UMEÅ UNIVERSITET

Development of *in silico* methods to aid chemical risk assessment

Focusing on kinetic interactions in mixtures

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvar i Lilla Hörsalen, KBE301, KBC huset, fredagen den 19 april, kl. 09:00.

Avhandlingen kommer att försvaras på engelska.

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Abstract

The environment and biota are constantly exposed to numerous chemicals through contaminated food, soil, water, and air. These chemicals can be taken up and distributed to reach sensitive tissues where they may cause various effects. Many of these chemicals lack data on their environmental and human health effects. Traditional toxicological tests relying on animal experiments are today being phased out in favor of cell-based and computational methods for early hazard detection and exposure assessment. This thesis focuses on developing computational tools for various stages of chemical risk assessment with a particular focus on bisphenols and per- and polyfluoroalkyl substances (PFAS).

In Paper I, quantitative structure-activity relationship (QSAR) models covering molecular targets of the thyroid hormone (TH) system were developed and applied to two data sets to prioritize chemicals of concern for detailed toxicological studies. In Papers II and III, experimental and computational approaches were combined to study toxicokinetics and maternal transfer in zebrafish. Our main focus was to study potential mixture effects on administration, distribution, metabolism, and elimination (ADME) processes, i.e., to reveal if co-exposed chemicals impact each other's ADME. Physiologically based kinetic (PBK) mixture models were developed to allow translation of external exposure concentrations into tissue concentrations.

Main findings of this thesis are summarized as follows:

- Application of QSAR models (Paper I) to two chemical inventories revealed that chemicals found in human blood could induce a large range of pathways in the TH system whereas chemicals used in Sweden with predicted high exposure index to consumers showed a lower likelihood to induce TH pathways.
- Two zebrafish experiments (Paper II and Paper III) did not reveal statistically significant mixture effects on ADME of chemicals.
- In Paper II, a PBK mixture model for PFAS accounting for competitive plasma protein binding was developed. The model demonstrated good predictive performance. Competitive plasma protein binding did not affect the predicted internal concentrations.
- In Paper III we developed a binary PBK model parametrized for two bisphenols and PFOS showing that competitive plasma protein binding has an effect on ADME of bisphenols at PFOS concentrations at µg/L levels. At these levels internal concentrations of bisphenols were shown to decrease, implying that PFOS outcompeted bisphenols from studied plasma proteins resulting in higher excretion rates.

Developed QSAR models showed good predictive power and the ability to identify and prioritize chemicals of concern with confidence. Additionally, PBK models aid in hypotheses testing and predicting exposure concentrations at which co-exposed chemicals could potentially influence each other's ADME properties. These tools will provide overall early tier data on exposure and effects using non-testing methods in assessment of risks of chemicals.

Keywords
Risk assessment, QSAR, PBK, thyroid hormone, ADME, zebrafish, maternal transfer, bisphenols, PFAS, toxicokinetics, mixture

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