

# Preface

Quantitative structure–activity/property relationship (QSAR/QSPR) models correlate biological activity (therapeutic or toxic) or other properties of chemicals/pharmaceuticals/toxicants/environmental pollutants with molecular structure information using chemometric and cheminformatic tools. These models have relevant applications in diverse disciplines like materials property modeling, environmental fate modeling, risk assessment, drug design, ADME/T modeling, food chemical and agrochemical design, nanomaterials design, etc. The research output in the mentioned areas is of paramount importance for data gap filling in case of non-availability of experimental data. Thus, model derived predictions have applications for regulatory purposes in chemical industries and for new analogue design in pharmaceutical, food and agricultural industries.

QSAR models aim to explore the specific quantitative relationships between a target activity (or property) and a set of structural and physicochemical features encoded within some numerical quantities popularly known as descriptors. Such models are helpful in predicting the target response for new molecules falling within the applicability domain of the developed models. It is also possible to derive a mechanistic interpretation of the structure–activity relationships, especially from models which have been developed using descriptors with definite physico-chemical meaning. The objective of structure–activity/property modeling is to analyze and detect the determining factors for the measured activity/property for a particular biological and/or chemical system in order to have an insight of the mechanism and behavior of the studied system. It is now very important to validate the developed QSAR models in order to check reliability of predictions for new compounds. The Organization for Economic Co-operation and Development (OECD) has recommended a set of five point guidelines for QSAR/QSPR model development and validation, especially for regulatory purposes.

QSAR has long been used in medicinal chemistry for lead optimization and drug design. QSAR increases the probability of success in finding an optimum lead with desired pharmacokinetic profile thus avoiding tedious experiments with thousands of compounds with less potential to become successful and hence avoiding colossal expenditure. QSAR is also a very popular tool for risk assessment of chemicals in

the absence of experimental data. Such approach is used by the United States Environmental Protection Agency and also encouraged in the European Union's REACH legislation. QSAR techniques are in consonance with the '3Rs concept' related to the moral principle regarding the use of sentient animals. As a result of increasing chemicals uses, applications of analogues, SAR and QSAR approaches by global Governmental organizations have increased.

There are four main areas where QSARs may be applied by governmental regulatory agencies:

- (i) Prioritization of existing chemicals for further testing or assessment
- (ii) Classification and labelling of new chemicals
- (iii) Risk assessment of new and existing chemicals
- (iv) Filling of data gaps.

In addition to the applications in chemical risk assessment and pharmaceutical development, the QSPR/QSAR findings can also be used to screen compounds with specific applications such as food additives, antioxidants and nanomaterials.

This volume aims at describing the fundamentals of QSAR modeling and showcasing some recent advancements of QSAR applications in Pharmaceutical, Chemical, Food, Agricultural and Environmental Sciences. There are 15 chapters on different topics of QSAR theory, methods and applications included in this book.

Chapter "[Towards the Revival of Interpretable QSAR Models](#)" authored by Chanin Nantasenamat and others gives a good introduction of the key topic QSAR. It highlights the basic steps of model development and validation, discusses various molecular descriptors and statistical techniques for model development. This chapter also discusses key issues influencing and contributing to the interpretability of QSAR models.

Chapter "[The Use of Topological Indices in QSAR and QSPR Modeling](#)" authored by John C. Dearden gives an overview of topological descriptors and their use in QSAR/QSPR studies. The author also mentions about biodescriptors, chirality and software availability in connection with topological descriptors.

Chapter "[Which Performance Parameters Are Best Suited to Assess the Predictive Ability of Models?](#)" has been authored by Karoly Heberger and co-authors. The authors have revisited the debate topic of choice of external validation versus cross-validation as a better tool for judging the predictive potential of QSAR/QSPR models. Using the sum of ranking differences (SRD) methodology coupled with ANOVA, the authors claim the superiority of cross-validation, at least in the case studies reported by them.

Chapter "[Structural, Physicochemical and Stereochemical Interpretation of QSAR Models Based on Simplex Representation of Molecular Structure](#)" authored by Victor Kuzmin and others shows the applicability of simplex descriptors to development of interpretable models using several case studies. The authors also demonstrate the applicability of the SiRMS approach to stereochemical interpretation.

