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Systems Toxicology: The Future of Risk Assessment

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Abstract

Risk assessment, in the context of public health, is the process of quantifying the probability of a harmful effect to individuals or populations from human activities. With increasing public health concern regarding the potential risks associated with chemical exposure, there is a need for more predictive and accurate approaches to risk assessment. Developing such an approach requires a mechanistic understanding of the process by which xenobiotic substances perturb biological systems and lead to toxicity. Supplementing the shortfalls of traditional risk assessment with mechanistic biological data has been widely discussed but not routinely implemented in the evaluation of chemical exposure. These mechanistic approaches to risk assessment have been generally referred to as systems toxicology. This Symposium Overview article summarizes 4 talks presented at the 35th Annual Meeting of the American College of Toxicology.

Keywords

systems toxicology; risk assessment

Introduction

Risk assessment, in the context of public health, is the process of quantifying the probability of a harmful effect to individuals or populations from human activities. The approach to quantitatively assess the health risks of chemical exposure has not changed appreciably in the past 80 years. The focus remains on low-throughput, high-dose studies that measure adverse outcomes in homogeneous animal populations. Conservative extrapolations are

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relied upon to relate animal studies to much lower dose human exposures. The relevance of this approach to predicting risks to humans at these typical low exposures is questionable. Furthermore, this approach has made little use of a mechanistic understanding of the mode of action by which chemicals perturb biological processes in human cells and tissues.

With increasing public health concern regarding the potential risks associated with chemical exposure, there is a need for more predictive and accurate approaches to risk assessment. Developing such an approach requires a mechanistic understanding of the process by which xenobiotic substances perturb biological systems and lead to toxicity. Supplementing the shortfalls of traditional risk assessment with mechanistic biological data has been widely discussed but not routinely implemented in the evaluation of chemical exposure. These mechanistic approaches to risk assessment have been generally referred to as systems toxicology. Systems toxicology borrows heavily from systems biology and attempts to model chemically induced pathophysiology of the body with computational tools.[1] Systems toxicology can be defined as the use of advanced analytical and computational tools to integrate classical toxicology and quantitative analysis of large networks of molecular and functional changes occurring across multiple levels of biological organization.[2]

Systems toxicology enables the integration of quantitative systems wide molecular changes in the context of chemical exposure measurements and a causal succession of molecular events linking exposures with toxicity. Computational models are then built to describe these processes in a quantitative manner. This scientific integration leads to the determination of how biological pathways are perturbed by chemical exposure and ultimately enables the development of predictive computational models of toxicological processes, thereby improving the accuracy of risk assessment.

In a recent symposium at the 35th Annual Meeting of the American College of Toxicology, supported by an educational donation provided by Philip Morris International R&D, 4 presentations described the current state of systems toxicology and the potential for its future application in chemical risk assessment. A summary of each presentation is outlined subsequently.

Translating Systems Toxicology-Based Assessment into Risk Management

Thomas Hartung, John Hopkins University, Bloomberg School of Public Health, Baltimore, MD, USA

Thomas Hartung laid out the need for a systems toxicology approach to risk management by talking about some of the groups and initiatives that are involved in developing the necessary tools, platforms, and applications. In addition, he emphasized the need for good cell culture practices[3] including stem cells and organotypic cultures to be used for high-content screening.[4,5] Empirical and mechanistic approaches to toxicity and risk management were contrasted. The need to understand pathways of toxicity (PoT)[6] and adverse outcome pathways (AOPs) in order to separate signal from noise and translate between model systems was also discussed. The use of combined omics approaches was highlighted. Two challenges were identified to validate a mechanistic approach to risk management. The first

was quality assurance of the data used to define PoT and AOP.[7] The second challenge was developing an integrated testing strategy.[8]

Experimental Enablers: The Pan-Omics View

Marcel Leist, University of Konstanz, Germany

Marcel Leist presented an overview of the importance of omics end points to systems toxicology and the necessity for concentration-dependent testing. He touched on single-omic, multi-omic, and fluxomics and defined multi-omics as the integration of signal transduction, regulation, and metabolism in a single mathematical model. The goal of this work is to identify the mechanism of action that results in toxicity. The current state of omics research was summarized. The first multi-omics studies have been attempted and large-scale omics projects are yielding results. Their combination with absorption, disposition, metabolism, and excretion data and physiologically based pharmacokinetic modeling is key for arriving at toxicological thresholds. The current studies are mostly proof of concept, and the candidate mechanisms identified are often lacking quantification and proof. In addition, many issues with data structure remain to be resolved.

