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## Integrative Systems Toxicology for Human Health

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# Summary

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## Summary

In industrialised economies large amounts of chemicals are produced and released into the environment. The accumulation of these chemicals in the ecosystem and the consequent exposure of human individuals to them are suspected of causing adverse effects on human health. For the so-called EDCs (Endocrine Disrupting Compounds) these effects include interference with hormonal regulation. REACH (Registration, Evaluation, Authorisation, and Restriction of Chemicals) and 3R (Replacement, Reduction and Refinement) principles have been proposed by the ECHA (European Chemicals Agency) and EFSA (European Food Safety Authority), respectively, in order to regulate the production and use of such chemicals. Both principles address the protection of human health and the environment through a better and earlier identification of the intrinsic properties of chemical substances. Simultaneously they aim to provide an alternative to animal testing by development of in-vitro and in-silico tools, incorporation of integrated assessment and testing approaches (IATAs), etc. The early identification of chemical-induced adverse effects poses several challenges. These include complexities inherent to the biological systems affected, complex mechanisms around structure, stability and solubility of the chemicals themselves, and the complex responses of organisms to exposure at various life stages and time scales. Emerging high-throughput analyses, OMICS and several in-silico tools such as PBPK (Physiologically based pharmacokinetic), PD (Pharmacodynamics), Systems Biology (SB) and AOPs (Adverse outcome pathways) offer opportunities to understand more of the biological complexity and multilevel connectivity. Along with the development of new tools and techniques in toxicological research, it is necessary to have a continuous re-evaluation of existing data, data curation, data integration, and knowledge-based translation of the integral results to implications that might be able to solve many current challenges in this field. However, there is a paucity of research that integrates in-vitro, in-vivo, and several in-silico models into platforms that directly tie the results of the new data driven approaches in with predictive adverse outcomes models.

The objective of the current thesis was to develop an Integrative Systems Toxicology Framework enabling to understand the adverse effects of chemicals on a biological system quantitatively. It should comprise exposure, subsequent molecular and physiological alterations, molecular and cellular response as well as the ultimate adverse effect. The platform should be aiming for mechanistic understanding of any chemical's interaction with living systems, more than for the conventional empirical end points and animal based testing. The intended approach should integrate all the approaches that are presently used to address parts of the overall problem, such as chemical exposures, physiology, pharmacokinetics, pharmacodynamics, and biological response.

In chapter I, the literature is reviewed with the aim of identifying proposed mechanisms of action of EDCs, which included the interactions of chemicals with molecular receptors,

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enzymes, proteins, gene-expression regulation and epigenetics thereby affecting the biological system, during and after the window of exposure. This chapter also investigates the normal endogenous pathways pertaining to the relevant hormones as this should aid in understanding the physiology dependent action of the corresponding EDCs. Then, the EDCs classified based on their target organs, the hormones of which they disrupt the action, the targets of those hormones, and the consequent adverse outcomes (response). Finally, a grouping strategy is proposed that is based on similar adverse outcomes. This chapter addresses many complications for the quantitative risk assessment, like multiple mechanisms, delayed response (time lag between exposure to adverse outcomes), dynamic interactions involving crosstalk and common mechanisms (complex mechanisms), and transgenerational effects. Finally, an integrative risk assessment framework is proposed connecting external exposure, internal exposure, and biological effects to the adverse outcomes. This framework includes the use of a PBPK model, a PD (pharmacodynamics) model and the coupling of these two models.

Chapter II includes the development and validation of a PBPK model in adult for Di-2-ethylhexyl phthalate (DEHP) and Flutamide, both categorized as EDCs. The model for DEHP includes four DEHP metabolites namely mono-(2-ethylhexyl) phthalate (MEHP), 5-OH MEHP, 2-ethyl-5-carboxypentyl phthalate (5-cx MEPP) and 5-oxo MEHP. An IVIVE (in-vitro in-vivo extrapolation) tool was successfully used in connection with the PBPK model to derive in-vivo kinetics from in-vitro studies using biologically appropriate scaling. A local parametric sensitivity analysis was performed and the statistical distributions of the most uncertain yet influential parameters were determined by Monte Carlo simulations of model uncertainty. Then the model was evaluated against published independent data on plasma and urine concentrations of DEHP metabolites for different dosing scenarios.

The development of the flutamide PBPK model includes bottom-up, top-down and cross-species extrapolation approaches. First, the model is developed for rat and then it is extrapolated to the human. Evaluated against experimentally observed data addressing 7 compartments, the rat model performed fairly: for most tissues the median values predicted by the model were less than a factor of 10 away from the average experimental values. The extrapolation of the model to predict flutamide kinetics in humans for two different scenarios of dosing (single and multiple) was also in good agreement with the observed data.

Chapter III focuses on the development of a Pregnancy PBPK (P-PBPK) model for Bisphenol-A (BPA) that includes the foetus as a sub compartment into the model structure. First, the adult PBPK model is developed and validated with the human BPA toxicokinetic data. This validated human PBPK model is then extended to become a P-PBPK model which includes the physiological changes during pregnancy and the foetus sub-model. The developed P-PBPK model is in concordance with biomonitoring data and shows that BPA readily transfers to foetal serum and amniotic fluid after maternal

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exposure. De-conjugation of BPA-conjugate (BPAG) in placenta and foetus causes increased BPA exposure in early foetal life. Importantly, free BPA in the foetal compartment are more in steady state and persist even as the maternal level of BPA declines. The mid-gestational period was found to be critical, as during this time the concentration of BPA in the foetus was relatively high. Moreover, this period is also considered as critical for the foetus' body development.

Chapter IV builds an in-silico replica simulation of the biological system's behaviour. It reconstructs the biochemical information on components' communication into mathematical equations. It includes the development and validation of a systems biology model for ROS (reactive active oxygen species). First, we build the models ab initio, starting from the physiology of the response to oxidative stress. Subsequently, we increase the complexity of the network step by step. Adding every new level of complexity in a domino approach enables us to identify design principles of ROS management. It demonstrates that both mitochondrial recovery and mitophagy may avert ROS-induced cell death. The model is validated against several independent in-vitro data sets.

Chapter V includes the integrative systems toxicology approach. This involves two cases: 1) PBPK coupled PD with a mechanistic pathway model (similar to AOP). Perfluoro octane sulfonic acid (PFOS) was selected as a case study to illustrate the ways to incorporate systems biological modeling in the field of toxicology via a Pharmacodynamics-coupled tissue dosimetry model (PBPK/PD). A PBPK and a mechanistic system pathway model are simulated individually in order to generate the component models. Subsequently the integrated PBPK/PD coupled mechanistic model (systems toxicology) was used for simulations. QIVIVE along with PBPK was used to evaluate the performance of the model using in-vitro data.

2) PBPK coupled PD with the detailed ROS systems biology model taking the case study for the flutamide. The previously developed flutamide PBPK (chapter 2) and ROS systems biology models were used to develop integrative systems toxicology. This integral model is used to predict the hepatotoxicity of flutamide, illustrating the wider application of integrative systems toxicology in the field of the Human health risk assessments.