The Final EUTOXRISK Symposium 19

CASE STUDY 11: *High throughput methods for prioritization for safety evaluation: defining low-tox or no-tox levels.*

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Regulatory context: REACH

Regulatory Question

Challenge

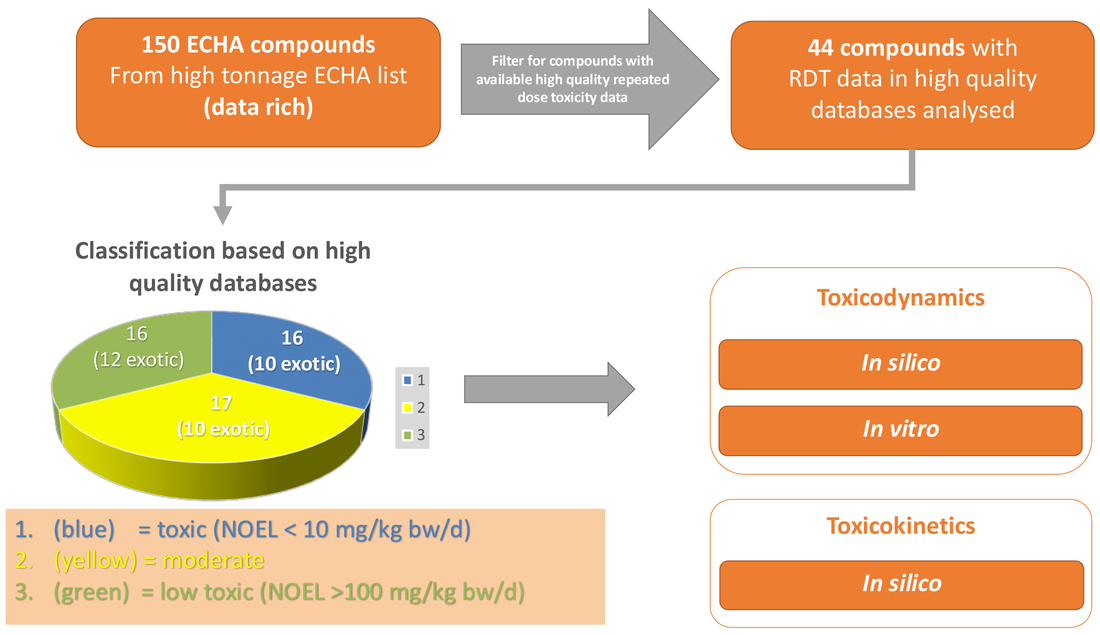
Prioritization for further testing of REACH chemicals that lack safety data.

Main hypothesis

High throughput mechanism-based NAMs do properly rank order ECHA substances based on liability and potency for in vivo toxicity.

Impact:

Ability to determine a performance metric on concordance would lead to confidence on the application of NAMs for prioritization of chemicals.



Overview on the Case Study Approach

Viability assessment:

Liver: HepG2, HepG2 + Adv-Cyps, PHH
Lung: PBEC bronchial epithelial cells
Neuronal: LUHMES
Kidney: RPTEC-TERT1

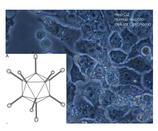
High throughput functional screening:

CALUX cell signaling reporters
HepG2 BAC-GFP cell stress response reporters

Transcriptomic

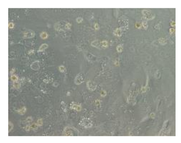
HepG2, PHH, PBEC, RPTEC, LUHMES

HepG2 AdV



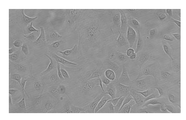
Organ system liver (metabolism)
Partner: HULAFE

PHH



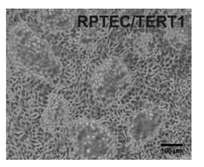
Organ system liver
Partner: Cyprotex

PBEC



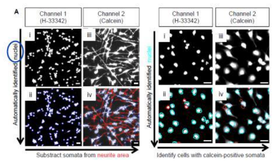
Organ system lung
Partner: LUMC

RPTEC



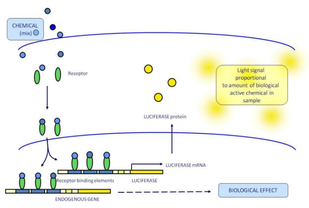
Organ system kidney
Partner: VUA

LUHMES

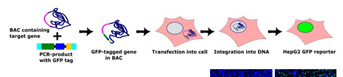


Organ system neuron
Partner: UKN

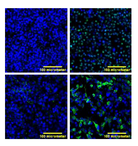
CALUX



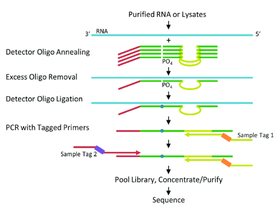
HepG2 BAC-GFP



Oxidative stress *SRXN1
DNA damge
ER stress
Inflammatory stress
Heat shock



High throughput transcriptomics TempO-Seq (HTTr)



1. HepG2
2. PHH
3. PBEC
4. RPTEC
5. LUHMES

Outcome of the Case Study

Integrative testing strategy to address the need of effective assessment of chemicals

- Broad set of *in vitro* test systems to support biological relevance
- High throughput assays to capture a broad set of specific MoA
- High throughput transcriptomics to capture broader biological changes in *in vitro* systems
- Support by *in silico* approaches for higher human relevance (PBTK, IVIVE)

Learnings and current remaining issues

- *In vitro* methods show largely signals according to their *in vivo* toxicity level
- Optimization of high throughput assay BMC determination needed for BAC-GFP
- HTTr is challenging for this set of chemicals
- Further data integration based on the IVIVE required

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www.eu-toxrisk.eu/