uncertainties in property estimation could be high and more credible predictions for half-lives, K_{oc} and K_H were necessitated. Unless half-lives of structurally similar compounds or isomers are differentiated, the effects of transformation products could not be understood[13].

Hydrophobic and non-ionized chemicals can be assessed successfully by QSPR integrated MM models. In case of polar and ionized compounds, requirement of some improvements was highlighted by Jagiello and coworkers[4]. In addition to an increasing volume of pharmaceuticals, existence of different functional groups complicates their fate determination. QSPR models can frequently predict physicochemical properties, pharmacokinetics, and bioconcentration factors for POPs and chemicals with persistent, bioaccumulative and toxic (PBT) characteristics. QSPR implementation for drugs could be restricted by AD and lack of validation. Therefore, local models for each specific chemical class were suggested[15]. In addition to uncertainties in MM models, physicochemical properties are generally obtained for neutral species. Hence, the credibility of QSPR-MM modeling could be lower in case of ionized chemicals assessment. Available MM models should then incorporate pH as a parameter and pKa of chemicals. Despite some difficulties, QSPR-MM modeling was evaluated as reasonable as long as a stronger association between modelers and experimentalists can be maintained[4]. Inaccurate data in physicochemical properties for environmental fate models can be reduced by correlations. For example, the smallest deviation from experimental partitioning coefficients or temperature dependences of physicochemical properties could be considered by applying mathematical relationships[14].

Di Guardo and coworkers[15] compiled improvements in MM models and highlighted that AD of MM models were extended for polar and ionizable organic chemicals. Also, these models were implemented for nanoparticles, and microplastics[15]. Furthermore, biological substances (i.e. proteins, bacteria, prions, etc.) might be modeled by MM models[5]. Also, model parameters have been updated. Additional environmental media, and processes have been integrated into MM models. Sensitivity and uncertainty analysis were utilized with MM models. Additionally, MM models were assessed as satisfactory for highly dynamic cases with high accuracy. In spite of these improvements, methodology development in partition coefficients for polar and ionizable chemicals, and more realistic environmental media might be introduced to environmental fate models[15].

By computational design, physical and chemical properties of chemicals and so their possible fate could be estimated. Further studies might be beneficial for better estimation of properties such as soil partitioning, and for all physicochemical properties of polar and ionizable chemicals. The more predictive success such property estimation tools have, the better chance we have of preventing negative environmental impacts of synthetic organic chemicals. Currently, screening is performed for organic chemicals in food additives, food packaging, pharmaceutical, and personal products, to some degree. Integrating computational methods to improve a holistic screening methodology for different types of organic chemicals could constitute a significant step towards application of pollution-prevention strategies in the chemical sector.

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