Computable causal network models for systems biology-based risk assessment

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‘Omics’ data that contain measurements of thousands of molecular species in a single experiment are a powerful tool to probe how environmental toxicants, including tobacco products, contribute to disease. However, to gain any meaningful mechanistic insight from these data, they need to be interpreted in the context of relevant biological processes. To address the needs of a systems biology-based risk assessment approach in a systems toxicology setting such as the “21st Century Toxicology”, we are building biological network models that can retrieve mechanistic information from ‘omics’ data.

The biological networks describe causal node-edge relationships using the Biological Expression Language (BEL), which allows for the semantic representation of these relationships in a computable format. The literature model, which is built from relationships mined from relevant scientific literature, is further enhanced with additional nodes derived from Reverse Causal Reasoning (RCR) analysis of transcriptomic data sets. The integrated model is manually reviewed and refined, and finally, validated using independent datasets.

To date, we have constructed a series of network models describing cell proliferation, cellular stress, DNA damage and the cellular fates induced by stress, as well as networks describing pulmonary and cardiovascular inflammation, tissue repair and angiogenesis. Our network backbones have strict boundaries focusing on non-diseased cells/tissues to capture the molecular events that are activated prior to disease onset.

The analysis of ‘omics’ data at network-level places the differentially expressed genes into the context of known biological signaling and provides invaluable mechanistic insight into the effects of potentially harmful exposures.

Biography
Marja Talikka completed her PhD in 2000 at the University of Helsinki. She pursued postdoctoral studies at the Rockefeller University focusing on proneural basic-helix-loop-helix transcription factors using the frog embryo as a model system. Her second postdoctoral research in the Swiss Institute for Cancer Research (ISREC) focused on the role of subtilisin-like proprotein convertases in Alzheimer’s disease. She joined Philip Morris International Biological Systems Research in 2011.

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