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Computational Methods for Assessing Chemical Risk

Focusing on Toxicokinetic Modelling in Zebrafish (*Danio rerio*)

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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, KBC byggnad KBE301,
fredag den 3 mars, kl. 09:00.
Avhandlingen kommer att försvaras på engelska.

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Department of Chemistry

Organization
Umeå University
Department of Chemistry

Document type
Doctoral thesis

Date of publication
10th of February 2023

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Title
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Abstract
New chemicals are constantly produced and large data gaps exist on hazards of currently used industrial chemicals, stressing the need for rapid, ethically sound and cost-efficient hazard assessment methods. Traditional methods for effect assessment based on animal testing, do not meet these requirements and thus the toxicology field has been moving towards the development of new approach methodologies which include *in vitro* approaches but also computational methods. The current work has mainly focused on computational tools but also employed *in vitro* and *in vivo* methodologies for the development and validation of the *in silico* approaches.

We firstly explored chemical variation of emerging chemicals as a basis for selecting sub-groups of per- and polyfluoroalkyl substances (PFASs) and bisphenols for Papers I and II. These compounds can be used for future testing and as case study compounds for *in silico* tools development. The PFASs selection showed compounds with large differences in structure and highlighted the lack of knowledge for large parts of the PFASs chemical domain. This likely is the main driver of the low predictive accuracy of some current fate models and the need for expanding their applicability domains.

In Paper II we investigated the toxicokinetics of selected bisphenols in a commonly studied model organism, the zebrafish (Danio rerio), and developed a physiologically-based toxicokinetic model. Novel data for fish biotransformation was derived and showed lower rates than those measured in humans, providing valuable insight for both model parameterization and for chemical safety assessment using fish. The model also demonstrated the ability to predict and rank hazard of these bisphenols in terms of organ-specific bioaccumulation making it a useful tool for chemical screening and prioritization efforts. The results indicate that bisphenols AP, C and Z as well as tetrabromo bisphenol A may have larger potential for bioaccumulation than the widely used bisphenol A (BPA), indicating that these compounds do not constitute safer industrial substitutions.

Lastly, we present in Paper III the development of a toxicokinetic model for the zebrafish embryo life-stage. Since the zebrafish embryo test is widely applied in toxicology research, the developed model provides a tool to better understand how varying testing conditions may affect dose at target thus providing a means to compare internal effect concentrations. Additionally, we applied the model in combination with data on estrogenic activity in order to rank the relative hazard of investigated bisphenols, which showed that bisphenols AF, C, B and Z may be more hazardous than BPA.

Overall the developed computational tools showed good predictive performance and improvements in parameterization, thus providing tools for understanding dose at target and toxicokinetic variation of emerging substances. Furthermore, the thesis presents novel data and findings for per- and polyfluoroalkyl substances and bisphenols, which are environmental pollutants of emerging concern of relevance for future hazard assessments and substitution processes.

Keywords
Bisphenols, Zebrafish, Perfluorinated compounds, Physiologically-based toxicokinetic modelling, Endocrine disruptors, Multivariate analysis

Language
English

ISBN
print: 978-91-7855-990-9
PDF: 978-91-7855-991-6

Number of pages
53 + 3 papers