Integrative Systems Toxicology for Human Health

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Hypothesis and Objectives

Hypotheses

Along with the development of new tools and techniques in toxicological research, it is necessary to continuous re-evaluation, curation, and integration of existing data, and knowledge-based translation that might be able to solve many current challenges in this field.

Integration of knowledge from a complete pipeline of systems biology into a holistic yet mechanistic framework will enhance the understanding of both biology and adverse effects due to chemically-induced toxicity to human health. The pipeline includes in vivo, in vitro, and in silico data resulting both from genomics and from more targeted studies.

Prediction of Adverse effects of various chemicals on human health may be improved if the time course concentrations of those chemicals in the human body are well known. In silico tools are cheap, quick and reliable techniques to estimate the body burdens of chemicals, being a serious alternative to in vivo or in vitro investigations. PBPK/PD models may simulate and predict the distribution and accumulation of environmental toxicants in the human body. Therefore, they may be a good alternative to biological monitoring of environmental chemicals.

Integration of wide range of in silico tools (QSAR, PBPK/PD, AOP, systems biology models etc.) and databases (OMICS, epidemiological and exposure data), under the umbrella of Integrative Systems toxicology would improve the prediction of chemical-induced adverse effects on human health. This integrative approach would lead to mechanistic understanding of adverse effects vs conventional empirical end points and animal based testing.

Mechanistic understanding of the system as a compendium of interconnected processes would lead to a better integrative in-silico predictive model. It comprises of the chemical exposures to their biological target interactions and subsequently the molecular and functional changes that occurs at the multiple level of biological system.

In a mechanism-based modelling approach it is easy to integrate dynamic physiological changes that occur at life stages. This would allow to develop population and organ specific predictive models. To generate similar predictions without modelling, e.g. based on in experiments only, would be extremely difficult. Overall by improving the toxicity prediction this integrative approach of systems toxicology might also minimize the need of animal testing, reducing the cost and time of toxicity tests.

General Objective

Development of an Integrative Systems Toxicology framework should enable one to understand quantitatively the adverse effects of chemicals on a biological system from the information on the exposure of the system to the sequence of molecular and physiological alteration, through the integration of exposome-internal exposure-molecular/cellular response with adverse effect.

Specific Objectives

1. To review the detailed toxic pathway for the Endocrine disruptors and their classifications based on target organs and their mode of action. Thereby designing principals/framework for the development of the next generation of PBPK/PD – Systems Biology models.
2. Development and Validation of an adult internal dosimetry model (PBPK).
3. Integration of dynamic physiology in the development of PBPK for special populations (Pregnant mother and fetus)
4. Parametrization of PBPK and Systems Biology models using QSAR and in-vitro data.
5. Development and validation of AOPs and Systems Biology Models.
6. To accommodate toxicity prediction of chemicals, by improving mechanistic understanding of chemical effects in dynamic-model-AOPs, through the use of molecular biology and systems toxicology approaches.
7. Coupling PBPK and PD models (AOPs & SB) to develop integrative systems toxicology.
8. Sensitivity and uncertainty analysis of the developed models.