In vitro test battery for testing molecular initiating events in chemical-induced cholestasis

Created on: 25-08-2025 - Last modified on: 28-08-2025

Organisation

Name of the organisation Vrije Universiteit Brussel (VUB)

Specific Research Group or Service

In Vitro Toxicology and Dermato-Cosmetology (IVTD)

Country Belgium

Geographical Area Brussels Region

Partners and collaborations

Ghent University (UGent)

SCOPE OF THE METHOD

The Method relates to	Human health
The Method is situated in	Translational - Applied Research
Type of method	In vitro - Ex vivo
Specify the type of cells/tissues/organs	human HepaRG cells

DESCRIPTION

Method keywords

in vitro

test battery

Molecular initiating event

Adverse outcome pathway

AOP network

MIE

new approach methodologies

NAM

weight-of-evidence assessment

Scientific area keywords

cholestasis

liver

liver injury

in vitro toxicology

chemical toxicity

Method description

Cholestatic liver injury is a complex adversity leading to the toxic accumulation of noxious bile salts in the liver and systemic circulation. Cholestasis can be instigated by a plethora of chemicals originating from several applicability domains. Current efforts fail to predict the cholestatic potential of chemicals due to, at least in part, gaps in the mechanistic understanding of this type of adversity. A recently introduced adverse outcome pathway (AOP) network on cholestatic liver injury generated using artificial intelligence pulls up transporter changes, bile canalicular changes and hepatocellular changes as molecular initiating events (MIEs). The present study used this AOP network as the mechanistic basis for the development of an *in vitro* test battery to predict MIEs of cholestatic hepatotoxicity, including assays to monitor transporter changes at the sinusoidal uptake, canalicular efflux and basolateral efflux pole as well as bile canalicular changes. For this purpose, human HepaRG cells

were exposed to known cholestatic chemicals covering various MIEs, non-cholestatic hepatotoxic chemicals and non-hepatotoxic chemicals. Subsequent application of the MIE test battery shows great potential for identifying cholestatic chemicals, while correctly predicting all negative control chemicals. In conclusion, the established *in vitro* test battery shows potential for early prediction of cholestatic chemicals.

Lab equipment

- Cell culture facility,
- Microscope.

Method status

Published in peer reviewed journal

PROS, CONS & FUTURE POTENTIAL

Advantages

Our established *in vitro* test battery, embedded in the AOP, has the potential to serve as a predictive tool for hazard identification of chemicals in various applicability domains. More specific, this *in vitro* test battery holds potential to be applied in preclinical research in pharmaceutical industry for picking up early on potentially cholestatic drugs and for the safety assessment of non-pharmaceutical chemicals. The integrated WoE approach expands its application potential by incorporating the predictive capacity of each individual measurement and the correlation between the assessed MIE and the adverse outcome, thereby enhancing the relevance of the outcome.

Future & Other applications

In future efforts, this battery will be expanded with further key events in the AOP framework as well as with more personalized approaches where potential underlying conditions such as inflammation can be included.

REFERENCES, ASSOCIATED DOCUMENTS AND OTHER INFORMATION

Links

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IVTD Research Group

Mathieu Vinken's Research Team

Other remarks

This work was financially supported by the European Commission under the Horizon2020 Research and Innovation Framework program (grant number 963845 “ONTOX”), the Flemish government (Methusalem program), the Research Foundation Flanders, the Scientific Fund Willy Gepts, the Center for Alternatives to Animal Testing and the Alternatives Research and Development Foundation.