The Final EUTOXRISK Symposium 13

Case Study 1- Integration of mechanistic evidence from new approach methodologies (NAMs) into a read-across assessment

Sylvia E. Escher[1],Alejandro Aguayo-Orozco[2], Emilio Benfenati[3], Annette Bitsch[1], Thomas Braunbeck[4], Katharina Brotzmann[4], Frederic Bois[10], Bart van der Burg[5], Jose Castel[6], Thomas Exner[9], Domenico Gadaleta[3], Iain Gardner[10], Daria Goldmann[18], Oliver Hatley[10], Nazanin Golbamaki[11], Rabea Graepel[12], Paul Jennings[13], Alice Limonciel[13], Anthony Long[11], Richard Maclennan[7], Enrico Mombelli[6], Ulf Norinder[8], Sankalp Jain[16], Liliana Santos Capinha[13], Olivier T. Taboureau[14], Laia Tolosa[6], Nanette G. Vrijenhoek[12], Barbara M. A. van Vugt-Lussenburg[5], Paul Walker[7], Bob van de Water[12], Matthias Wehr[1], Andrew White[15], Barbara Zdrazil[16], Ciarán Fisher[10]

Background

- Read-across case studies to learn how to integrate different types of NAM data into human risk assessment (RA)
- Read-across aim - Predict the toxicity of data poor target compounds (TCs) by using data rich source compounds (SCs)
- Multi-disciplinary team needed to solve regulatory question

Regulatory questions

Show that SCs and TCs are similar with regard to their toxicological properties:

- Can we use NAMs to show that a group of compounds share a similar mode of action?
- Can we use modelling approaches to extrapolate an *in vitro* effect concentration to a point of departure for RA?

Develop a Concept for Integration of NAM Data into Regulatory Risk Assessment

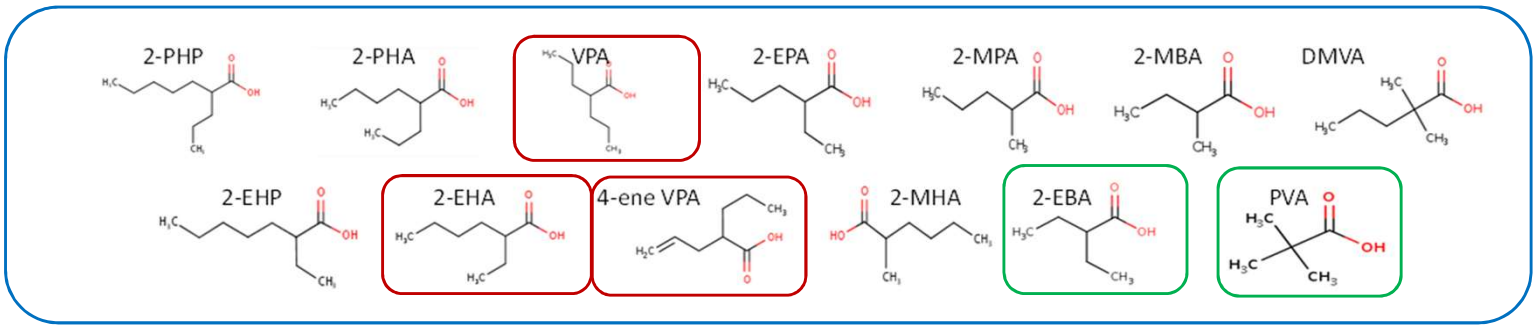


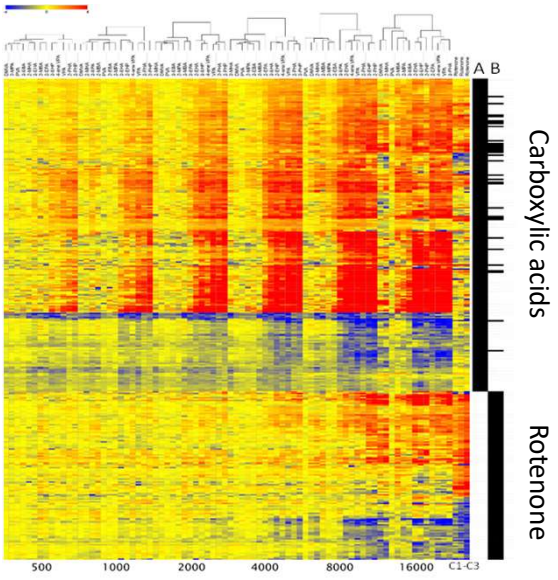
Figure 1: Group of structurally similar compounds, coloured boxes indicate SCs with known in vivo studies.

Read-across hypothesis

- Develop a hypothesis on relevant toxicological effects based on *in vivo* studies of data-rich SCs
- VPA, 4-ene VPA and 2-EHA (red boxes) induced liver steatosis in preclinical animal studies
- 2-EBA and PVA (green box) did not induce liver steatosis up to the highest dose tested *in vivo*
- Read-across hypothesis followed the precautionary principle – > all compounds will induce liver steatosis

Transcriptome data from human liver cells (HepG2) showed a dose dependent & consistent pattern of differentially expressed gened; rotenone had a different mode of action

Similarity based on omics data



The EU-ToxRisk project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 681002

1 Fraunhofer Institute for Toxicology and Experimental Medicine, Chemical Safety and Toxicology, Germany
2 Novo Nordisk Foundation Center for Protein Research, University of Copenhagen, Denmark
3 Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy
4 Aquatic Ecology and Toxicology Group, Center for Organismal Studies, University of Heidelberg, Heidelberg, Germany
5 BioDetection Systems, Amsterdam, The Netherlands
6 Instituto de Investigación Sanitaria La Fe, Valencia, Spain
7 Cyprotex, Cheshire, United Kingdom
8 MTM Research Centre, Örebro University, Sweden
9 Edelweiss Connect GmbH, Basel, Switzerland
10 Certara UK Ltd, Simcyp Division, Sheffield, United Kingdom
11 Lhasa Limited, Leeds, United Kingdom
12 Leiden Academic Centre for Drug Research (LACDR), Leiden University, Leiden, The Netherlands
13 Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
14 Université de Paris, France
15 Unilever Safety and Environmental Assurance Centre, Sharnbrook, Bedfordshire, United Kingdom
16 University of Vienna, Department of Pharmaceutical Sciences, Division of Pharmaceutical Chemistry, Vienna, Austria