The toxicant 1-methyl-4-phenylpyridinium was used to demonstrate the utility of the combination of metabolomics, fluxomics, and transcriptomics. Pronounced changes were seen on the transcriptome and metabolome level when cellular adenosine triphosphate levels and viability were still at control levels. This study[9] confirmed known findings using an unbiased approach. In addition, new findings and pathways were identified (activating transcription factor 4 activation, serine pathway-trans-sulfuration) and confirmed by a small interfering RNA approach.

There was also a discussion on the use of transcriptomics in developmental biology, which resulted in several findings with histone deacetylase (HDAC) inhibitors and mercurials. These included a reflection of concentration-dependent effects on genes, dramatic direct and indirect effects on the transcriptome based on the length of exposure, dramatic effects depending on exposure at a particular time during development, powerful separation of HDAC inhibitors from other compounds, and visualization and quantification of overall responses and the ability to map responses.

Computational Enablers: From Data Integration to Dynamic Modeling

Thomas B. Knudsen, US Environmental Protection Agency, Research Triangle Park, NC, USA

Thomas Knudsen discussed the multiscale problem. In any complex biological system, uncertainty at the microscale hinders our ability to predict outcome at a macroscopic level. Reducing this uncertainty is necessary for a more mechanistic, quantitative, and dynamic understanding of toxicological processes. Computational models that integrate complex data into multiscale simulations can advance translation in predictive toxicology. “Virtual tissue models” (VTMs), which are knowledge-driven computer models that can simulate how disruption of cell functions leads to observable adverse effects at the tissue level, are especially useful tools for unraveling the spatiotemporal dyamics of a complex system. He

described a predictive signature for vascular disruption based on ToxCast high-throughput screening data and a correlation with prenatal developmental toxicity. A VTM was built to implement the predictive signature and to permit a more detailed mechanistic and quantitative understanding of how chemicals disrupt angiogenesis.[10] To further simulate how cellular changes may invoke prenatal developmental toxicity in a complex system, multicellular agent-based models (ABMs) were framed from biological rules assigned to cellular "agents" that then interact with one another in a shared environment (www.CompuCell3D.org) to predict higher order (emergent) properties. These ABMs implement toxicological changes in top of cell–cell signaling fields in a VTM, leading to defects such as digit defects, cleft palate, and hypospadias. Ultimately, it is possible to design, model, and test complex biological systems in silico for predictive toxicology.

Implementing Systems Toxicology Approaches

Julia Hoeng, Philip Morris International R&D, Neuchâtel, Switzerland

Julia Hoeng described the implementation of system toxicology approaches to assess prototypic modified risk tobacco products (pMRTPs).[11,12] During her talk, she presented a new study that combines physiological, tissue, and cellular end points with large-scale molecular measurements to compare the effects of ongoing smoking, smoking cessation, and switching to a pMRTP in an animal model of disease. In this study, a mouse model of cigarette smoke-induced chronic obstructive pulmonary disease demonstrated decreased pulmonary function accompanied by increased infiltration of inflammatory cells and mediators in the lungs, increased perturbation of major biological networks,[13] and time-dependent progression of pulmonary emphysema (confirmed by histopathology) as a result of cigarette smoke exposure. Using this model, she showed that all these parameters were markedly reduced following a switch to pMRTP, similar to cessation, while the loss of lung function was halted. The systems toxicology approach utilized here added a strong supportive mechanistic layer to traditional toxicology end points.

Utilization of in vitro systems toxicology for product testing was also discussed. The results highlight the suitability of the Vitrocell 24/48 system (VITROCELL Systems GmbH, Waldkirch, Germany) to assess the effect of cigarette smoke on human organotypic tissue cultures exposed at the air–liquid interface. Such organotypic cultures recapitulate a significant part of the in vivo biology.[14,15] She underlined that modeling transport and evolution of aerosol droplets is important for understanding aerosol deposition in the in vitro exposure system and accurately predicting the exposure doses for a given experiment. In addition, the organotypic nasal and bronchial tissue culture models have the potential to significantly reduce animal experimentation in the field of respiratory toxicology. Applying a systems toxicology approach aligned with the principles of 21st-Century Toxicology enables mechanistic assessment of aerosol effects on the respiratory tract biology beyond classical cell viability and gross morphology end points.[16]

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