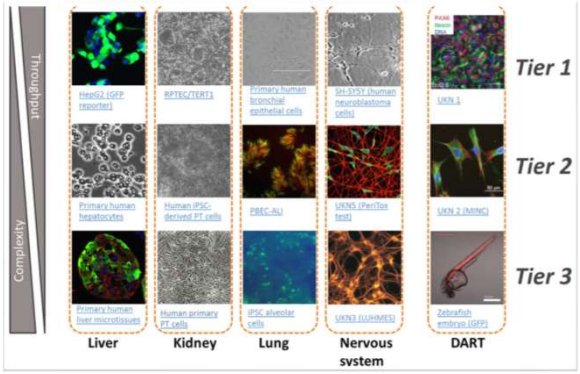
The Final EUTOXRISK Symposium 11

Impact #1
More effective and faster toxicity testing to better predict human risk and meet regulatory needs

Tiered testing

EU-ToxRisk testing is organised in a tiered fashion: *in silico* and high-throughput *in vitro* methods precede more costly complex methods.



Human-relevant NAMs

New approach methodologies (NAMs) are any technology, methodology, approach or combination thereof that can be used to provide information on chemical hazard and risk that avoid the use of intact animals.

EU-ToxRisk NAMs are based on human material, tackling species-specific toxicity differences issues.

High-throughput strategies

High-throughput methods are central to the EU-ToxRisk testing strategy: large-scale experiments where combinations of robotic automation, instruments for detecting assay-specific outputs and data processing pipelines are used to evaluate the biological effects in hundreds to thousands of samples, typically in *in vitro* test systems

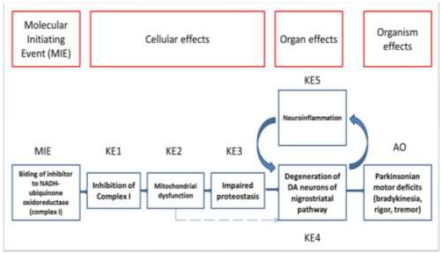
High-throughput transcriptomics (HTT): using gene expression profiling as an endpoint for rapidly evaluating the effects of large numbers of chemicals on, e.g., cultured cell systems.

High-content screening (HCS): evaluation of multiple biochemical and morphological parameters in intact biological systems.

EU-ToxRisk delivered and tested a tiered testing approach built on human-relevant NAMs and incorporating quantitative AOPs, HCS methodologies, uncertainty assessment, and ADME data for qIVIVE.

Adverse outcome pathways

An adverse outcome pathway (AOP) is a structured representation of biological events leading to adverse effects relevant to risk assessment. AOPs link existing knowledge along one or more series of causally connected key events (KEs) from a molecular initiating event (MIE) to the ultimate adverse outcome (AO), together representing the level of biological organization relevant to risk assessment.



EU-ToxRisk exploits the use of novel high-throughput tests to identify KEs of relevant AOPs, thereby facilitating faster decision-making and increasing overall confidence.

Uncertainty assessment

Uncertainty analysis quantifies uncertainties in all relevant variables to support the decision-making process. Uncertainty refers to a lack of data or to an incomplete understanding of the context of the risk assessment decision. It can be either qualitative or quantitative. Uncertainty in risk assessment can be present in the characterization of the exposure scenario, the parameter estimates, or model predictions.

Strategies to address and report on uncertainty were explored in the various EU-ToxRisk case studies.

Exposure considerations

The EU-ToxRisk testing strategy includes relevant human exposure considerations. This allows for adaptations of hazard data requirements to use scenarios; and allows parameterizing of computational prediction models to human data (safe vs toxic).

In the extrapolation of *in vitro* effect concentration to predicted *in vivo* toxic dose level (qIVIVE), consideration of metabolism is required at two levels: (1) estimation of the in vivo point-of-departure, (2) application of biokinetic/biodynamic models in extrapolating the *in vitro* dose.

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