

A step forward in using QSARs for hazard and exposure assessment of chemicals

Aleksandra Rybacka

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Fakultetsopponent: Dr Uko Maran

Institute of Chemistry, Faculty of Science and Technology, Tartu University, Estonia



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Aleksandra Rybacka

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Abstract

According to the REACH regulation chemicals produced or imported to the European Union need to be assessed to manage the risk of potential hazard to human health and the environment. An increasing number of chemicals in commerce prompts the need for utilizing faster and cheaper alternative methods for this assessment, such as quantitative structure-activity or property relationships (QSARs or QSPRs). QSARs and QSPRs are models that seek correlation between data on chemicals molecular structure and a specific activity or property, such as environmental fate characteristics and (eco)toxicological effects.

The aim of this thesis was to evaluate and develop models for the hazard assessment of industrial chemicals and the exposure assessment of pharmaceuticals. In focus were the identification of chemicals potentially demonstrating carcinogenic (C), mutagenic (M), or reprotoxic (R) effects, and endocrine disruption, the importance of metabolism in hazard identification, and the understanding of adsorption of ionisable chemicals to sludge with implications to the fate of pharmaceuticals in waste water treatment plants (WWTPs). Also, issues related to QSARs including consensus modelling, applicability domain, and ionisation of input structures were addressed.

The main findings presented herein are as follows:

- QSARs were successful in identifying almost all carcinogens and most mutagens but worse in predicting chemicals toxic to reproduction.
- Metabolic activation is a key event in the identification of potentially hazardous chemicals, particularly for chemicals demonstrating estrogen (E) and transthyretin (T) related alterations of the endocrine system, but also for mutagens. The accuracy of currently available metabolism simulators is rather low for industrial chemicals. However, when combined with QSARs, the tool was found useful in identifying chemicals that demonstrated E- and T- related effects *in vivo*.
- We recommend using a consensus approach in final judgement about a compound's toxicity that is to combine QSAR derived data to reach a consensus prediction. That is particularly useful for models based on data of slightly different molecular events or species.
- QSAR models need to have well-defined applicability domains (AD) to ensure their reliability, which can be reached by e.g. the conformal prediction (CP) method. By providing confidence metrics CP allows a better control over predictive boundaries of QSAR models than other distance-based AD methods.
- Pharmaceuticals can interact with sewage sludge by different intermolecular forces for which also the ionisation state has an impact. Developed models showed that sorption of neutral and positively-charged pharmaceuticals was mainly hydrophobicity-driven but also impacted by Pi-Pi and dipole-dipole forces. In contrast, negatively-charged molecules predominantly interacted via covalent bonding and ion-ion, ion-dipole, and dipole-dipole forces.
- Using ionised structures in multivariate modelling of sorption to sludge did not improve the model performance for positively- and negatively charged species but we noted an improvement for neutral chemicals that may be due to a more correct description of zwitterions.

Overall, the results provided insights on the current weaknesses and strengths of QSAR approaches in hazard and exposure assessment of chemicals. QSARs have a great potential to serve as commonly used tools in hazard identification to predict various responses demanded in chemical safety assessment. In combination with other tools they can provide fundamentals for integrated testing strategies that gather and generate information about compound's toxicity and provide insights of its potential hazard. The obtained results also show that QSARs can be utilized for pattern recognition that facilitates a better understanding of phenomena related to fate of chemicals in WWTP.

Keywords

QSAR, *in silico*, non-testing tools, risk assessment, exposure assessment, hazard assessment, carcinogenicity, mutagenicity, reproductive toxicity, endocrine disruption, estrogen, androgen, transthyretin, sorption

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