Chapter "[The Maximum Common Substructure \(MCS\) Search as a New Tool for SAR and QSAR](#)" is authored by Giuseppina Gini and others. This chapter discusses relevance of a similarity measure exclusively based on the maximum

common substructure and its implementation in a new software tool developed by the authors and integrated into the ToxRead software. The authors' approach can be used for read across, where only local information about one or two similar molecules is used, or in assessing the prediction of QSAR results, or in refining the results of SAR systems that apply structural alerts.

Chapter "[Generative Topographic Mapping Approach to Chemical Space Analysis](#)" is written by Alexandre Varnek and others. This chapter describes Generative Topographic Mapping (GTM) and its application as a predictive tool for analysis of chemical space. The strengths of GTMs in chemical space navigation and analysis are critically reviewed.

Chapter "[On Applications of QSARs in Food and Agricultural Sciences: History and Critical Review of Recent Developments](#)" authored by Jerzy Leszczynski and others) presents the currently available information on diverse groups of molecules with applications in agriculture and food science that have been subjected to *in silico* modeling studies. The authors have also enlisted available agrochemical, food and flavor databases along with an extensive list of software tools and online resources for QSAR and other related *in silico* modeling studies.

Chapter "[Quantitative Structure-Epigenetic Activity Relationships](#)" authored by Jose Medina-Franco and others) has analyzed the progress of QSAR models developed for compound databases screened with epigenetic targets. This chapter also analyzes epigenetic activity landscape modeling, activity cliffs, and activity cliff generators and their relevance to develop QSAR models.

Chapter "[QSAR/QSPR Modeling in the Design of Drug Candidates with Balanced Pharmacodynamic and Pharmacokinetic Properties](#)" is authored by Anna Tsantili-Kakoulidou and others. It showcases the application of QSAR/QSPR in drug discovery process. This chapter discusses several case studies related to application of QSAR in modeling pharmacodynamics and pharmacokinetics of drug substances.

Chapter "[Strategy for Identification of Nanomaterials' Critical Properties Linked to Biological Impacts: Interlinking of Experimental and Computational Approaches](#)" authored by Iseult Lynch and others discusses on physicochemical properties of nanomaterials in connection with their toxicological outcome and application of QSAR in prediction of nanomaterial uptake and toxicity. This chapter also highlights the gaps between measured physicochemical parameters and calculated QSAR descriptors for nanomaterials.

Chapter "[In Silico Approaches for the Prediction of In Vivo Biotransformation Rates](#)" is authored by Ester Papa and others. This chapter illustrates the development and application of *in silico* models for *in vivo* biotransformation rates and half lives of chemicals. This chapter also describes the complementary role of *in vitro* biotransformation rate estimation and the subsequent *in vitro*-to-*in vivo* extrapolation calculations for refining bioaccumulation model predictions.

Chapter "[Development of Monte Carlo Approaches in Support of Environmental Research](#)" written by Emilio Benfenati and others shows application of the CORAL software for evaluation of environmental effects of various chemical compounds. The mechanistic interpretation and domain of applicability of the models for

various environmentally important endpoints was also discussed from different case studies.

Chapter “[Environmental Toxicity of Pesticides, and Its Modeling by QSAR Approaches](#)” is authored by A. Amrane and others. The chapter reviews pollution by pesticides and their effects on the entire ecosystem. A critical review of QSAR models for the prediction of the toxicity of pesticides is also provided.

Chapter “[Counter-Propagation Artificial Neural Network Models for Prediction of Carcinogenicity of Non-congeneric Chemicals for Regulatory Uses](#)” written by N. Fjodorova and others focuses on QSAR models for prediction of carcinogenic potency based on counter-propagation artificial neural network algorithm. These models were developed in the scope of CAESAR and PROSIL projects and implemented in online available internet platform VEGA.

Chapter “[Big Data in Structure-Property Studies—From Definitions to Models](#)” authored by Jaroslaw Polanski discusses what big data is and how important big data can be in drug design. This chapter also analyzes the big data types that are available in drug design as well as the methods that are used for their analyses.

I hope that this collection of 15 chapters will be helpful to the researchers working in the field of QSAR modeling. I am especially thankful to the Series editor Prof. Jerzy Leszczynski for his help during development of this book and to the publisher for bringing out this volume.

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