The Final EUTOXRISK Symposium 14

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

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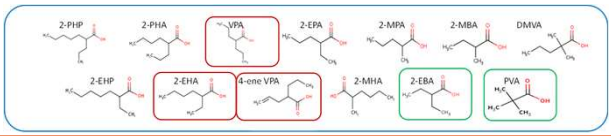
Characterise trends in shared mode of action and derive a point of departure for risk assessment



AOP informed testing

- Existing knowledge on liver steatosis compiled into AOP network, considering early molecular initiation events (MIEs) and key events (KEs) leading to the adverse outcome (AO)
- Some MIEs/KEs already known for source compound valproic acid (VPA) (coloured red/yellow)
- Red MIEs and KEs selected for testing in relevant in vitro test systems

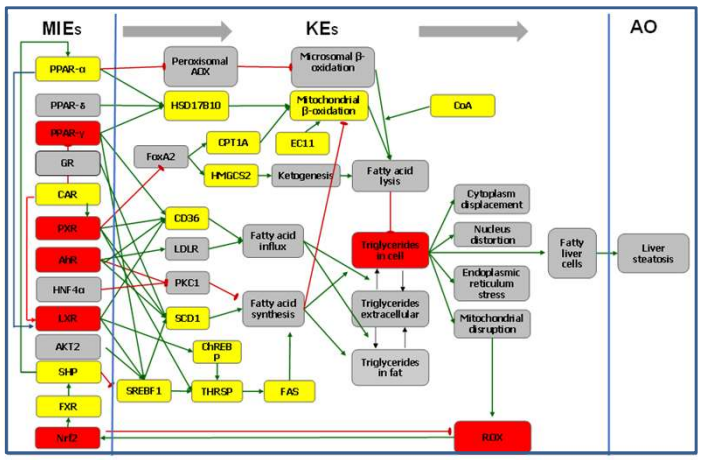
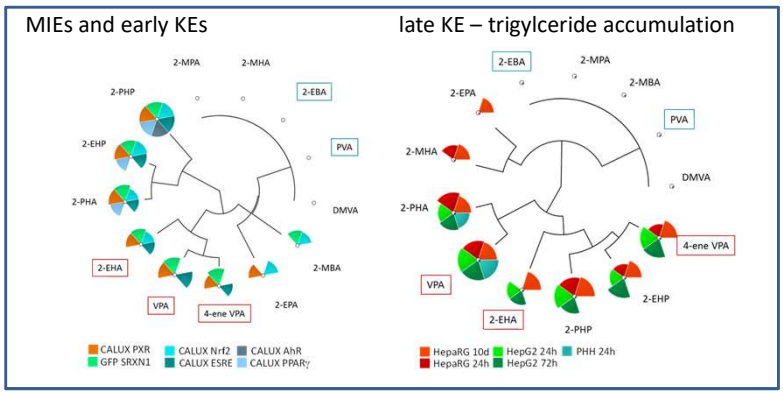


Figure 1: *The AOP network for microvesicular liver steatosis illustrates the activation and inhibition of molecular initiation events (MIEs) progressing to key events (KEs) and resulting in the adverse outcome (AO) liver steatosis; red lines indicate inhibition, green lines activation; coloured MIEs/KEs are obtained from studies testing VPA (red/yellow).*

Conclusions

- Early MIEs/KEs can be used to prove similar mode of action
- PBK simulations for all analogues identify a trend for increasing clearance and so decreasing systemic exposure with decreasing side chain length
- The late KE „triglyceride accumulation“, close to the AO steatosis, is useful to predict a PoD for RA

MIEs and KEs in AOP



- MIEs/KEs data show trend in category; activity decreases with length of aliphatic side chain

In-vitro-to-*in-vivo*-extrapolation-linked physiologically based kinetic (IVIVE-PBK) modelling

Compound specific inputs:

- physicochemical properties obtained from the literature
- intrinsic hepatic clearance quantified *in vitro*
- QSAR based predictions of fraction unbound in plasma (fu)
- Assumptions of PBK modelling approach verified against clinical *in vivo* data for the analogue VPA
- Verified IVIVE-PBK model assumptions applied to model and predict human oral equivalent doses (hOEDs) for all VPA analogues

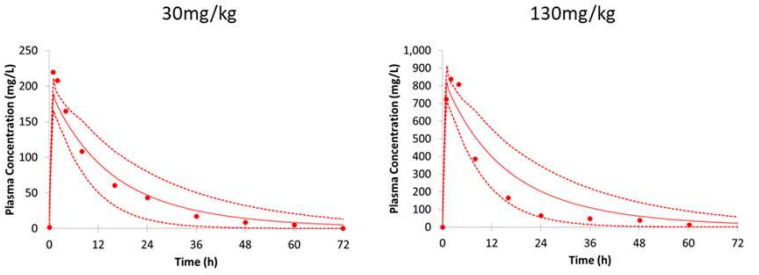


Figure 2. *Verification of IVIVE-PBK model performance for VPA: Model is based on ADME parameters generated in vitro and QSAR predictions. Simulated concentration time profiles (solid red line) and 5th, 95th percentile (dashed red lines) are compared with clinical data (data points; George et al. 2018). Two doses (30 and 130 iv mg/kg bw) are modelled using a QSAR predicted fraction unbound in plasma of 0.31.*

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http://www.eu-toxrisk.eu/